CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215256Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 25, 2021
To:	Martin White, M.S. Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Savani, PharmD Regulatory Reviewer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	WEGOVY (semaglutide)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 215256
Applicant:	Novo Nordisk Inc.

1 INTRODUCTION

On December 4, 2020, Novo Nordisk Inc. submitted for the Agency's review an original New Drug Application (NDA) 215256 for WEGOVY (semaglutide) injection, for subcutaneous use. This NDA is proposing an indication of weight management.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) on January 7, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for WEGOVY (semaglutide) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft WEGOVY (semaglutide) MG and IFU received on December 4, 2020, and received by DMPP and OPDP on May 14, 2021.
- Draft WEGOVY (semaglutide) Prescribing Information (PI) received on December 4, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 14, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

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MEENA R SAVANI
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MARCIA B WILLIAMS
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LASHAWN M GRIFFITHS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 25, 2021

To: Martin White, Regulatory Project Manager, Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Monika Houston, Associate Director for Labeling, (DDLO)

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for WEGOVY™ (semaglutide) injection, for subcutaneous use

NDA: 215256

In response to DDLO's consult request dated January 7, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for WEGOVY.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling downloaded from SharePoint on May 24, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 23, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Meena Savani at (240) 402-1348 or Meena.Savani@fda.hhs.gov.

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/s/

MEENA R SAVANI
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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY

Date: May 21, 2021

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: Martin White, RPM
DDLO

Subject: IRT Consult to NDA-215256 (SDN001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 5/13/2021 regarding the Division's QT related question. We reviewed the following materials:

- Previous IRT review for IND-126360 dated 10/05/2017 in DARRTS (link);
- Previous IRT review for NDA-209637 dated 05/03/2017 in DARRTS (link); and
- Sponsor's proposed product label (SN0001; link).

1 IRT Responses

Previously, the IRT agreed with the sponsor's proposal to characterize QT effects using the data from Phase-3 study to support the weight management indication (Dt: 10/05/2017). The expected steady-state peak concentrations (~116 nmol/L vs ~73 nmol/L) with the proposed therapeutic dose are higher (~58%) than those observed with 1.5 mg dose in the thorough QT study (Study NN9535-3652). However, considering - 1) a shallow exposure-response relationship between ΔΔQTcI and plasma concentrations of semaglutide observed in the thorough QT study; 2) peptide nature of semaglutide; and 3) no considerable impact of intrinsic and extrinsic factors of the exposures of semaglutide, the sponsor's approach of extending the findings of previous thorough QT study appears reasonable. In addition, relatively lower exposures of semaglutide were observed in the target population (obese) compared to the healthy subjects.

Below are proposed edits to the label submitted to SDN001(link) from the IRT. Our changes are highlighted (*addition*, ~~*deletion*~~). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of semaglutide on cardiac repolarization was tested in a thorough QTc trial. Semaglutide did not prolong QTc intervals at doses up to 1.5 mg at steady state. (b) (4)

(b) (4)

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

2 Internal Comments to the Division

- *None.*

3 Background

3.1 Product Information

Novo Nordisk is developing semaglutide as an adjunct to a reduced calorie meal plan and increased physical activity for chronic weight management (b) (4) in adult patients. Semaglutide (MW: 4113.58 g/mol; the peptide backbone is produced by yeast fermentation) is glucagon-like peptide-1 (GLP-1) receptor agonist. Previously, semaglutide is approved for the treatment of diabetes (type 2) as once-weekly subcutaneous administration (Ozempic solution; NDA-209637) or once-daily oral administration (Rybelsus; NDA-213051 & NDA-213182).

The product is formulated as sterile solution containing 0.25, 0.5, or 1 mg semaglutide (in 0.5 mL single dose pen) for subcutaneous administration. The maximum proposed therapeutic dose for the present indication is 2.4 mg once weekly (the starting dose is 0.25 mg qW. After 4 weeks, the dose is increased to 0.5 mg qW, followed by 1.0 mg qW, 1.7 mg qW and finally the maintenance dose of 2.4 mg qW. All escalation steps are given for 4 weeks). The peak concentrations of ~119 nmol/L (Tmax: 1-3 days; half-life: ~1 week) were observed at steady state with the anticipated therapeutic dose (Study # 4590 and POP-PK). The product exhibit dose-proportional increase in exposures up to 2.4 mg once weekly.

Since semaglutide is primarily metabolized by proteolytic degradation (cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain; no major metabolites were identified), it has no significant drug interaction liability. Semaglutide is excreted in the urine (~3% as unchanged drug) and feces. The sponsor states that renal (mild, moderate, severe, or ESRD) or hepatic (mild, moderate, severe) impairment did not have any impact on the exposure of semaglutide (single dose of 0.5 mg semaglutide). The sponsor proposed no dose adjustment based on age, gender, race, ethnicity, body weight, renal function, injection site or glycemic status.

Previously, the IRT agreed with the sponsor's proposal to characterize QT effects using the data from Phase-3 study to support the weight management indication (Dt: 10/05/2017).

3.2 Sponsor's Position related to the Question

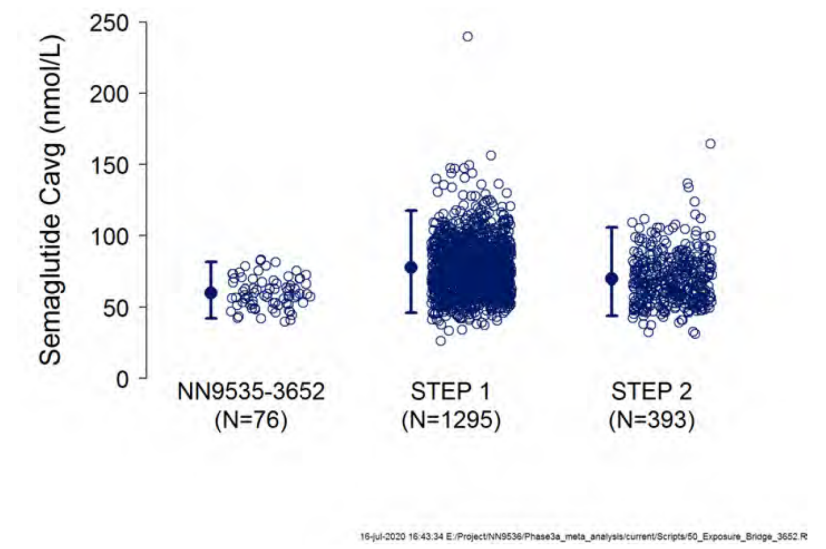
The sponsor states that the risk of QT prolongation of semaglutide was adequately characterized in the previous thorough QT study in healthy subjects conducted under NDA-209637 (Dt: 05/03/2017). Refer to the sponsor's summary of clinical pharmacology studies (m2.7.2)

The potential effect of semaglutide on cardiac repolarization by QTc has previously been studied for Ozempic®. No prolongation of the QTc interval was observed with semaglutide in doses up to 1.5 mg and no semaglutide exposure-QTc relation was observed in the QTc trial for Ozempic®.

In addition, as expected, body weight was the most important covariate resulting in lower exposure with higher body weight and vice versa, while other investigated covariates had a minor or no influence on semaglutide exposure. Further, semaglutide elimination is not organ specific, thus, conditions such as renal or hepatic impairment are not associated with higher semaglutide exposure.

As evident from Figure 4-1, comparable exposures were observed between the semaglutide 2.4 mg weight management program (STEP 1 and STEP 2) and trial NN9535-3652. Therefore, the QTc trial (NN9535-3652) is considered adequate to support the weight management indication with semaglutide 2.4 mg.

Figure 4-1 Exposure of semaglutide – Semaglutide 2.4 mg vs. semaglutide QTc assessment - modelling



N: Number of subjects contributing with PK data (STEP 1 and 2) or completing the trial (NN9535-3652). Data are individual Cavg values (open symbols) and geometric means with 90% ranges (closed symbols with error bars) obtained with semaglutide 2.4 mg (STEP 1 and STEP 2) or semaglutide 1.5 mg (trial NN9535-3652). Cavg values in STEP 1 and 2 were derived as described for estimation of steady-state exposure in Section 1.3.3.2. Cavg values in trial NN9535-3652 were derived from noncompartmental analyses.

Based on the population PK analysis, an estimated expected highest exposure scenario in the clinical setting based on the covariates included in the final model (including only significant covariate factors) was evaluated to be the exposure of a normo-glycaemic Black female with moderate renal impairment and with a body weight of 74 kg (5th percentile in the PK population).

The estimated average concentration at steady state for this subject profile was 116 nmol/L (90% prediction interval 87−155 nmol/L). Based on the full profiles from previous clinical pharmacology trials, the influence of covariates on Cavg and Cmax is close to identical. Cmax is approximately 25% above the Cavg. Adding 25% to the Cavg from the expected highest clinical exposure scenario above, gives an approximate expected Cmax of 145 nmol/L.

Reviewer's comment: Based on population pharmacokinetics, body weight is a significant covariate and higher exposures are expected in subjects with lower body weight (e.g., 74 kg: 1.4-fold and 143 kg: 0.8-fold, compared to exposure relative to body weight 110 kg). Relatively, lower exposures of semaglutide were observed in the target population (obese) compared to the healthy subjects.

3.3 Nonclinical Cardiac Safety

Refer to the sponsor's highlights of clinical pharmacology and clinical safety (m2.7.2; Appendix 5.1), the sponsor's non-clinical overview (m2.4), and the previous IRT review for NDA-209637 dated 05/03/2017 in DARRTS (link).

In vitro cardiovascular studies were also performed to evaluate potential effects on the cardiac action potential. In addition, cardiac electrophysiology was monitored by ECG in the repeat dose toxicity studies in cynomolgus monkeys.

Semaglutide was well tolerated in the monkey, and no adverse effects were observed in the cardiovascular telemetry study, evaluating single doses of up to 0.5 mg/kg corresponding to 6-fold the exposure at the MRHD based on Cavg. GLP-1R agonists have been reported to decrease the arterial blood pressure in humans and to cause an increase in heart rate of 2-3 beats per minute (88). These effects were not detected in the acute, single dose study in monkeys.

Semaglutide had no effect in the hERG study or Purkinje fiber study investigating cardiac ion channels when tested up to 8.2 μM (109-fold the expected human Cavg at a clinical dose of 2.4 mg qW).

3.4 Clinical Cardiac Safety

Refer to the sponsor's highlights of clinical pharmacology and clinical safety, integrated summary of safety (link), and the sponsor's clinical overview (m2.5)

Clinical cardiac safety was evaluated based on the phase 3a pool (phase 3a trials: STEP 1, STEP 2, STEP 3 and STEP 4), the number of exposed subjects to semaglutide 2.4 mg was 2650 and patient years of exposure was 3309.5.

There was no apparent treatment difference in the reporting of AEs within the HLGT Cardiac arrhythmias (semaglutide 2.4 mg: 2.3%, 2.1◦events per 100 PYE, placebo: 2.0%, 1.9 events per 100 PYE) in the phase 3a pool. The most frequently reported events were atrial fibrillation and tachycardia. One event of atrial fibrillation led to premature treatment discontinuation. Also, AEs of increased heart rate (grouped preferred terms) were reported in a small proportion of subjects with no apparent imbalance between the treatment groups (semaglutide 2.4 mg: 0.8%, placebo: 0.6%).

In all the phase 3a trials, a 12-lead ECG was performed at the randomization visit, the week 20 visit and the end-of-treatment visit. The ECGs were to be interpreted by the investigator and

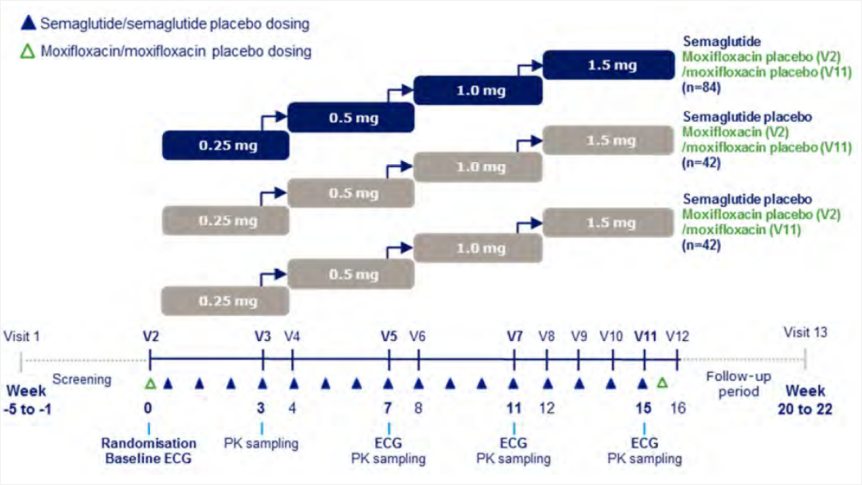
categorized as normal or abnormal, and, if abnormal, furthermore indicated whether or not the finding was clinically significant.

Overall, the proportion of subjects with ECG abnormalities did not differ between the treatment groups for any of the abnormality categories. The effects of semaglutide s.c. 2.4 mg once weekly on cardiovascular outcomes are currently being investigated in a dedicated cardiovascular outcome trial, SELECT (trial NN9536-4388), in subjects with established cardiovascular disease and obesity or overweight and without T2D. Reporting of results from SELECT is expected during 2024.

3.5 Summary Results of Prior QTc Assessments

The sponsor conducted a thorough QT study under NDA-209637. In our previously assessment, no significant QTc prolongation effect of semaglutide (0.5 mg, 1.0 mg, and 1.5 mg) was detected (TQT study # NN9535-3652; Dt: 05/03/2017). It was a randomized, blinded, 3-arm parallel study with a nested crossover design (n=168). Healthy subjects were randomized to receive semaglutide (dose escalation regimen of 0.25 mg, 0.5 mg, 1.0 mg, and 1.5 mg), semaglutide placebo, moxifloxacin placebo, and a single dose of moxifloxacin 400 mg. Within the studied exposure range (up to 1.5 mg), no exposure-response relationship was seen between baseline- and placebo-adjusted QTcF and QTcI intervals and semaglutide concentrations.

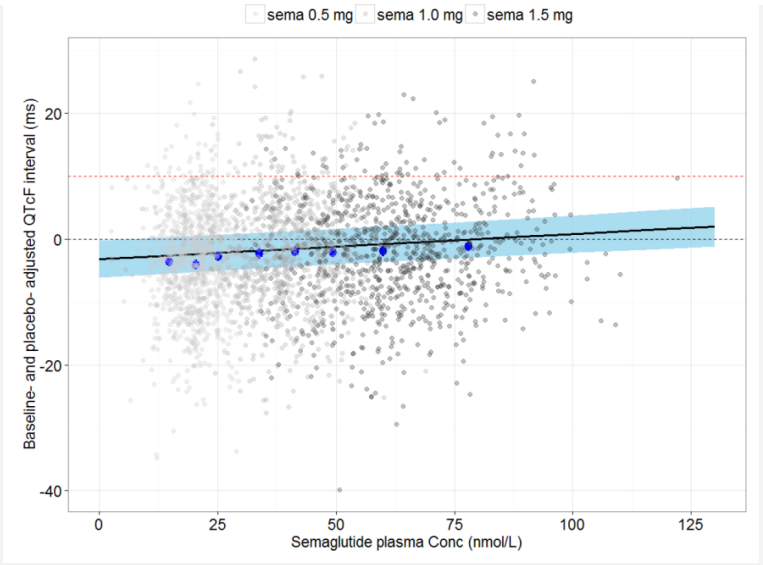
Study Design:

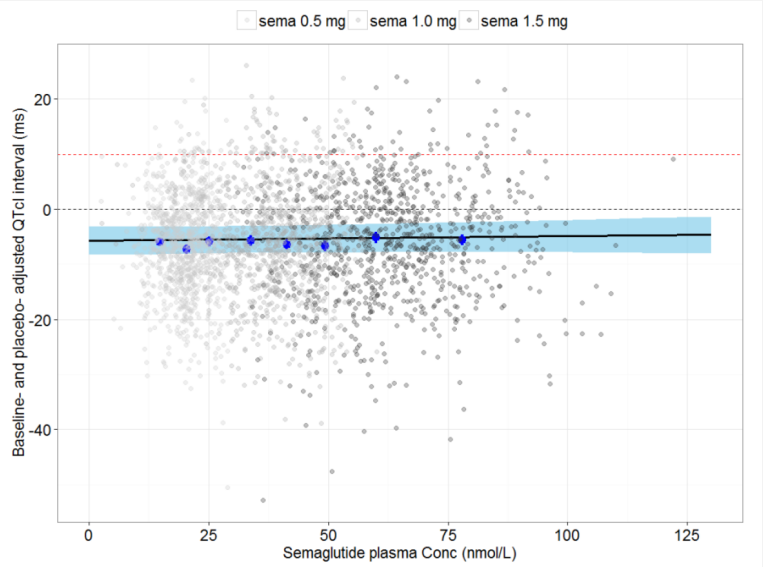


The exposure-response relationship was assessed by baseline- and placebo-adjusted QTcI at steady state of semaglutide 0.5, 1.0 and 1.5 mg versus corresponding semaglutide plasma concentrations. No significant exposure-response relationship was identified between ΔΔQTcI and semaglutide concentrations.

The mean (90% CI) ΔΔQTcF and ΔΔQTcI at mean steady-state Cmax of 74.19 nmol/L following supratherapeutic dosing regimen 1.5 mg once weekly is estimated to be -0.22 (-3.07, 2.63) and -5.11 (-7.77, -2.46) ms, respectively.

Figure: The relationships between ΔΔQTcF and ΔΔQTcI and semaglutide concentrations.





<u>Reviewer's comment</u>: Based on the previous assessment, the mean (90% CI) ΔΔQTcF and ΔΔQTcI at mean steady-state Cmax of 74.19 nmol/L following supratherapeutic dosing regimen 1.5 mg once weekly is estimated to be -0.22 (-3.07, 2.63) and -5.11 (-7.77, -2.46) ms, respectively. The expected steady state peak concentrations (~116 nmol/L vs 72.6 nmol/L) with the proposed therapeutic dose are higher (~60%) than those observed with 1.5 mg dose in the thorough QT study (Study NN9535-3652). However, a shallow exposure-response relationship between ΔΔQTcI and plasma concentrations of semaglutide was observed in the thorough QT study.

3.6 Relevant Details of Planned Phase 3 Study

Not applicable.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov.

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/s/

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	May 21, 2021
Reviewer:	Christian Hampp, PhD Division of Epidemiology I
Team Leader:	Yandong Qiang, MD, PhD, MPH, MHS Division of Epidemiology I
Division Director:	Simone P. Pinheiro, ScD, MSc, ALM Division of Epidemiology I
Subject:	ARIA Sufficiency Assessment for pregnancy safety of semaglutide in the treatment of obesity
Drug Name:	Wegovy® (semaglutide)
Application Type/Number:	NDA 215256
Applicant/sponsor:	Novo Nordisk
OSE RCM #:	2020-2565

EXECUTIVE SUMMARY

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If “No”, please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	X

1. BACKGROUND INFORMATION

1.1. Medical Product

On December 4, 2020, Novo Nordisk submitted a New Drug Application (NDA 215256) for semaglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, for the proposed indication of weight management. NDA 215256 is a 505(b)(2) application referencing IND 126360 and NDA 209637 for Ozempic (semaglutide) injection prefilled pen, which is indicated for use in adult patients with type 2 diabetes mellitus. Ozempic is a subcutaneous injection administered at a starting dose of 0.25 mg once weekly, and can be increased to 0.5 mg once weekly after 4 weeks, up to a maximum of 1 mg once weekly.[1]

The proposed indication for NDA 215456 is as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)

The starting dose of semaglutide is 0.25 mg injected subcutaneously once-weekly, which can be escalated to 2.4 mg once-weekly according to the following schedule to minimize gastrointestinal adverse reactions:

Dose Escalation Schedule

Weeks	Weekly Dose
1 through 4	0.25 mg
5 through 8	0.5 mg
9 through 12	1 mg
13 through 16	1.7 mg
Week 17 and onward	2.4 mg

1.2. Describe the Safety Concern

Preclinical data

The pharmacology/toxicology review by Dr. Elena Braithwaite, Division of Pharm/Tox for Cardiology, Hematology, Endocrinology and Nephrology (DPT-OCHEN), includes an evaluation of embryofetal development and pre- and postnatal development studies that were conducted in rats, rabbits, and cynomolgus monkeys.(1) In rats, findings included decreased placental and fetal weights, and major malformations, including cardiovascular abnormalities

[1] Semaglutide is also available in tablet form (Rybelsus, NDA 213051) for the treatment of type 2 diabetes mellitus, with a starting dose of 3 mg once daily, which can be increased in a stepwise fashion to 14 mg once daily if additional glycemic control is needed.

(retro-esophageal aortic arch, double aortic arch, and membranous ventricular septal defect) and short tibia at doses below the maximum recommended human dose (MRHD). In rabbits, there were minor skeletal abnormalities (additional sternebral centers, bridge of ossification/partially fused/fused sternebra, unossified/incompletely ossified metacarpals/phalanges) and minor visceral abnormalities (dilated renal pelvis, additional liver lobe, and forepaw flexure) observed at 0.9-fold the MRHD.

Cynomolgus monkey experienced decreased maternal body weight that was associated with reduced food consumption during the semaglutide dosing phase at all doses examined. A few sporadic abnormalities (focal reddening of the skin, kinked and stiff wrist, blood accumulation under the skull causing misshapen right brain hemisphere, fused kidneys, liver cysts and shift in alignment of the vertebrae, ribs, and first sternebra, at the cervico-thoracic border) were observed in fetuses (at $\geqslant$2-fold the MRHD). Pregnant monkeys also experienced an increased incidence of early pregnancy loss (at 3-fold the MRHD). Reduced infant body weights at birth were also observed; but, by Day 91, body weights were similar across all groups. Semaglutide treatment did not result in neurobehavioral impairment during a neurobehavioral test battery conducted on post-partum day 1 and 7.

Because these findings in animals are potentially due to the weight loss that occurred in the animals, and it is not clear if the findings are clinically relevant.

Clinical experience

According to a review by the Dr. Carrie Ceresa, Division of Pediatric and Maternal Health (DPMH), 29 pregnancies were reported in females treated with semaglutide across 4 clinical trials within the clinical development program for semaglutide 2.4 mg.(2) These and other exposed pregnancies are included in the Novo Nordisk safety database, which contains a total of 98 pregnancies exposed to semaglutide (including Ozempic and Rybelsus), with known fetal outcomes in 47 pregnancies. They include 26 live births without congenital anomalies, 1 live birth with congenital anomaly,[2] 9 fetal losses (spontaneous abortion), and 11 terminations without known fetal defects.

Dr. Ceresa summarized the sponsor's review of the literature and conducted her own literature review. None of the retrieved publications contain pregnancy exposure cases to semaglutide.

The reviewer concluded that the data are insufficient to determine if there is a drug associated risk of maternal or fetal adverse reactions.

Weight management and pregnancy

According to the DPMH review, women with a BMI $\geqslant$ 30kg/m^2 are at risk for gestational diabetes, pre-eclampsia, and cesarean delivery. Also, women with excessive pregnancy weight gain are at risk for postpartum weight retention, obesity and type 2 diabetes. Yet, fetal/neonatal

[2] One case of "small left ear fold/anomaly of external ear congenital" involved exposure to semaglutide during pregnancy at unknown gestational timing. The mother was HIV positive and the pregnancy was conceived while mother had an IUD in place. The infant was born at 38 weeks and 4 days gestation and had a small left ear fold that resolved itself 4 weeks after birth. This event was categorized as "unlikely" related to study drug.

adverse outcomes, such as fetal growth restriction, can occur in obese women who try to lose weight during pregnancy.

Consequently, the draft labeling of semaglutide (below) states that (b) (4)

(b) (4)

Nevertheless, because women of childbearing age represent a large proportion of antiobesity drug users, (3) a substantial number of pregnancies could be affected by early exposure to semaglutide.

Draft Labeling

As of the date of this memo, Section 8.1 of the draft labeling states:

(b) (4)

(b) (4)

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of childbearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☒ Electronic database study with chart review
☒ Electronic database study without chart review
☐ Other, please specify:

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☐ Outcomes
☒ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Covariates
BMI is not comprehensively and reliably available in Sentinel claims data. Because it is an important predictor of treatment initiation, and is associated with various pregnancy complications, the ability to ascertain BMI is critical.

Analytical Tools
The requested PMR targets more than one outcome, including major congenital malformations (MCM), spontaneous abortions, stillbirths, small for gestational age, and preterm birth. Moreover, the MCM outcome covers several subclasses of potential interest (e.g., congenital malformation of the circulatory system, congenital malformation of the nervous system, or cleft lip and cleft palate). ARIA might address the complexity presented by multiple discrete outcomes by means of an appropriate data mining approach. However, a suitable data mining approach (e.g., TreeScan) is not yet available for signal detection of birth defects and other pregnancy outcomes in ARIA.

2.5. Please include the proposed PMR language in the approval letter.

As of the date of this memo, the FDA drafted the PMR language below:

1. Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to semaglutide during pregnancy to an unexposed reference population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

2. Conduct an additional pregnancy study that uses a different observational design from the Pregnancy Exposure Registry, using claims or electronic medical record data, to assess the associations between semaglutide exposure during pregnancy with pregnancy outcomes and infant outcomes including but not limited to major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age, preterm birth, and postnatal growth and development.

3. REFERENCES

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research| Office of Surveillance and Epidemiology (OSE)

Epidemiology: ARIA Sufficiency Memorandum

Date:	May 21, 2021
Reviewer:	Christian Hampp, PhD Division of Epidemiology I
Team Leader:	Yandong Qiang, MD, PhD, MPH, MHS Division of Epidemiology I
Division Director:	Simone P. Pinheiro, ScD, MSc, ALM Division of Epidemiology I
Subject:	ARIA Sufficiency Memo: An assessment of the Sentinel Active Risk Identification and Analysis (ARIA) system to evaluate the association between semaglutide and medullary thyroid carcinoma (MTC) during the postmarketing safety surveillance of semaglutide injection (b) (4) (b) (4)
Drug Name:	Wegovy® (semaglutide)
Application Type/Number:	NDA 215256
Applicant/sponsor:	Novo Nordisk
OSE RCM #:	2020-2565

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	X
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

On December 4, 2020, Novo Nordisk submitted a New Drug Application (NDA 215256) for semaglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, for the proposed indication of weight management. NDA 215256 is a 505(b)(2) application referencing IND 126360 and NDA 209637 for Ozempic (semaglutide) injection prefilled pen, which is indicated for use in adult patients with type 2 diabetes mellitus. Ozempic is a subcutaneous injection administered at a starting dose of 0.25 mg once weekly, and can be increased to 0.5 mg once weekly after 4 weeks, up to a maximum of 1 mg once weekly.[a]

The proposed indication for NDA 215456 is as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)

The starting dose of semaglutide is 0.25 mg injected subcutaneously once-weekly, which can be escalated to 2.4 mg once-weekly according to the following schedule to minimize gastrointestinal adverse reactions:

Dose Escalation Schedule

Weeks	Weekly Dose
1 through 4	0.25 mg
5 through 8	0.5 mg
9 through 12	1 mg
13 through 16	1.7 mg
Week 17 and onward	2.4 mg

1.2. Describe the Safety Concern

Medullary Thyroid Carcinoma (MTC), accounting for approximately 5-8% of all thyroid carcinoma cases,(1) is a malignant thyroid neoplasm caused by production of calcitonin by the proliferation of the parafollicular C-cells.(1, 2)

Nonclinical toxicology data indicate that long-acting GLP-1 receptor agonists cause dose-related and treatment-duration-dependent thyroid C-cell tumors (adenomas or carcinomas) in rodents.

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[a] Semaglutide is also available in tablet form (Rybelsus, NDA 213051) for the treatment of type 2 diabetes mellitus, with a starting dose of 3 mg once daily, which can be increased in a stepwise fashion to 14 mg once daily if additional glycemic control is needed.

Non-clinical studies showed that semaglutide was associated with an increase in thyroid C-cell adenomas and combined C-cell adenomas and carcinoma in male and female mice and male (C-cell carcinoma and adenomas) and female (C-cell adenomas) rats.(3) A hypothetical mechanism is that long-term exposure to long-acting GLP-1 receptor agonists may stimulate the GLP-1 receptors on the thyroid C cells of rodents, which is sufficient to increase cyclic adenosine monophosphate (cAMP) and initiate the release of calcitonin.(2, 4) However, the GLP-1 receptors in humans are expressed less frequently and do not induce cAMP elevation and calcitonin secretion (2) and there appeared no reports of MTC following GLP-1 receptor agonists in clinical studies among humans.(4, 5) The causal link between GLP-1 receptor agonists and thyroid C-cell tumors, including MTC, in humans remains unknown because of limited duration of follow-up and interspecies differences.(5) No cases of MTC among humans were identified during the clinical development phase of semaglutide for weight management.

FDA first approved long-acting GLP-1 receptor agonist, Victoza®, on January 25, 2010. Table 1 summarizes the currently FDA approved long-acting GLP-1 receptor agonists.

Table 1. List of FDA approved long-acting GLP-1 receptor agonists, May 12, 2021

Brand Name	Active Ingredient	Sponsor/Application Tracking Number	FDA Approval Date	Boxed Warning with Thyroid C-Cell tumor*
Victoza	Liraglutide recombinant	Novo Nordisk /NDA022341	January 25, 2010	Yes
Bydureon	Exenatide synthetic	Astrazeneca /NDA022200	January 27, 2012	Yes
Tanzeum	Albiglutide	GSK /BLA125431	April 15, 2014	Yes
Saxenda	Liraglutide recombinant	Novo Nordisk /NDA206321	December 23, 2014	Yes
Trulicity	Dulaglutide	Eli Lilly /BLA125469	September 19, 2014	Yes
Xultophy	Insulin degludec and liraglutide	Novo Nordisk /NDA208583	November 21, 2016	Yes
Ozempic	Semaglutide	Novo Nordisk/NDA209637	December 5, 2017	Yes
Rybelsus	Semaglutide	Novo Nordisk/NDA213182	January 16, 2020	Yes

*Including medullary thyroid carcinoma (MTC).

Although "FDA concluded increases in the incidence of carcinomas among rodents translated into a low risk for humans, because statistically significant increases occurred only at drug-exposure levels many times those anticipated in humans, and the increase in cancers did not affect overall survival rates,"(6) the product labeling of all long-acting GLP-1 analogs listed in

Table 1 include thyroid C-cell tumor in the Boxed Warning because of increased risk of MTC among rodents. The following Boxed Warning is part of the current Ozempic labeling (7):

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 OZEMPIC 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).**
- **OZEMPIC 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).**

Under Sections 505(o)(3), 505(k)(1), and 505(k)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA), FDA issued a postmarketing requirement (PMR) for the sponsors of long-acting GLP-1 receptor agonists to join a MTC case series registry to investigate the relationship between long-acting GLP-1 receptor agonist treatment and the development of MTC in humans. The sponsors formed an MTC Registry Consortium to address this PMR after FDA approved more than one GLP-1 receptor agonist. Within the MTC Registry Consortium, the sponsors monitor the annual incidence and change in incidence of MTC through the North American Association of Central Center Registries (NAACCR); and document demographic and medical risk factors related to the MTC diagnosis among cases in the MTC participating State Cancer Registries (SCRs). The MTC case series registry verifies prior GLP-1 receptor agonist treatment through treating physicians.

Because of the potential association between long-acting GLP-1 receptor agonists and risk of MTC, and in order to ensure that the benefits of long-acting GLP-1 receptor agonists outweigh the potential risk of MTC, FDA also requires a class wide Risk Evaluation and Mitigation Strategy (REMS) for approved long-acting GLP-1 receptor agonists as these drugs are indicated for a large patient population with wide range of potential prescribers for prescription and dispensing.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	X

1.4. Statement of Purpose

Since the FDA approval of the first long-acting GLP-1 receptor agonist, Victoza (liraglutide), FDA requires all subsequently approved GLP-1 receptor agonists to join an MTC case series registry for a class-wide postmarketing surveillance to systemically monitor the annual incidence of MTC in the United States for at least 15 years and characterize the MTC cases regarding their medical history and possible risk factors, including history of GLP-1 receptor agonist treatment. The sponsors[b] and the American Thyroid Association (ATA) initiated the MTC case series registry in 2010.

Per the request of the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) in the Office of New Drugs (OND), the Division of Epidemiology-I (DEPI-I) conducted an assessment of the Sentinel Active Risk Identification and Analysis (ARIA) system to determine, instead of the class-wide MTC case series registry for GLP-1 receptor agonists, if Sentinel ARIA is sufficient to assess the MTC safety signal in human, under Food and Drug Administration Amendments Act (FDAAA) 2007, for postmarketing safety surveillance of semaglutide for weight management.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Skipped. Insufficiency in exposure and study outcome preclude further discussion.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

Skipped. Insufficiency in exposure and study outcome preclude further discussion.

2.2 Is ARIA sufficient to assess the intended population?

Skipped. Insufficiency in exposure and study outcome preclude further discussion.

[b] Currently, the MTC case registry covers exenatide extended release (Bydureon, AstraZeneca), albiglutide (Tanzeum, of GlaxoSmithKline), dulaglutide (Trulicity, Eli Lily), liraglutide for diabetes treatment (Victoza, Novo Nordisk), liraglutide for weight management (Saxenda, Novo Nordisk), semaglutide injection for diabetes treatment (Ozempic, Novo Nordisk), and semaglutide tablets for diabetes treatment (Rybelsus, Novo Nordisk).

3 EXPOSURES

3.1 Treatment Exposure(s)

During the period between 2000 and 2020, the Sentinel Distributed Database accumulated over 350 million patients of all ages, with 70 million patients currently accruing new data.(8) Although Sentinel allows for the evaluation of data on a large number of patients:

- Market uptake rates of semaglutide for (b) (4) are uncertain and Sentinel only represents a fraction of all semaglutide users;
- In the Sentinel system, approximately 50% of enrollment episodes with medical and pharmacy coverage are shorter than 2 years, and only 25% are longer than 5 years.(9) Yet, MTC is a rare, long latency outcome (Section 4), requiring long-term follow-up of a large number of exposed patients.

3.2 Comparator Exposure(s)

Skipped.

3.3 Is ARIA sufficient to identify the exposure of interest?

No. The number of patients in Sentinel with exposure to semaglutide for (b) (4) and long-term follow-up would likely be insufficient to support an ARIA evaluation, especially in the context that MTC is a rare, long latency event (Section 4).

4 OUTCOME(S)

4.1 Outcomes of Interest

MTC is a rare disease with long latency. It occurs in people at all ages and the incidence varies with age, sex, and racial/ethnic group.(10-12) According to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, the incidence of MTC in the United States ranged from 0.10 per 100,000 person-years in black males to 0.22 per 100,000 person-years in white females during the period between 1992 and 2006.(10) Each year, there are only approximately 600 incident cases of MTC in the United States.(6) There are four types of thyroid cancer: papillary, follicular, medullary, and anaplastic. MTC accounts for 1-2% of all thyroid cancers. Most (75%) MTC cases are sporadic, while 25% are familial, occurring in association with multiple endocrine neoplasia type 2 syndrome. MTC can be cured only by complete resection of the thyroid tumor and metastases. Furthermore, MTC takes decades to develop symptoms/signs inducting medical visit and studies of limited duration are insufficient to characterize an increase in MTC risk.(1, 13-15)

In addition, there is only one ICD-10 code for thyroid cancer and it is nonspecific: C73 "malignant neoplasm of thyroid gland." There are several surgical removal codes, shown below, but they are also nonspecific to MTC and surgery is the primary treatment modality for thyroid cancer in general. Although laboratory measurements for calcitonin and carcinoembryonic

antigen (CEA) are also performed as part of the evaluation, their results would not be available in Sentinel ARIA. CEA is a tumor marker that is also routinely used in colon cancer screening and is elevated in other malignancies such as breast, pancreas and lung cancers. There are no known validation studies using ICD10 code and CEA procedure code (92378) to identify MTC. Also, genetic screening results using the RET germline mutation would not be available in Sentinel and would only identify a proportion of the patients with genetically based MTC.

SURGEON CPT CODE[1]	PROCEDURE
60210	Partial thyroid lobectomy, unilateral; with or without isthmusectomy
60212	Partial thyroid lobectomy, unilateral; with contralateral subtotal lobectomy, including isthmusectomy
60220	Total thyroid lobectomy, unilateral; with or without isthmusectomy
60225	Total thyroid lobectomy, unilateral; with contralateral subtotal lobectomy, including isthmusectomy
60240	Thyroidectomy, total or complete
60252	Thyroidectomy, total or subtotal for malignancy; with limited neck dissection
60254	Thyroidectomy, total or subtotal for malignancy; with radical neck dissection
60260	Thyroidectomy, removal of all remaining thyroid tissue following previous removal of a portion of thyroid
60270	Thyroidectomy, including substernal thyroid; sternal split or transthoracic approach
60271	Thyroidectomy, including substernal thyroid; cervical approach
60500	Parathyroidectomy or exploration of parathyroid

4.2 Is ARIA sufficient to assess the outcome of interest?

No. The Sentinel ARIA system is unlikely to include a sufficient number of patients with the outcome of interest, and with a duration of follow-up needed to evaluate any increased risk in the development of MTC. Moreover, administrative codes used to identify thyroid cancers are not specific.

5 COVARIATES

5.1 Covariates of Interest

Skipped. Insufficiency in exposure and study outcome preclude further discussion.

5.2 Is ARIA sufficient to assess the covariates of interest?

Skipped. Insufficiency in exposure and study outcome preclude further discussion.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

Skipped. Insufficiency in exposure and study outcome preclude further discussion.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Skipped. Insufficiency in exposure and study outcome preclude further discussion.

7 NEXT STEPS

In order to fulfill the postmarketing requirement of the FDA approval of the first long-acting GLP-1 receptor agonist, Victoza (liraglutide), the sponsor and the American Thyroid Association (ATA) initiated a MTC case series registry in 2010 to observe all new cases of MTC diagnosed in the United States for at least 15 years. FDA then obligated the subsequently approved long-acting GLP-1 receptor agonists to join the MTC case series registry for a class-wide postmarketing surveillance to systemically monitor the annual incidence of MTC in the United States and characterize the MTC cases regarding their medical history and possible risk factors including history of GLP-1 receptor agonist treatment.(16, 17)

In alignment with other long-acting GLP-1 receptor agonists in the class, DEPI-I recommends that FDA issue a postmarketing requirement (PMR) for semaglutide for weight management to assess the MTC safety signal, under Section 505(o)(3)(B) Food and Drug Administration Amendments Act (FDAAA). Given the challenges in obtaining a population with sufficient exposure, duration of follow-up, and number of events, given the rarity of MTC, DEPI-I concurs with the use of an MTC registry design.

As of the date of this memo, FDA has developed the following PMR language:

> *Conduct a medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of semaglutide for the treatment of obesity into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to the use of semaglutide for the treatment of obesity.*

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NDA:	215256
Subject:	Immunogenicity review memo – Semaglutide 2.4 mg once weekly subcutaneous injection as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management [redacted] (b) (4) in adult patients with an initial body mass index of >30kg/m^2 (obesity) OR >27 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity.
Review Date:	5/3/2021
PDUFA due Date:	06/04/2021
Primary Reviewer:	Mohanraj Manangeeswaran, Ph.D
Secondary Reviewer:	Daniela Verthelyi, M.D., Ph.D
Applicant:	Novo Nordisk Inc
Associated IND:	126360
Proposed Proprietary Name:	**NA**
Nonproprietary Name:	**Semaglutide**
Dosage form:	Injection, solution
Indication:	Treatment of patients for chronic weight management
Clinical Division:	OND/ODEII/DMEP
RPM:	Martin White

1. Recommendation:

New drug application for Semaglutide 2.4 mg once weekly subcutaneous injection as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management is recommeded for approval from an immunogenicity standpoint.

2. Executive summary:

The sponsor conducted clinical trials to assess the immunogenicity of Semaglutide administered subcutaneously in obese patients and overweight patients with type II diabetes. The screening and confirmatory assays used in monitoring the ADA response were validated and found suitable for their intended purpose, however the assay used to assess neutralizing activity was found to lack sufficient sensitivity (1165ng/mL in the presence of 2nM semaglutide). The sensitivity of 1165 ng/mL in the presence of residual levels of semaglutide present in the clinical samples can only detect NABs in samples that have a % B/T value of more than 40. Antibody positive samples in the clinical trials had much lower levels of antibodies. **The sensitivity of the NAB assay is not sufficient to assess the neutralizing ability of the antibodies**. Previously, PMCs were issued to develop a sensitive NAB assay for subcutaneous semaglutide (Ozempic) and oral semaglutide (Rybelsus) programs for the treatment of T2DM. The sponsor made a good-faith effort and was not able to develop a sensitive assay that is tolerant to on-board semaglutide and capable of monitoring low levels of antibodies present in clinical samples. In light of this previous experience and lack of safety and efficacy concerns with the approved semaglutide (Ozempic, chronic use in T2D patients) available in the market, PMCs need not be issued to the Sponsor to develop a suitable NAB assay but claims about the lack of neutralizing antibodies in treated patients will not be allowed in the label. The clinical studies included 2 phase 3a trials, 1 phase 2 trial, and two clinical pharmacology trial. The overall incidence of ADA for the different trials was 2.9% (50/1709). Among those subjects that seroconverted, 54% were found to crossreact with endogenous GLP1 but MRD adjusted ADA titers were low (15-240; median 30) The neutralizing activity of the antibodies is unknown at this time. No impact on PK, PD, safety or efficacy was evident.

3. Review memorandum:

Summary of drug and use in proposed indication

This is an original NDA submitted by Novo Nordisk Inc. on December 4th, 2020, seeking marketing approval for subcutaneous administration of semaglutide once a wekk as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management.

Semaglutide is a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, a target receptor for native GLP-1. The GLP-1 peptide hormone belongs to the superfamily of glucagon-related peptides. Physiologically, GLP-1 is secreted by the endocrine L-cells of the intestine in response to food intake and also by neurons of the hind brian. Secreted GLP-1 binds to GLP-1 receptor (GLP-1R) and induces glucose-dependent release of insulin as well as increased synthesis of insulin, glucokinase and glucose transporters. GLP-1 also induces glucose-dependent lowering of glucagon secretion, which in turn lowers the hepatic glucose output. Thus, GLP-1 stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner. Patients with T2DM have reduced response to GLP-1 but can respond to the blood glucose lowering effect of GLP-1 when admininstered at supraphysiological levels. In addition, GLP-1 can lower energy

intake via inducing feelings of satiety and fullness and lowering feelings of hunger. GLP-1 receptors expressed in the hypothalamus and hind brain are implicated in reduced food intake. The decreased apetite, early satiety, and preference for low fat and low sugar diets may results in weight loss. GLP-1 receptor agonists are designed to mimic the effect of endogenous GLP-1. The half-life of native GLP-1 is 1.5 minutes after i.v administration and so are not suitable for therapeutic use.

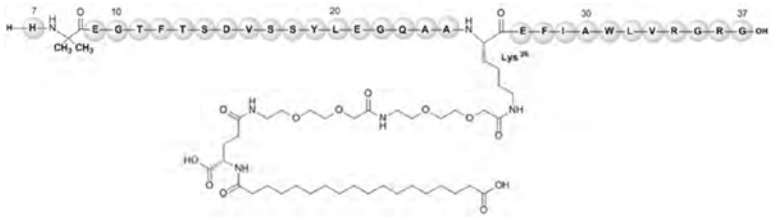
Semaglutide is a long acting analogue of the endogenous GLP-1 molecule and so belongs to the GLP-1 receptor agonist class of drugs. When compared to human native GLP-1, the semaglutide molecule has 94% structural homology to native GLP-1 with three main modifications

1. Amino acid substitution at position 8 (alanine to alfa-amino isobutyric acid (Aib), a synthetic amino acid). This is expected to make semaglutide less susceptible to DPP-4 degradation.

2. Lysine to Arginine at position 34

3. Acylation of the peptide backbone with a spacer and C-18 fatty di-acid chain linked to the lysine at position 26. The fatty di-acid chain and the spacer are expected to mediate strong non-covalent binding to albumin, thereby reducing renal clearance and extending half-life of the product.

Structure of semaglutide:



Semaglutide formulation is a clear and colorless (b) (4) solution for injection available in a pre-filled disposable pen injector.The route of administration for semaglutide is once-weekly (OW) subcutaneous injection. It is intended to improve glycemic control in patients with T2D as an adjunct to diet and excercise.

Following subcutaneous (SC) administration, semaglutide has a relatively long terminal half-life ($t_{1/2}$) which allows for once weekly dosing. The Applicant claimed that the prolonged action profile of semaglutide is due to the following mechanisms: delayed absorption from the subcutaneous tissue, increased binding to albumin (decrease in renal clearance and protection from metabolic degradation), and an increased resistance to enzymatic degradation by dipeptidyl peptidase 4 (DPP-4) enzymes. Native GLP-1 and GLP-1 receptor agonists lower energy intake via inducing feeling of satiety and fullness and lowering feelings of hunger.

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Regulatory history:

Novo Nordisk submitted an original NDA 215256 for semaglutide once weekly (OW) subcutaneous (SC) injection indicated for chronic weight management in adults who are obese or overweight with

a weigt-related comorbidity. Semaglutide (NDA 209637-Ozempic) 0.5 mg and 1 mg, once weekly SC injection is approved worldwide for treatment of type 2 diabetes (T2D). It is also approved in the US for reducing cardiovascular risk in patients with T2D. Oral Semaglutide (NDA 213051-Rybelsus) 7 mg and 14 mg is approved in the US, Canada and EU for the treatment of T2D. Another GLP-1 analogue, Liraglutide (NDA 206321- Saxenda) 3 mg daily subcutaneous administration is approved worldwide for weight management in adults who are obese (BMI >30) or overweight (BMI>27) with a weight-related comorbidity. There is established clinical experience with GLP-1 receptor agonist class of products and also for oral and subcutaneous semaglutide for diabetes.

Past immunogenicity experience with the product class:

There are several GLP-1 receptor agonists that are commercially available. In the past, products that had low homology to human GLP-1 had a high incidence of anti-drug antibodies (ADA) that was associated with loss of efficacy particularly, in subjects with high ADA titers, whereas those with high homology, such as semiglutide, have shown low incidence of ADA that did not impact on safety and efficacy.

Products with high homology include: Liraglutide (Victoza and Saxenda), which has 97% homology to native GLP-1, have one amino acid substitution and are acylated in position 26. Dulaglutide (Trulicity) consists of dipeptidyl peptidase-IV-protected GLP-1 analogue that is covalently linked to a human IgG4-Fc heavy chain by a small peptide linker. Albiglutide (Eperzan /Tanzeum) is a GLP-1 dimer fused to human albumin. These GLP-1 RA that are human GLP-1 analogues reported low incidence of ADAs. In contrast, Exenatide (Byetta and Bydureon) and Lixisenatide which are GLP-1RA derived from peptide exendin-4 found in Gila monsters show higher immunogenicity. Lixisenatide is a GLP1-RA derived from the first 39 amino acids of exendin-4, without proline at position 38 and with six additional lysine residues. Exenatide and lixisenatide has been associated with high rates of treatment emergent ADA and also loss of efficacy in patients with high ADA titer.

The table below summarizes the past immunogenicity experience of various GLP-1RA.

Table 2-1 Marketed GLP-1 receptor agonists – observed immunogenicity and impact on efficacy and safety

GLP-1 receptor agonist	Ozempic®	Rybelsus®	Victoza®	Saxenda®	Trulicity®	Byetta®	Bydureon®	Adlyxin® Lyxumia®
Active drug	Semaglutide	Semaglutide	Liraglutide	Liraglutide	Dulaglutide	Exenatide	Exenatide	Lixisenatide
Homology to human GLP-1	94%	94%	97%	97%	90%	53%	53%	< 53%
Level of ADA in Phase 3	1–2% (low titres)	0.5% (low titres)	8.6% (low titres)	2.8% (low titres)	1.6% (low titres)	38% (low titres) 6% (high titres)	45% (low titres) 12% (high titres)	70%
Level of cross-reactivity to GLP-1	0.6%	0.2%	4.8–6.9%	-	0.9%	None	None	None
Level of *in vitro* neutralising ADA	0%	0%	1.0–2.3%	1.2%	0.9%	-	-	-
Impact on efficacy	None	None	None	None	None	Half of those with highest titre had no glycaemic response	6% had an attenuated glycaemic response	2.4% had an attenuated or no glycaemic response
Impact on safety	None	None	None	Mild injection site reactions	-	Injection site reactions	Greater incidence of injection site reactions with higher titre	Mild injection site reactions and allergic reactions

ADA: anti-drug antibodies; GLP-1: glucagon-like peptide 1; %: Percentage of the treated patients with antibody measurements; - : information not available. Based on.[5, 6, 8-22]

Reviewers comments:
The Sponsor reports 0% neutralizing antibodies for Rybelsus and Ozempic. However, the neutralizing assay used by the Sponsor is not sensitive enough to assess the neutralizing ability of the antibodies present in the clinical samples. The label reports that "The neutralizing ability of the antibodies is uncertain at this time"

Semaglutide has 94% homology to native human GLP-1.According to the past experience of ADA response in its product class and based on previous clinical experience with subcutaneous semaglutide and oral semaglutide, semaglutide is not expected to be highly immunogenic.

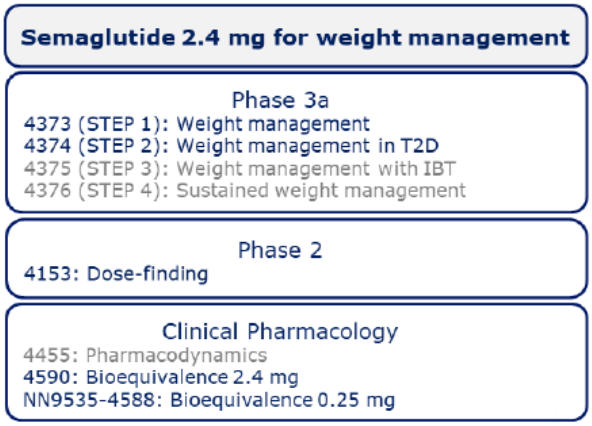
Immunogenicity risk [redacted]:
The semaglutide for chronic weight management program used two formulations, one was used with the PDS290 pen-injector and one formulation used with the single dose pen-injector. The semaglutide formulation used in phase 3a trials contained semaglutide [redacted]. This formulation was also used in SC semaglutide for T2D and the risk is captured as part of the clinical experience for Ozempic. The other formulation is the one used for the to-be-marketed semaglutide and was used in the single-dose pen-injector in the bioequivalence trials 4590 and 4588 contained [redacted].
Assessor's comments:
[redacted] seen in the first formulation is captured both by the current clinical trials for obesity and also in clinical trials for diabetes (Ozempic).
To-be-marketed formulation was used in the single-dose pen-injector in the bioequivalence trials and the immunogenicity risk of the [redacted] is captured in those trials. There was no anti-semaglutide antibodies reported in these trials.

Overview of clinical trials:

Development of ADA in the SC 2.4 mg once weekly development programme for weight management was assessed in the following 5 clinical trials:

1) Two phase 3a clinical trials (4373 &4374)
2) One phase 2 dose finding trials (4153-dose finding)
3) Two bioequivalence trials (trials - 4590, 4588)

Figure 1-1 Overview of completed clinical trials in the development programme for semaglutide 2.4 mg for weight management



Blue text indicates trials with antibody assessments.
IBT: Intensive Behavioural Therapy; T2D: type 2 diabetes.

In the phase 3a trials, STEP 1 included subjects without T2D while STEP 2 included subjects with T2D and compared with placebo in both trials. In addition to semaglutide 2.4 mg, STEP 2 included a semaglutide 1 mg treatment arm, to bridge to the semaglutide SC for T2D (Ozempic). Both STEP

1 and STEP 2 trials had durations of 68 weeks with an additional 7 weeks of off-drug follow-up. For semaglutide 2.4 mg, the 68 weeks of treatment included 16 weeks of dose escalation and 52 weeks on maintenance dose. 1 mg treatment arm in STEP 2 included 8 weeks of dose escalation and 60 weeks on maintenance dose.

In the phase 2 trial (4153), the effect and safety including antibody assessments were evaluated for five dose levels of SC semaglutide, 0.05, 0.1, 0.2, 0.3 or 0.4 mg once daily and compared to placebo and liraglutide 3 mg after 52 weeks of treatment.

In the clinical pharmacology trials (4590 and 4588), bioequivalence was evaluated between the intended to-be-marketed product and the phase 3 drug product. In these trials, at a minimum, antibody assessments were evaluated at baseline and follow-up.

The sampling time points for all the clinical trials where a sample was drawn for the analysis of ADA are given below.

Table 3-1 Antibody sample collection time points

Antibody sample collection time point	STEP 1 (Phase 3a)	STEP 2 (Phase 3a)	4153 (Phase 2)	4590 (Clin. Pharm.)	NN9535-4588[a] (Clin. Pharm.)
Week 0 (baseline)	X	X	X	X	X
Week 2	X				
Week 4	X	X	X		
Week 8	X	X	X		
Week 11					X (FU[d])
Week 12	X	X			
Week 16			X	X	
Week 21				X	
Week 27				X (FU[c])	
Week 28	X	X	X		
Week 40			X		
Week 52	X	X	X		
Week 59			X (FU[b])		
Week 68	X	X			
Week 75	X (FU[b])	X (FU[b])			

Clin. Pharm.: clinical pharmacology trial; FU: Follow-up.

[a]Trial NN9535-4588 evaluated semaglutide 1.0 mg dose.

[b]Follow-up: 7 weeks post end of treatment + a visit window of 0 to +5 days.

[c]Follow-up: 7 weeks post end of treatment + a visit window of 0 to +4 days

[d]Follow-up: 5 weeks post end of treatment + a visit window of +1 day.

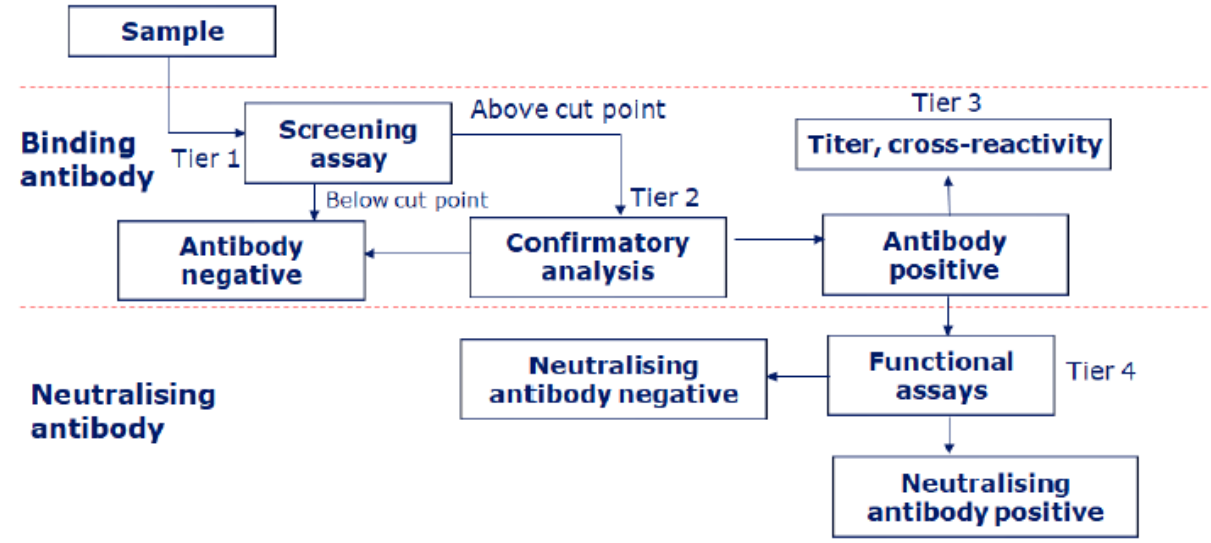
For the trials with semaglutide 2.4 mg, the follow-up antibody sample was taken after a drug washout period of 7 weeks (with a visit window of 0 to +5 days) corresponding to approximately 7 elimination half-lives to prevent interference in the antibody assays from residual semaglutide. In trial 4588 with semaglutide 1 mg, the follow-up sample was collected 5 weeks after end of treatment, with a visit of +1 day.

Assessors comment:
The sample collection time points for the assessment of antibodies is acceptable.

ADA screening strategy:

Tiered antibody assay approach was used to monitor the development of ADA. The overview of the strategy is given below.

Figure 3-1 Tiered antibody assay approach



Antibody analysis was performed with a tiered approach. Tier 1: screening analysis, Tier 2: confirmatory analysis, Tier 3: cross-reactivity to endogenous GLP-1, Tier 4: *in vitro* neutralising antibody analysis.

Assays to monitor Anti-drug antibodies

Screening Radio immuno assay (RIA):

In the screening assay, a known amount of radiolabelled semaglutide is added to the sample and the sample is precipitated with Polyethylene glycol (PEG 6000). Antibodies present in the sample bound to radiolabelled semaglutide. Radioactivity in the precipitate was meaured using a gamma counter and served as a measure of the level of ADA present in the sample. Values were reported as percentage of radioactivity in the precipitate compared to total radioactivity added to the sample (%B/T). Sponsor reports that there is a linear relationship betweent the amount of antibody present

in the sample and the %B/T measured. Linear relationship is shown in figure below: Dilution of anti-semaglutide control antibody GLIP-C-1F27 in normal human serum.

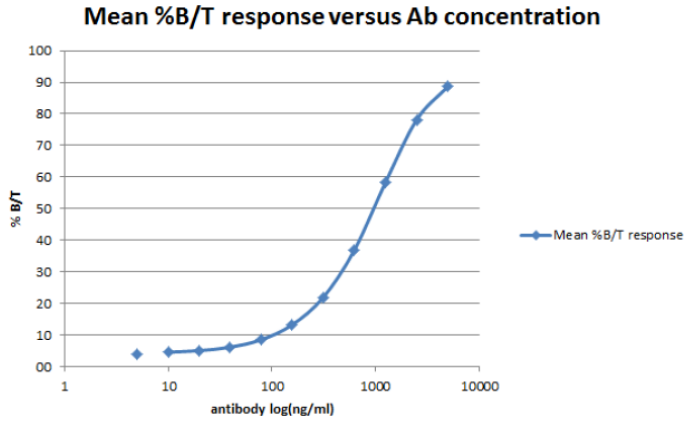


Figure 3–2 Two-fold dilution of an anti-semaglutide antibody (GLIP-C-1 F27) in the anti-semaglutide antibody RIA

Details of the antibody (isotype) were not provided, however any isotype would be suitable for a RIA assay.

Reviewers comments:
These assays are semi-quantitative, the %B/T values can be used to monitor the level of ADA

Confirmatory assay:
Samples that were positive in the screening assay were subjected to confirmatory assay. In this assay the samples were re-analyzed with or without surplus unlabelled semaglutide (5 µg/mL). Samples that had reduced radioactivity in the presence of unlabelled semaglutide were confirmed as positive for ADA.

Cross-reactivity assay:
Confirmed antibody positive samples were then tested for cross-reactivity to endogenous GLP-1. This was done by doing the RIA analysis in the presence (5 µg/mL) or absence of unlabelled GLP-1. Samples that showed reduced radioactivity in the presence of unlabelled GLP-1 were confirmed to cross react with endogenous GLP-1

Overview of the binding antibody assays used in the different clinical trials are given below. These assays were previously used for the oral and subcutaneous semaglutide program for T2DM and previously reviewed.

Table 3-2 Antibody binding assays used during clinical development

Analysis	Method (Validation study number)	Clinical Phase	Trials	Pre-treatment of samples	Validation
Anti-semaglutide antibody assay (Section 3.2.1.3)	RIA, (Study 216142 [M 5.3.1.4])	Clin.Pharm.	4590 NN9535-4588,	Samples pre-treated with acid and PEG	(b) (4)
Anti-semaglutide antibody assay (Section 3.2.1.2)	RIA, (Study 216142 [M 5.3.1.4])	Phase 2	4153	Samples pre-treated with acid and PEG	
Anti-semaglutide antibody assay (Section 3.2.1.2)	RIA, (Study 216142 [M 5.3.1.4])	Phase 3a	STEP 1 STEP 2	Samples pre-treated with acid and PEG	
Anti-semaglutide antibody assay (Section 3.2.1.4)	RIA, (Study 214096 [M 5.3.1.4])	Phase 3a Unscheduled samples only	STEP 1 STEP 4	Samples pre-treated with acid and PEG	Validated by Novo Nordisk

Clin.Pharm.: clinical pharmacology trial; PEG: polyethylene glycol; RIA: radioimmunoassay

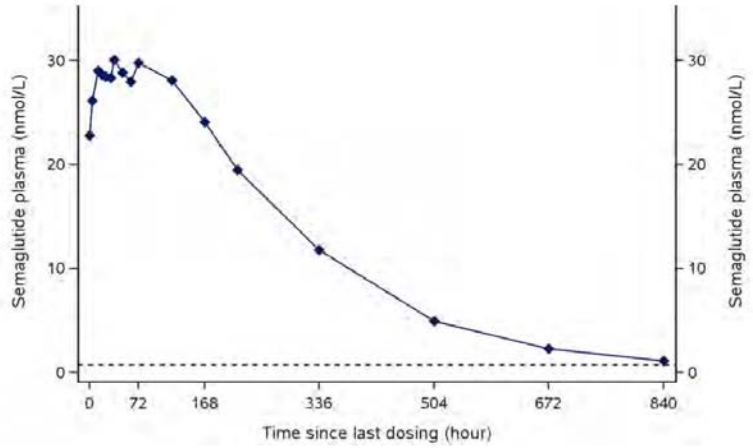
Positive control antibody:
Anti-semaglutide polyclonal antibodies raised in rabbit and three mAbs, raised against liraglutide (GLIP-C-1 F27), semaglutide (GLIP162-3F15) and GLP-1 (GLPb1 7F1) were tested. Polyclonal antibodies showed poor binding both in direct ELISA and in the RIA method. Of the three mAbs, GLIP-C1-F27 mAb had the best binding response and high %B/T values.

Reviewers comments:
Liraglutide has high homology (97%) with native GLP-1 and semaglutide. The use of anti-liraglutide antibody as the positive control is acceptable.

Suitability controls: Six levels of quality control (QC) samples, negative (0 ng/mL mAb), low T2D (80 ng/mL mAb), low OB (60 ng/mL mAb), low (100 ng/mL mAb), medium (900 ng/mL mAb) and high (2500 ng/mL mAb) positive controls were included in the validation study. Four levels of QC samples negative, low (80), low and high were used in subsequent analyses of samples from clinical trials. All QC samples were prepared in normal human serum with or without spiking of anti-semaglutide antibody. Positive QC samples were spiked with GLIP-C-1F27.

Summary metrics of method validation from anti-semaglutide antibody assay used for phase II and phase 3a studies is given below.

Semaglutide concentration versus time profile following administration of 1.0 mg semaglutide at steady state in patients with T2D patients is given below (from trial 3635).



In patients with T2D, the mean steady state concentrations following SC administration of 0.5 mg and 1.0 mg semaglutide were approximately 16 nmol/L and 30 nmol/L respectively.

Levels of on-board levels of semaglutide after treatment.

Figure 5-1 Observed semaglutide concentrations versus time since first dose

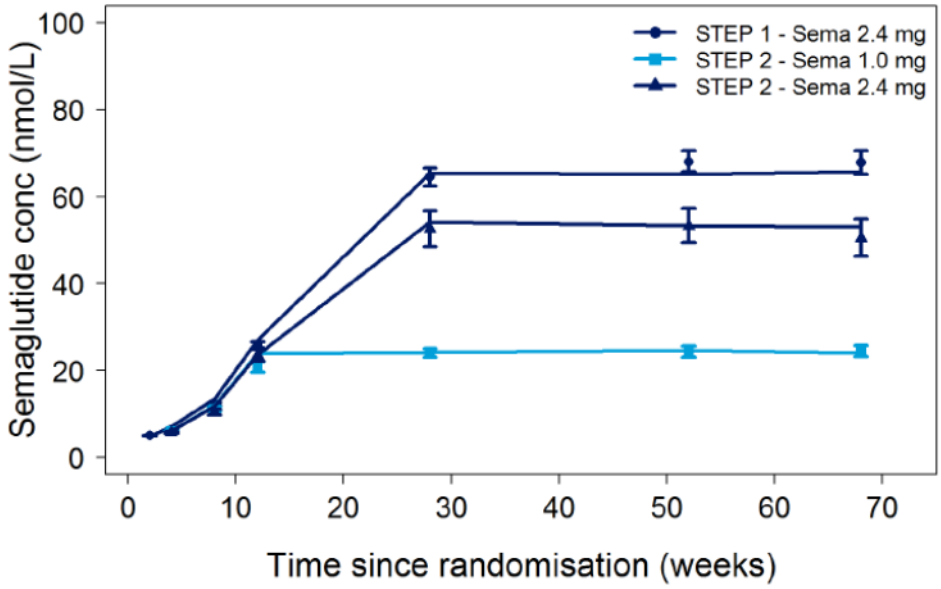
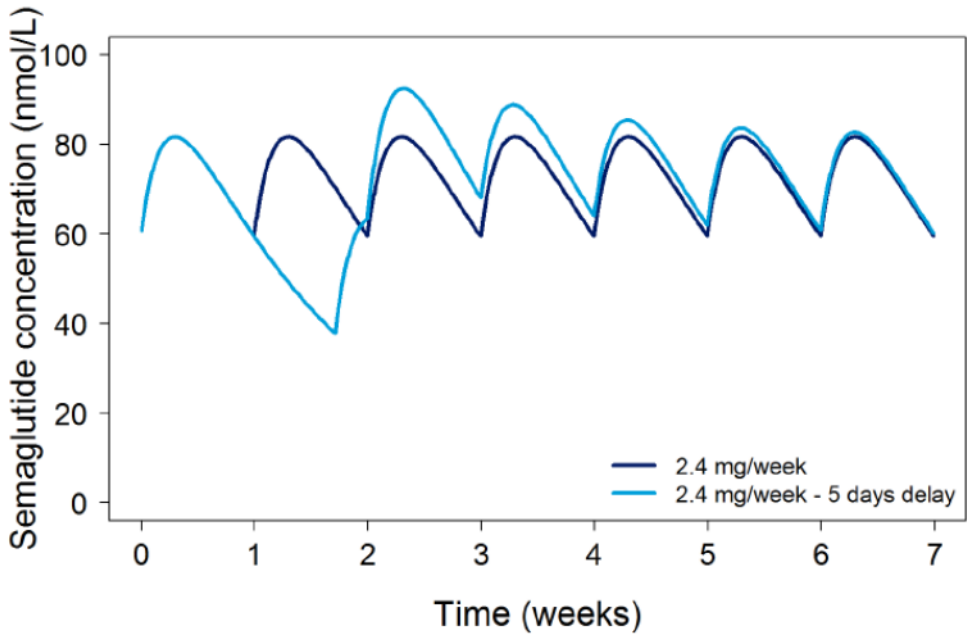


Figure 5-7 Simulated semaglutide concentration profiles following delayed doses

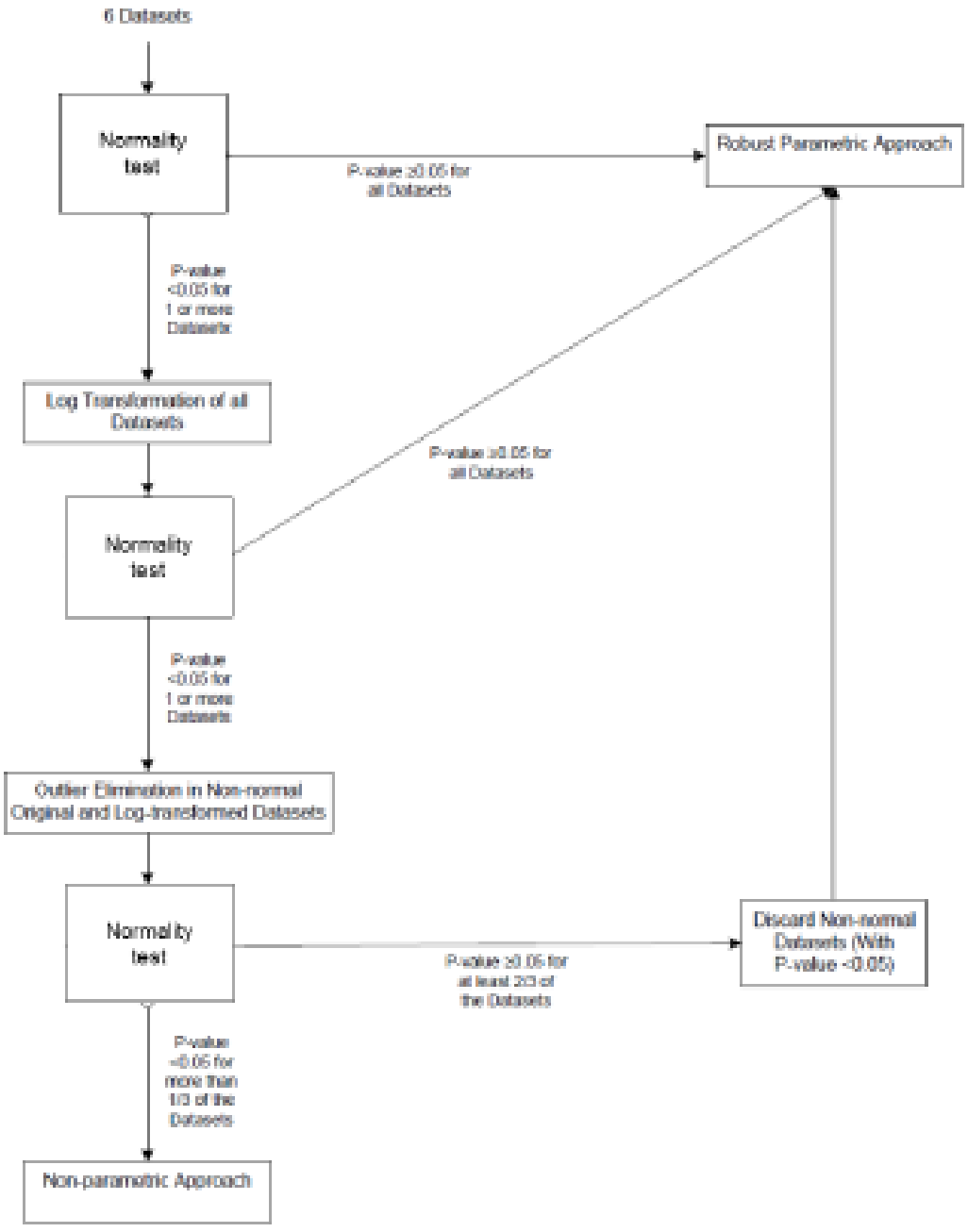


Validation of RIA assay used to analyze phase 3a samples: Validation study no. 216142

This is the assay used for assessing samples from phase 3a clinical trials. Assay in validation study no 207194 was re-validated after modifying the assay to limit the acid incubation time for an assay run to be maximum 7 minutes and with type 2 diabetes and obese clinical trial populations. This also validated optional use of Tecan Genesis liquid handling system. In this method, after initial acidic pre-treatment (between 5-7 minutes) and PEG precipitation to remove free semaglutide from samples, the precipitate containing the antibodies is dissolved in assay buffer in excess unlabelled semaglutide or in excess unlabelled GLP-1 and incubated with I125 labelled semaglutide (tracer) overnight at 5 C. The following day, antibodies are precipitated with any bound antigen and the precipitate is measured in a gamma counter for 5 minutes. The radioactive signal from the tracer is expressed in percent of the total amount of added radioactiveity (%B/T)

50 human sera from type 2 diabetic patients (T2D) and 50 sera from obese patients were analysed for the validation. For each medical condition, the analysis of the 50 individuals was performed 6 times in series A, B and C for a total of 12 analytical runs. For each medical condition, the 6 analytical runs were at least performed by 2 different analysts and during a period of 2 weeks.

SCP calculation scheme [7]



7.2.4 Results of anti-semaglutide antibody RIA validation study 216142

Parameter	Description	Result
MRD	Volume of sample in assay	10 µl (6.7%) in a total of 150 µl, i.e. MRD = 15.
Screening cut point (SCP)	50 T2D sera analysed 6x Calculated using robust-parametric approach with 5% false positive rate	8.8982 %B/T
Normalisation factor (NF)	SCP – Mean QC neg	1.4762
Normalised screening cut point	Mean QC neg + NF	Mean QC neg + 1.4762
Confirmatory cut point	%Inhibition of results with (Series B) or without unlabelled semaglutide (Series A) for T2D samples. Calculated to give a 1% false positive rate.	20.18%
Cross reactivity cut point	%Inhibition of results with (Series C) or without native GLP-1 (Series A) for T2D samples. Calculated to give a 1% false positive rate.	16.20%
Normalised titer cut point	Mean QC neg + 2xNF	Confirmed positive samples with results ≥ normalised titer cut point subjected to titration. Confirmed positive samples with results < normalised titer cut point assigned MRD adjusted titer = 15.
Control mAb for assay parameters and QC preparation	anti-semaglutide mAb	mAb GLIP-C1-F27
Sensitivity screening assay	anti-semaglutide mAb	67.21 ng/ml
Sensitivity confirmatory assay	anti-semaglutide mAb	39.06-78.13 ng/ml confirmed positive
Sensitivity cross reactivity assay	anti-semaglutide mAb	39.06-78.13 ng/ml confirmed cross reactive
Recovery	10 T2D sera spiked with anti-semaglutide mAb:	All had %Recovery compared to serum pool within +/- 20%, except one individual spiked with 150 ng/ml Ab[1].
	100 ng/ml mAb	9 of 10 individuals (95%) ≥ SCP[1]
	150 ng/ml mAb	9 of 10 individuals (95%) ≥ SCP[1]
	2500 ng/ml mAb	10 of 10 individuals (95%) ≥ SCP
Drug Interference	Sensitivity (1.25 nM semaglutide)	115 ng/ml
	Sensitivity (40 nM semaglutide)	380 ng/ml
	Sensitivity (100 nM semaglutide)	552 ng/ml

Parameter	Description	Result
Drug tolerance	100 ng/ml anti-semaglutide mAb	0.63 nM semaglutide
	500 ng/ml anti-semaglutide mAb	85 nM semaglutide.
Interference	Interference from haemolysis examined on QC samples	No interference at any level. All results < 20% difference to non-haemolysed sample.
	Interference from lipidemia examined on QC samples	No interference at any level. All results < 20% difference to non-lipaemic sample
Robustness	Effect of incubation time, analyst, drift and manual handling versus robot liquid handling system investigated	No effect, i.e. the assay is robust to variations in these parameters
Precision screening assay	QC neg (0 ng/ml mAb)	2.0-7.9 %CV / 5.6 %CV
(intra assay / inter assay precision)	QC lowT2D (80 ng/ml mAb)	1.3-6.5 %CV / 5.6 %CV
	QC low (100 ng/ml mAb)	0.5-6.0 %CV / 4.9%CV
	QC med (900 ng/ml mAb)	0.5-3.4 %CV / 5.0 %CV
	QC high (2500 ng/ml mAb)	0.7-4.7 %CV / 3.3 %CV
Precision confirmatory assay	QC neg (0 ng/ml mAb)	12.5-42.3 %CV / 16.8 %CV
(intra assay / inter assay precision)	QC lowT2D (80 ng/ml mAb)	3.5-25.8 %CV / 18.8 %CV
	QC low (100 ng/ml mAb)	4.0-16.3 %CV / 7.6 %CV
	QC med (900 ng/ml mAb)	0.5-11.1 %CV / 4.0 %CV
	QC high (2500 ng/ml mAb)	0.3-1.6 %CV / 1.0 %CV
Precision cross reactivity assay	QC neg (0 ng/ml mAb)	16.2-43.5 %CV / 25.9 %CV
(intra assay / inter assay precision)	QC lowT2D (80 ng/ml mAb)	4.1–15.0 %CV / 13.1 %CV
	QC low (100 ng/ml mAb)	4.7-17.6 %CV / 7.7 %CV
	QC med (900 ng/ml mAb)	0.7-2.2 %CV / 2.3 %CV
	QC high (2500 ng/ml mAb)	0.1-1.9 %CV / 1.0 %CV

1: The certificate for the subject with recovery < 80% at 150 ng/ml Ab level and testing < SCP at 100 and 150 ng/ml mAb showed that this subject received treatment with Victoza (liraglutide) 1.8 mg, explaining the reduced recovery and sensitivity for this subject.

Reviewers comments:
The parameteres validated are in-line in with previous validation study. Cut point, sensitivity and drug tolerence reported are acceptable.
The parameters given above are for T2D serum samples and the samples from obese samples were also evaluated and had comparable sensitivity (50.44 ng/mL obese vs 67.21 ng/ml T2D). The other parameters were also comparable.
Revalidation of screening and confirmatory anti-semaglutide antibody RIA assay is acceptable.

Validation of RIA assay used to analyze Phase 3a unscheduled samples: Validation study no. 214096

These samples were unscheduled and are not included in the immunogenicity samples. These samples were collected due to suspicion of hypersensitive reaction. These samples were assessed for the presence of anti-semagltudite antibodies using assay validation by study 214096. Serum samples from 25 T2D patients and 25 obese individuals were used for the validation study. The 50 serum samples were analysed without semaglutide in 6 assay set-ups (three assay set-ups by two analysts). Outliers were inspected using the outlier box-plot approach. Since outliers were evenly distributed in both extremities, they were not excluded from the data set. Analysis of normality using Shapiro-Wilk W test provided evidence of normal distribution in 5 out of 6 assay set-ups. The assay set-ups were statistically different and the assay set-up variance were not statistically different and so a floating cut point was used. The screening cut point was set to detect 5% false positive samples (95% confidence level).

7.2.5 Results of anti-semaglutide antibody RIA validation study 214096

Parameter	Description	Result
Minimum Required Dilution (MRD)	Volume of sample in assay	10 µl (6.7%) in a total of 150 µl, i.e. MRD = 15.
Assay screening cut point	25 T2D sera and 25 obese sera	Mean QC neg (%B/T) + NF
	Normalisation factor (NF)	1.2
Specificity cut point	Signal inhibition: 100 x (A-B)/A (Drug)	>40%
	Signal inhibition: 100 x (A-C)/A (CrossR)	>24%
Sensitivity	GLIP-C1 F27 Control mAb	32 ng/ml
Recovery	60 ng/ml anti-semaglutide mAb	19 of 20 individuals (95%) ≥ screening cut point
Drug Interference	Sensitivity (40nM semaglutide)	500 ng/ml
	Sensitivity (4nM semaglutide)	250 ng/ml
	Sensitivity (0.4 nM semaglutide)	62.5 ng/ml
Drug tolerance	250 ng/ml anti-semaglutide mAb	25 nM semaglutide
	500 ng/ml anti-semaglutide mAb	100 nM semaglutide
Haemolysis	QC neg, QC low and high in grade 1-4 haemolysis	all samples between 92 - 121% of no haemolysis
Assay precision (inter-assay)	QC neg (%B/T)	16.3 %CV
	QC low (%B/T)	14.8 %CV
	QC high (%B/T)	6.4 %CV
Assay precision (intra-assay)	QC neg (%B/T)	10.6 %CV
	QC low (%B/T)	8.6 %CV
	QC high (%B/T)	5.2 %CV
Drifting	Drifting at 3 levels; QCneg, QClow and QChigh, Student's t test	No drifting at any of the three levels, neg, low and high (p>0.05)
QC samples	QC neg	Normal healthy human serum without reference mAb
	QC low	Normal healthy human serum with 60ng/ml GLIP-C-1F27
	QC high	Normal healthy human serum with 2500ng/ml GLIP-C-1 F27

Reviewers comments:
The screening cut point, sensitivity and drug tolerence are comparable to the previous validation studies for anti-semaglutide RIA assays. Validation of study 214096 is acceptable.

IgE assay for ADA to Semaglutide:

An ImmunoCAP method for the detection of drug specificIgE antibodies was previously developed, validated and used to assess clinical trial samples suspected to have hypersensitivity reaction during treatment of subcutaneous semaglutide for NDA 209637. In this assay, control antibody was

produced by coupling semaglutide specific IgG to unsepcific human IgE by BS3 coupling. This assay did not have desired sensitivity. The control IgG GLIP C-1F27 antibody was isotype switched to have IgE backbonbe. This anti-semaglutie IgE mAb was used in a supplementary study (#307690) to reassess the validation parameters based on the control antibody. The sensitivity of the new control anti-semaglutide IgE mAb was investigated using the validated immno CAP assay.

7.2.7 Results of anti-semaglutide IgE immunoCAP supplementary study 307690

Parameter	Description	Result
Assay cut point	Lower Level of Quantification (LLOQ)	0.1 kUA/L
Control antibody used	mAb GLIP-C1 F27 with IgE backbone	Anti-semaglutide IgE
Sensitivity	Results from 3 set of experiments	0.5 - 1.0 ng/ml anti-semaglutide IgE
Interference from semaglutide	Anti-semaglutide IgE measured in presence of 0 – 100 nM semaglutide:	
	0.5 ng/ml anti-semaglutide IgE	Tolerates < 1 nM semaglutide
	1.0 ng/ml anti-semaglutide IgE	Tolerates 1 nM semaglutide
	5.0 ng/ml anti-semaglutide IgE	Tolerates 100 nM semaglutide
	50 ng/ml anti-semaglutide IgE	Tolerates 100 nM semaglutide
Recovery	Three concentrations of anti-semaglutide IgE spiked in 8 individual type 2 diabetes sera:	All subjects > LLOQ on all 3 ab levels. Mean results and %CV listed for each level:
	1 ng/ml anti-semaglutide IgE	0.29 kUA/l, 2.87 %CV
	5 ng/ml anti-semaglutide IgE	1.26 kUA/l, 16.1 %CV
	50 ng/ml anti-semaglutide IgE	13.4 kUA/L, 8.1 %CV

Reviewers comments:
The sensitivity was approximately 0.5-1 ng/mL. The previous assay had a sensitivity of 185ng/mL. The sensitivity and drug tolerence of the anti-semaglutide IgE assay are acceptable.

Neutralizing antibody assays:

In-vitro neutralizing effect was measured using a BHK cell-based neutralizing antibody assay. In this assay, the cells are transfected with the human GLP-1 receptor. Cellular stimulation is measured as cAMP production upon GLP-1 receptor activation with semaglutide. The cAMP formed binds to the cAMP response element (CRE) in the luciferase promotor leading to luciferase production and a read out as Relative Luminescence Units (RLU). The assay is based on anti-semaglutide antibodies binding to semaglutide and blocking its interaction with the receptor. This reduced the production of cAMP and thereby production of luciferase. Thus reduction in luciferase directly corelates with the level of neutralizing anti-semaglutide antibodies. Controls included in the neutralising antibody assays include Non Specific Binding (NSB) which represents the background in the assay, MAX which represent the maximal response in the presence of the drug without antibody and QC samples at negative, low and high positive. The neutralizing effect was calucated

as a percent neutralisation based on the RLU response in the test sample (X) in relation to the RLU response in the NSB and MAX samples by using the following formula:

%N= (1-(X-NSB/MAX-NSB))*100

To test the level of cross-reactive neutralizing antibodies to native GLP-1, native GLP-1 is used instead of semaglutide in the assay.

Control antibody for NAB assays:
Several monoclonal and polyclonal anti-semaglutide antibodies have been assessed to find a suitable control antibody for the NAB assay. The mAb raised against liraglutide (GLIP-C-1F27) was the most suitable in-vitro neutralizing antibody in the NAB assay. The NAB assay using this antibody did not tolerate residual levels of on-board drug in the clinical samples and so the sensitivity was poor in the presence of semaglutide. Yeast display platform was tested to derive mAbs from the human IgG yeast display library. Two mAbs NNC1212-0000-7141 and NNC1212-0000-7148 performed similar to GLIP-C1 F27 in the binding antibody assay and was superior to GLIP_C1 F27 mAb in the semaglutide and GLP-1 NAB assays. NAB NNC1212-0000-7141 was used in supplemental validation studies demonstrating the sensitivity of the NAB assay in the presence of semaglutide.

The cutpoint for the in-vitro neutralizing antibody assay was calculated using 90 individual human serum samples from Normal, T2D and obese individuals (30 each), analysed six times with standard concentration of semaglutide but in the absence of antibodies. The cut point was set to detect 1% false positive samples. Sponsor stated that the assay had low tolerance to on board drug. To reduce the on-board drug interference they pre-treated the serum samples with 18% PEG6000 . Despite this, the sensitivity of the assay remained poor (34ug/ml). Due to the acylation of semaglutide, a higher concentration of albumin in the assay led to a higher concentration of semaglutide needed for stimulation of cells and hence a poorer sensitivity of the assay. It was found that the best sensitivity and drug tolerence was obtained at a sample volume of 30% and a FBS concentration of 20% combined with a drug concentration of 400 pg/mL in the assay.

QC samples were included in four levels; one negative control, and three positive controls, low positive control 1 (LPC1) at 460 ng/mL, LPC 2 at 685 ng/mL and High Positive control (HPC) at 5000 ng/mL. LPC 1 failed in many of the assays and LPC2 was used as the low positive control for the assay. Evaluation of QC samples in normal human serum, OB serum and T2D serum indicated that positive control levels could be used for all three types of serum. Sensitivity of the NAB assay had a range of 420-875 ng/mL of the mAb GLIP-C-1 F27 and the assay sensitivity was 2000 ng/mL of mAb GLIP-C-1 F27 in the presence of 2 nmol/L of semaglutide. The sensitivity of the assay in OB (from obese donors) serum was further validated in the absence and presence of 2 nM semaglutide using the newly identified control antibody NNC1212-0000-7141. No other assay parameters or reagents were changed. The sensitivity of this assay was 245.4ng/mL in the absence of semaglutide. The sensitivity was 1164.7 ng/mL in the presence of 2 nM semaglutide.

Neutralization antibody (NAB) assays used in the clinical development of semaglutide 2.4 for weight management are given below.

Table 3-3 *In vitro* neutralising antibody assays used during clinical development of semaglutide 2.4 mg for weight management

Analysis	Method (validation study number)	Clinical Phase	Trials	Pre-treatment of Samples	Validation
Neutralising anti-semaglutide antibody assay (Section 3.2.2.2)	BHK cell based (Study 304600 [M 5.3.1.4] and Study 321593 [M 5.3.1.4])	Phase 3a	STEP 1 (4373) STEP 2 (4374)	Pre-treatment of samples with 10% PEG6000 to reduce matrix interference	(b) (4)
Neutralising anti-GLP-1 neutralising antibody assay (Section 3.2.2.4)	BHK cell based (Study 304601 [M 5.3.1.4] and Study 321594 [M 5.3.1.4])	Phase 3a	STEP 1 (4373) STEP 2 (4374)	Pre-treatment of samples with 10% PEG6000 to reduce matrix interference	

BHK: baby hamster kidney; PEG: poly ethylene glycol

Critical parameters of the NAB assay validation are shown in the sponsor's table below:

7.2.5 Results of *in vitro* neutralising anti-semaglutide antibody validation study 304600

Parameter	Description	Result
Minimum Required dilution (MRD)	Volume of sample used in assay	30 %
Neutralising cut point/floating cut point set at 99% confidence level	30 individual sera each from three populations; normal healthy, obese and T2D	-
Normalisation Factor (NF)	Neutralising cut point – mean QC neg[1]	NF (NHS): 14.0%N NF (Obese): 30.4%N NF (T2D): 23.6%N
Plate specific neutralising cut point Set at 99% confidence level	Floating cut point (FCP)	Mean QCneg (%N) + NF
Sensitivity	Sensitivity reference mAb GLIP-C1 F27	NHS: 420.3 ng/mL Obese: 875.5 ng/mL T2D: 665.2 ng/mL
Selectivity, 80% of subjects at each level should be positive Unspiked samples should be negative	10 obese sera spiked with 5000 ng/mL reference mAb, 840 ng/mL reference mAb and 1260ng/mL reference mAb or 0 ng/mL mAb (NC)	Obese 5000 ng/mL: 9/10 positive 840 ng/mL 10/10 positive 1260 ng/mL 10/10 positive NC: 10/10 negative
	10 T2D sera spiked with 5000 ng/mL reference mAb, 650 ng/mL reference mAb and 975 ng/mL reference mAb or 0 ng/ml mAb (NC)	T2D 5000 ng/mL 10/10 positive 650 ng/mL: 4/10 positive, failed 975 ng/mL: 8/10 positive NC: 10/10 negative
Drug interference	Sensitivity in presence of 2 nM semaglutide	1000–2000 ng/mL
Drug tolerance	LPC 1 (460 ng/mL) LPC 2 (685ng/mL) HPC (5000 ng/mL)	1 nM drug can be tolerated 2 nM drug can be tolerated 2 nM drug can be tolerated
Assay precision[2] (inter-assay variation)	QC low (LPC1) (%N) QC low (LPC2) (%N) QC high (HPC) (%N)	46.6 %CV, not accepted 12.7 %CV, accepted 4.6 %CV, accepted
Assay precision[3] (Intra-assay variation)	QC low (LPC1) (%N) QC low (LPC2) (%N) QC high (HPC) (%N)	51.9 %CV, not accepted 11.6 %CV, accepted 4.1 %CV, accepted
Haemolysis	QC low(LPC1 and LPC2) and high(HPC) in haemolysis grade 1–4	No interference from haemolysis
Lipemia	QC low(LPC1 and LPC2) and high(HPC)	All PCs showed acceptable performance, except LPC 1in two lipemic samples.

Parameter	Description	Result
Drifting	Drifting at three levels; QC neg (NC), QC low (LPC1 and LPC2) and QC high (HPC) over time	No drifting at any level over time
	Drifting of Stimulation Index over time	No drifting over time of stimulation Index
Freeze-thaw stability	Freeze-thaw stability of reference mAb	Passed up to 6 FT cycles. All PCs were positive and all NCs were negative
Bench-Top stability	O/N storage of QCs at ambient temperature	All PCs except for LPC1 were positive. NCs were negative
Robustness (incubation time)	3 hours +/- half an hour	No impact of +/- half an hour incubation
Robustness (standard drug concentration for stimulation of cells)	400 pg/ml semaglutide +/- 20%	No impact on PCs and NCs of varying concentration of drug from 320 pg/ml to 480 pg/ml
QC samples	QC neg (NC) QC low (LPC1) QC low (LPC2) QC high	NHS NHS + 460 ng/mL GLIP-C-1 F27 NHS + 685 ng/mL GLIP-C-1 F27 NHS + 5000 ng/mL GLIPC-C1 F27

1. QC neg in validation report= NC (Negative Control)
2. Inter assay variation ≤ 30% acceptable. All PC should be positive. NC should be negative
3. Intra assay variation ≤ 20% acceptable. All PC should be positive. NC should be negative

7.2.6 Results of *in vitro* neutralising anti-semaglutide antibody supplementary validation study 321593

Parameter	Description	Result
Sensitivity[1] Mean of 5 runs + (t0.05df x SD)	Sensitivity reference mAb NNC1212-0000-7141	Obese serum: 245.4 ng/mL Range over 5 assay runs: 104.0–210.4 ng/ml, median 124.7 ng/ml
Drug interference in follow up samples[1] Mean of 5 runs + (t0.05df x SD)	Sensitivity reference mAb NNC1212-0000-7141 in presence of 2 nM semaglutide	Obese serum: 1164.7 ng/mL Range over 5 assay runs: (633.9–1094.0 ng/ml, median 654.6 ng/ml)

1. Sensitivity determined by 4PL regression at the cut point. Cut point determined as QC neg + NFobese (30.4)

Assessor's comments:

Developmental studies by the sponsor in optimizing the sample volume, FBS concentration and the use of new positive control antibody has increased the sensitivity of the NAB assay.

However, the sensitivity of 1100 ng/mL in the presence of residual levels of semaglutide present in the clinical samples can only detect NABs in samples that have a % B/T value of more than 40. Antibody positive samples in the clinical trials had much lower levels of antibodies. *The sensitivity of the NAB assay is not sufficient to assess the neutralizing ability of the antibodies.*

In-vitro neutralizing anti-GLP-1 antibody assay:

Anti-semaglutide antibody positive samples cross-reacting with endogenous GLP-1 were analyzed for in vitro neutralizing effect using the same cell based assay described above but stimulated cells with recombinant human GLP-1 rather than semaglutide. The concentration of GLP-1 used for the stimulation of cells was 1.5 ng/mL (EC80) recombinant human GLP-1. Sensitivity was determined using equimolar mix of three anti-GLP-1 mAbs GLIP-C-1 F27, Mab26.1, GLPF5A4. The sensitivity was in the range of 550-590 ng /mL in the absence of residual drug. In the presence of 2 nm/L semaglutide the sensitivity was 1500 ng/mL. The sensitivity of the assay was further validated in OB (obese donor) serum in the presence or absence of 2 nm semaglutide using the newly identified mAb NNC1212-0000-7141. In the absence of semaglutide, the sensitivity of this assay was 65.6 ng/mL. In the presence of 2 nM semaglutide the calculated sensitivity was 896.6 ng/mL.

Critical parameters of the anti-GLP-1 NAB assay validation are shown in the sponsor's table below:

7.2.7 Results of *in vitro* neutralising anti-GLP-1 antibody validation study 304601

Parameter	Description	Result
Minimum Required dilution (MRD)	Volume of sample used in assay	30 %
Neutralising cut point/floating cut point set at 99% confidence level	30 individual sera each from three populations; normal healthy, obese and T2D	-
Normalisation Factor (NF)	Neutralising cut point – mean QC neg[1]	NF (NHS): 10.9%N NF (Obese): 25.1%N NF (T2D): 24.5%N
Plate specific neutralising cut point	Floating cut point (FCP)	Mean QCneg (%N) + NF
Sensitivity	Sensitivity reference mAb (equimolar mix of GLIP-C-1F27, Mab26.1, GLPF5A4	NHS: 572.4 ng/mL Obese: 550.9 ng/mL T2D: 590.4 ng/mL
Selectivity, 80% of subjects at each level should be positive Unspiked samples should be negative	10 obese sera spiked with 5000 ng/mL reference mAb, 465 ng/mL reference mAb and 695 ng/mL reference mAb or 0 ng/mL mAb (NC)	Obese 5000 ng/mL: 10/10 positive 465 ng/mL 10/10 positive 695 ng/mL 10/10 positive NC: 10/10 negative
	10 T2D sera spiked with 5000 ng/mL reference mAb, 590 ng/mL reference mAb and 880 ng/mL reference mAb or 0 ng/ml mAb (NC)	T2D 5000 ng/mL 10/10 positive 590 ng/mL: 7/10 positive, failed 880 ng/mL: 8/10 positive NC: 10/10 negative

Drug interference	Sensitivity in presence of 2 nM semaglutide	1500 ng/mL
Drug tolerance	LPC 1 (460 ng/mL) LPC 2 (685ng/mL) HPC (5000 ng/mL)	1 nM semaglutide can be tolerated 1 nM semaglutide can be tolerated 2 nM semaglutide can be tolerated
Assay precision[2] (inter-assay variation)	QC low (LPC1) (%N) QC low (LPC2) (%N) QC high (HPC) (%N)	35.7 %CV, not accepted 13.0 %CV, accepted 3.3 %CV, accepted
Assay precision[3] (Intra-assay variation)	QC low (LPC1) (%N) QC low (LPC2) (%N) QC high (HPC) (%N)	20.8 %CV, not accepted 18.4 %CV, accepted 2.4 %CV, accepted
Haemolysis	QC low (LPC1 and LPC2) and high (HPC) in haemolysis grade 1–4	No interference from haemolysis
Lipemia	QC low (LPC1 and LPC2) and high (HPC)	HPCs showed acceptable performance, LPC 1 failed. LPC 2 failed in 1lipemic sample. Selectivity in obese sera passed 100% Lipemia does not impact the PC.
Drifting	Drifting at three levels; QC neg (NC), QC low (LPC1 and LPC2) and QC high (HPC) over time	No drifting at any level over time
	Drifting of Stimulation Index over time	No drifting over time of stimulation Index
Freeze-thaw stability	Freeze-thaw stability of reference mAb	Passed up to 6 FT cycles. All PCs were positive and all NCs were negative
Bench-Top stability	O/N storage of QCs at ambient temperature	No impact on any level of PC and NC.
Robustness (incubation time)	3 hours +/- half an hour	No impact of +/- half an hour incubation
Robustness (standard drug concentration for stimulation of cells)	20 pg/ml semaglutide +/- 20%	No impact on PCs and NCs of varying concentration of drug from 16 pg/ml to 24 pg/ml
QC samples	QC neg (NC) QC low (LPC1) QC low (LPC2) QC high	NHS NHS + 460 ng/mL reference mAb NHS + 685 ng/mL reference mAb NHS + 5000 ng/mL reference mAb

1. %N = % Neutralisation

7.2.8 Results of *in vitro* neutralising anti-GLP-1 antibody supplementary validation study 321594

Parameter	Description	Result
Sensitivity[1] Mean of 5 runs + (t0.05df x SD)	Sensitivity reference mAb NNC1212-0000-7141	Obese serum: 65.6 ng/mL Range over 5 assay runs: 39.0–60.7 ng/mL, median 48.3 ng/mL
Drug interference in follow up samples[1] Mean of 5 runs + (t0.05df x SD)	Sensitivity reference mAb NNC1212-0000-7141 in presence of 2 nM semaglutide	Obese serum: 896.6 ng/mL, Range over 5 assay runs: 442.6–744.7 ng/mL, median 612.4 ng/mL

1. Sensitivity determined by 4PL regression at the cut point. Cut point determined as QC neg + NFobese (25.1)

Assessor's comments:

Developmental studies by the sponsor in optimizing the sample volume, FBS concentration and the use of new positive control antibody has increased the sensitivity of the NAB assay.

The NAB assay is inadequate. The neutralizing antibody assays appears to have low sensitivity making it inadequate to determine whether any antibodies present have neutralizing activity.

The sensitivity of anti-semaglutide NAB is 1100 ng/mL in the presence of 2 nM residual semaglutide present in the clinical samples. This level of sensitivity can only detect NABs in samples that have a % B/T value of more than 40. None of the antibody samples had such high levels of antibodies. Moreover, many of the samples collected before the final washout period will have levels of semaglutide much higher that 2 nM. The sensitivity of the NAB assay is not sufficient to assess the neutralizing ability of the antibodies.

Summary of clinical immunogenicity data from phase 3 trials:

The summary consists of data from the following 5 clinical trials

1) Two phase 3a clinical trials; STEP 1 (4373) and STEP 2 (4374)
2) One phase 2 dose finding trial (4153)
3) Two Bioequivalence trials; 4590 (2.4 mg) and 4588 (0.25 mg)

The total number of subjects that were antibody positive in STEP1 was 39 (39/1306 =3%). The total number of subjects that were antibody positive for the semaglutide 2.4 mg group in STEP 2 was 12 (12/403 = 3%). One subject in STEP1 had pre-existing anti-semaglutide antibodies at baseline (was negative for all other time points tested). Therefore, treatment induced antibodies were detected in 50 subjects corresponding to 2.9% of subjects receiving 2.4 mg SC semaglutide. Of the 51 subjects that showed anti-semaglutide antibodies, 21 subjects showed anti-semaglutide antibodies that cross-reacted with endogenous GLP-1. One of these 21 subjects had anti-semaglutide antibodies at baseline and cross-reacted with endogenous GLP-1 and the other 20

subjects had treatment induced anti-semaglutide antibodies that cross-reacted with endogenous GLP-1. Subjects were categorized as transient (subjects negative at baseline and follow-up but positive in-between) or persistant (tested negative for anti-semaglutide antibodies at baseline but tested positive at follow-up or tested negative for anti-semaglutide antibodies at baseline and follow-up but tested positive at two or more timepoints in between where the first and last positive sample was separated by 16 weeks). Of the 51 subjects that were positive for anti-semaglutide antibodes, 29 subjects were characterized as persistant and 22 subjects were characterized as transient.

In the positive samples the level of antibody response was low (mean less than 5% B/T) for all weeks. The minimum required diluted (MRD) was 15 and MRD adjusted titer in antibody positive samples ranged from 15-240 and the median MRD adjusted titer was 30.

Assessor's comment:
The rate of antibody positive subjects is low (3%). Reported %B/T values for antibody positive samples correspond to low levels of antibodies in the positive samples. This is corroborated by the low titers of anti-semaglutide antibodies in anti-semaglutide antibody positive samples.

Due to COVID-19 pandemic, in-person follow-up visit in some of the patients were converted to telephone visit and samples were not collected for antibody assessment. In these subjects where the follow-up sample was not available, transient or persistant classification of subjects was based on positivity of the last assessed sample. This is acceptable.

In Step 2, anti-semaglutide antibodies were assessed for both semaglutide 1 mg and semaglutide 2.4 mg treatment groups. The proportion of subjects positive for anti-semaglutide antibodies post baseline was 1% (4/398 subjects) for semaglutide 1 mg and 3% (12/402 subjects) for semaglutide 2.4 mg. For all 16 subjects positive for anti-semaglutide antibodies, the antibody levels were <19% B/T and the median MRD adjusted titers was 15 (no dilution) and the range was from 15-120 (0-8 fold dilution). The same specification as in STEP 1 was used for classification of transient or persistance antibody response in STEP 2 trial. Of the 12 subjects positive for antibodies in the semaglutide 2.4 mg arm, 5 subjects had persistant and 7 subjects had transient anti-semaglutide antibodies. Of the 12 subjects positive for anti-semaglutide antibodies, 7 subjects had antibodies cross-reactive to endogenous GLP-1. All 4 subjects in the semaglutide 1 mg arm had antibodies cross-reactive to endogenous GLP-1.

Assesor's comments:
The rate of antibody response in the semaglutde 1 mg arm is comparable to the previous sub-cutaneous semaglutide clinical trials for Ozempic (T2DM).
The rate of antibody response in the semaglutide 2.4 mg arm is comparable to STEP 1 trial. The level of antibodies in the positive subjects are low as demonstrated by the % B/T value and MRD adjusted antibody titers.

In the bioequivalence trial (4590), testing bioequivalence between semaglutide 2.4 mg formulations used in the PDS290 pen-injector and the single-dose pen-injector, no subjects developed anti-semaglutide antibodies.

In the bioequivalence trial (4588), testing bioequivalence of semaglutide 0.25 mg and 1 mg between formulations used with the PDF290 pen injector and the single-dose pen-injector, no subjects developed anti-semaglutide antibodies.

In the dose finding phase 2 trial (4153), no subjects developed anti-semaglutide antibodies.

Assessor's comments: In all the three trials, two bioequivalence trials and one dose finding trial, none of the subjects tested showed anti-semaglutide antibodies. In all the three trials the false positive rate was more than 6% suggesting that the reported results are not false negatives.

Table 1

Overall summary of clinical immunogenicity data

Trial	Design	Dose/route	Number of subjects	Patient population	Duration	Antibody positive (%)	Cross-reacting	Neutralizing	Titer Binding
4373-STEP1 Phase 3a	Randomized DB, 2-arm, placebo controlled	Semaglutide 2.4 mg or placebo controlled, OW, SC	1961 Sema 2.4 mg-1306 Placebo-655	Overweight or obesity	75 wks 68+7	Treated N= 1306 Pos = 39 **Pos % = 3%**	21/39 (54%)	NA	Median 30 Range Min:15 Maz:240
4374-STEP 2 Phase 3a	Randomized DB, DD, three arm placebo controlled	Semaglutide 2.4 mg and 1 mg or placebo controlled, OW, SC	1210 Sema 1 mg -403; sema 2.4 mg-404; placebo-403	Overweight or Obese + T2D	75 wks 68+7	Treated N = 403 Pos = 12 **Pos %= 3 %**	7/12 (58%)	NA	Median15 Range Min: 15 Max: 120
4153-phase 2	Randomized, DB, placebo controlled, 16 arm-Liraglutide 3mg control	Semaglutide 0.05, 0.1, 0.2, 0.3, 0.4 and placebo or liraglutide 3mg, OD, s.c,	Total 957; Placebo 136; 8 arms-102-103	Obese subjects with T2D	60 wks 52 +8	0	0	NA	NA
4590 Bioequivalence	Randomized OL, parallel group 2arm	Semaglutide 0.25-2.4 mg dose escalation 4W OW, SC. Old vs new formulation	68 PDS pen injector- 34 Single dose pen inj-34	Overweight or obesity	27-30 wks	0	0	NA	NA
4588 Bioequivalence	Randomized OL, parallel group, 3 arm	Semaglutide 0.25, 0.5 and 1 mg, OW, SC old vs new formulation	66 DV3396(33) vs PDS290 (33)pen injectors	Overweight or obesity	80-99 days	0	0	NA	NA

The titers need to be multiplied by 15 to get the dilution adjusted titer.
Abbreviation used in the table: T2D- type 2 diabetes patients; OW- Once weekly; OD-once a day; DB-double blind; placebo-placebo controlled trial; OL-open label; Sema-Semaglutide; Tx-treatment; SC-subcutaneous

Assessor's comments:

Semaglutide 2.4 mg treatment groups had low rates (3%) of ADA positive subjects.
The MRD adjusted titer of anti-semaglutide antibodies in confirmed positive subjects with ADA are generally low (median 15-30; range 15-240).

Approximately 55% (28/51) of the samples testing positive for anti-semaglutide antibody showed cross-reactivity with endogenous GLP- 1. Among the subjects confirmed positive for anti-semaglutide antibodies, the rate of subjects showing cross-reactivity to endogenous GLP-1 is high. However, considering the high homology between semaglutide and native GLP-1, this is expected.

The sponsor reports that neutralizing antibodies are not present in antibody positive samples. The NAB is assay is not sensitive enough to assess the neutralizing ability of the antibodies present in the antibody positive samples.

Drug induced Hypersensitivity reactions:

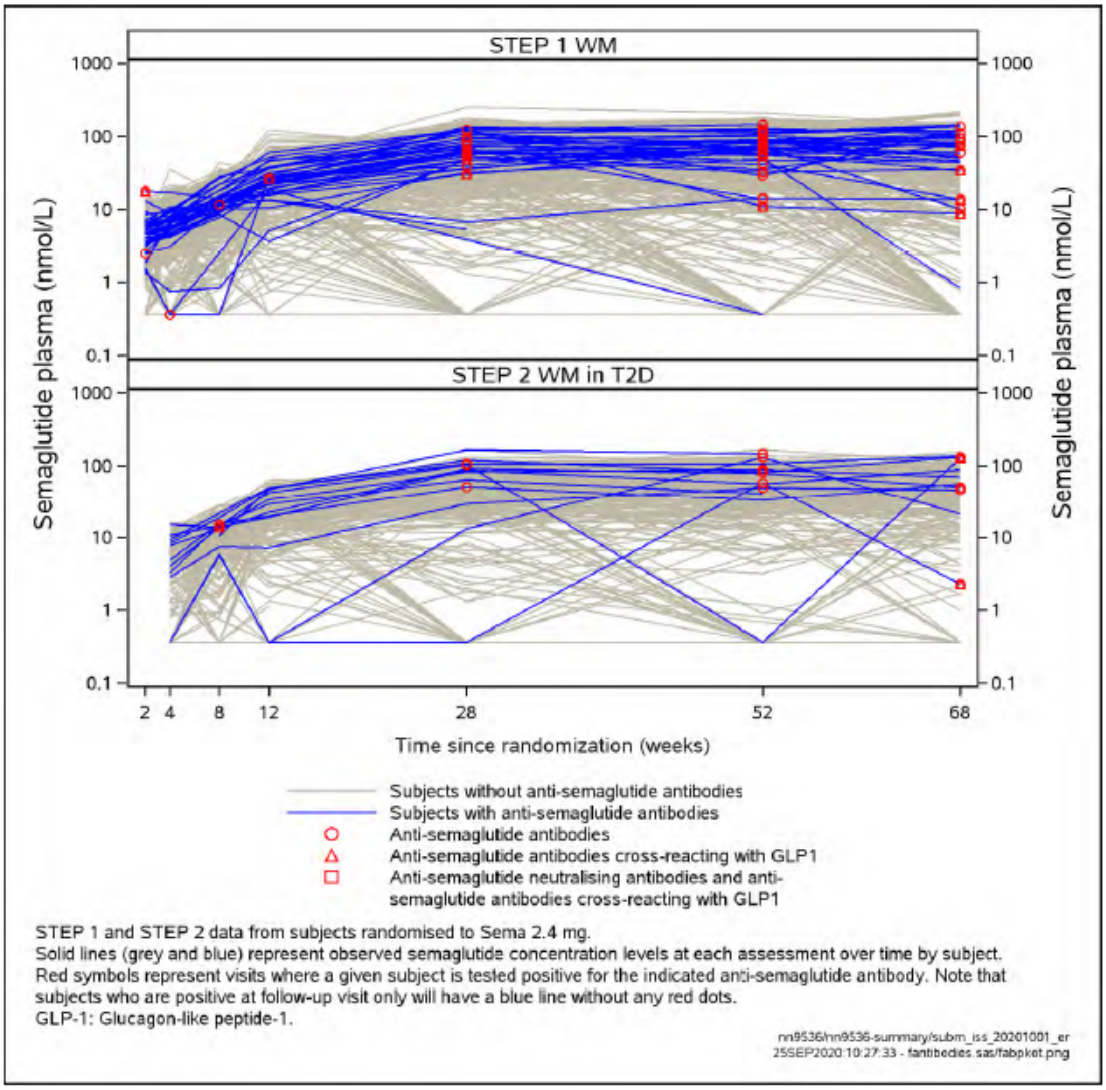
In the five clinical trials that included assessment of anti-semaglutide antibodies and the three other clinical trials for semaglutide 2.4 mg for weight management, no subjects had suspicion of severe acute hypersensitivity related to the drug product. In STEP 1 trial, 1 subject in the semaglutide 2.4 mg group reported eosinophilia (ID (b) (6)). The sample from this subject was analysed both anti-semaglutide binding antibodies and IgE antibodies were negative for this sample. This adverse event lead to temporary disruption of the trial product but was reported as resolved. In STEP 4 trial for weight maintenance (this trial did not assess antibodies to semaglutide), one subject reported serious adverse event of Pancytopenia. The sample was analysed for anti-semaglutide binding antibodies and was found negative. This SAE led to permanent treatment discontinuation and was not resolved at end of trial.

Assessor's comment:
There are no reports of severe acute hypersensitivity related to subcutaneous administration of semaglutide for weight management. Available data does not suggest that semaglutide can cause severe allergic reactions.

Effect of anti-semaglutide antibodies on semaglutide pharmacokinetics:

To assess the potential relationship between the presence of anti-semaglutide antibodies and pharmacokinetics, semaglutide plasma concentrations were measured for subjects in STEP 1 and STEP 2 at the same visits as antibody assessments. The semaglutide plasma concentrations were similar for subjects with anti-semaglutide antibodies compared to subjects without antibodies.

Figure 4-1 Semaglutide pharmacokinetic concentration by occurrence of anti-semaglut antibodies – spaghetti plot – on-treatment – STEP 1 and STEP 2

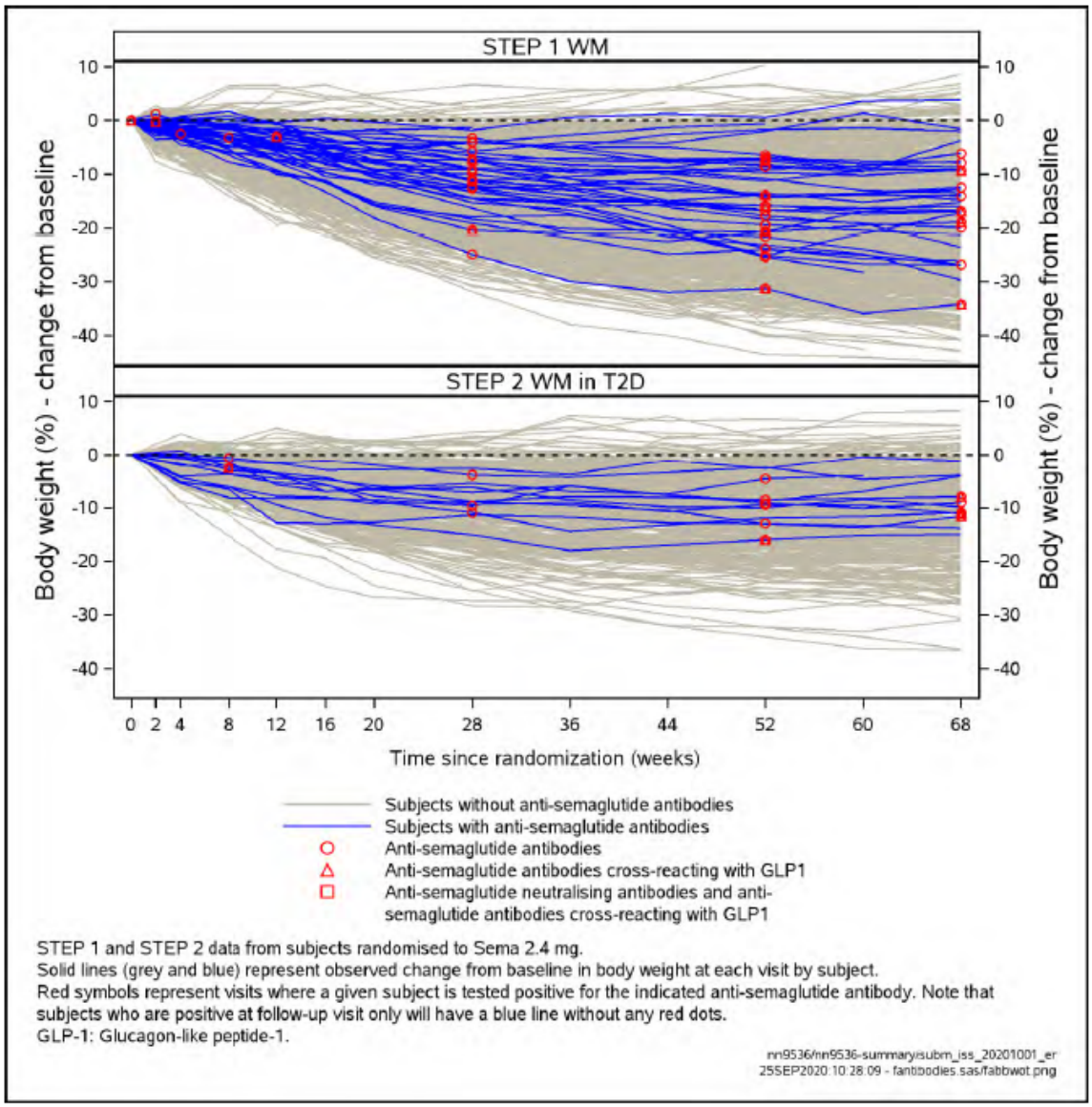


Assessor's comment:
Anti-semaglutide antibodies did not seem to affect the PK of semaglutide.

Impact of anti-semaglutide antibodies on Efficacy:

Pattern of body weight (%) change from baseline for subjects with or without antibodies is similar. Subjects that seroconverted and showed anti-semaglutide antibodies during the trial continued to show weight loss or weight maintenance compared to baseline. However, the mean of body weight change from baseline at follow-up (Week 68) for subjects with antibodies was lower (-14.9) than subjects without antibodies (-16.9) indicating the lower efficacy of semaglutide treatment in subjects with the development of anti-semaglutide antibodies.

Figure 4-2 Body weight (%) change from baseline by occurrence of anti-semaglutide antibodies – spaghetti plot – on-treatment – STEP 1 and STEP 2



STEP 1 and STEP 2 data from subjects randomised to Sema 2.4 mg.
Solid lines (grey and blue) represent observed change from baseline in body weight at each visit by subject.
Red symbols represent visits where a given subject is tested positive for the indicated anti-semaglutide antibody. Note that subjects who are positive at follow-up visit only will have a blue line without any red dots.
GLP-1: Glucagon-like peptide-1.

rm9536/rm9536-summaryisubm_iss_20201001_er
25SEP2020:10:28:09 - fantibodies.sas/fabbwot.png

Table 4-4 Body weight (%) change from baseline by occurrence of anti-semaglutide antibodies – on-treatment – STEP 1 and STEP 2

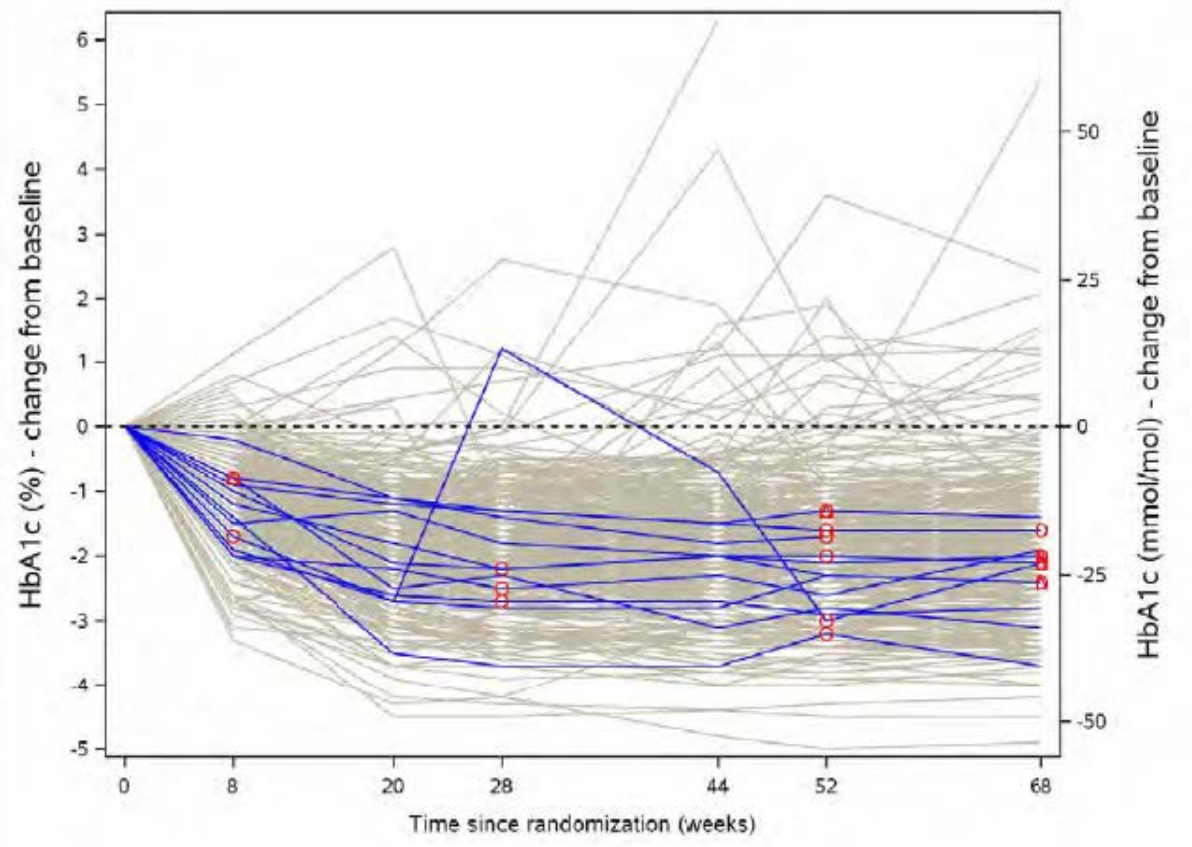
	STEP 1 WM		STEP 2 WM in T2D	
	Subjects with antibodies	Subjects without antibodies	Subjects with antibodies	Subjects without antibodies
Number of subjects	39	1267	12	391
Body weight (%)				
Change from baseline at week 68 visit				
N	34	1025	11	340
Mean (SD)	-14.9 (8.7)	-16.9 (9.4)	-9.0 (4.3)	-10.8 (7.9)
Median	-14.4	-16.1	-9.9	-10.0
P5 ; P95	-29.7 ; -1.6	-33.9 ; -2.6	-15.0 ; -1.2	-24.9 ; 0.9
Min; Max	-34.2 ; 3.8	-44.9 ; 8.5	-15.0 ; -1.2	-36.6 ; 8.2

STEP 1 and STEP 2 data from subjects randomised to Sema 2.4 mg.
Subjects are categorised with/without antibodies if they have ever/never tested positive for anti-semaglutide antibodies during the trial.
WM: Weight management, T2D: Type 2 diabetes, N: Number of subjects, SD: Standard deviation, P5: 5th percentile, P95: 95th percentile.

Assessor's comments:
The investigation of the effect of ADA on efficacy was limited as the rate of ADA was low. The limited data available indicates that the occurrence of ADA did not significantly affect the weight change from baseline suggesting that the ADA did not impact on product efficacy.

Effect on HbA1c:
STEP 2 included subjects with overweight or obesity, and T2DM. Change in HbA1c from baseline followed the same trend in subjects with and without anti-semaglutide antibodies. Subjects that seroconverted continued to show reduction in HbA1c or maintained the reduction after development of anti-semaglutide antibodies. There was no difference in this trend in antibody positive subjects irrespective of whether the antibodies were cross-reacting or not with endogenous GLP-1.

HbA1c change from baseline by occurrence of anti-semaglutide antibodies – spaghetti plot – on-treatment – STEP 2



Assessor's comment:
The development of anti-semaglutide antibodies (cross-reacting with endogenous GLP-1 or not) did not affect the HbA1c reduction in T2DM patients. Although, the levels of blood glucose cannot be directly extrapolated from the HbA1c, this PD marker is linked to blood glucose and may indirectly suggest that development of anti-semaglutide antibodies may not increase the blood glucose in T2DM patients. With the available data, it will not be possible to predict the effect of anti-semaglutide antibodies on blood glucose in patients without T2DM in STEP 1 trials. Development of hypoglycemia is reported as adverse event in STEP 1 trial and no cases of hypoglycemia was reported in semaglutide treatment group. The effect of anti-semaglutide antibodies on blood glucose levels in non-T2DM in not known.

Impact of anti-semaglutide antibodies on safety

In STEP1 and STEP 2, 51 subjects postive for ADA showed 47 adverse events (AE) during the treatment period. The majority of these AE were mild or moderate. Two of the subjects reported serious adverse events (SAE), gastroenteritis and hypersensitivity. One subject (ID (b) (6)) positive of anti-semaglutide antibodies only at week 2 discontinued treatment due to Asthenia (day 141). This subject later reported several SAE of loss of consciousness (day 282-303) followed by cardiovascular death (day 311). Another subject reported hypersensitivity reaction that was non-

serious but severe. This subject recovered while continuing trial product and the event was judged by the investigator as unlikey related to the drug product.

Assessor's comments:

No link was evident between adverse events and the presence of ADA. Therefore development of ADA does not appear to the affect safety or efficacy of semaglutide. However, the number of subjects and the levels of antibodies in those subjects were low and a conclusion on the effect of antibodies on safety or efficacy cannot be included in the label.

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/

MOHANRAJ MANANGEESWARAN
05/06/2021 11:59:41 AM

DANIELA I VERTHELYI
05/06/2021 07:45:33 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: April 30, 2021 **Date consulted:** March 24, 2021

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health (DPMH)
Office of New Drugs (OND)

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
DPMH, OND

Lynne P. Yao, MD, OND, Division Director
DPMH, OND

To: Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Drug: TRADENAME **(**semaglutide injection)

NDA: 215256

Applicant: Novo Nordisk

Subject: Pregnancy and Lactation Labeling Recommendations and Formatting

Proposed Indication: As an adjunct to a reduced calorie meal plan and increased physical activity for chronic weight management (b) (4) in adult patients with an initial body mass index (BMI) of:

- 30 kg/m2 or greater (obesity) or
- 27 kg/m2 or greater (excess weight) in the presence of at least one weight-related comorbid condition.

Materials
Reviewed:

- March 24, 2021, PLLR consult for semaglutide, DDLO, DARRTS Reference ID 4767552
- December 4, 2020, NDA application for semaglutide injection, NDA 215256
- September 3, 2019, DPMH consult for Rybelsus (semaglutide tablet) NDA 213051, Jane Liedtka, MD., Medical Officer, DARRTS Reference ID 4484773[1]
- September 12, 2017, DPMH consult for Ozempic (semaglutide) injection NDA 209637, Jane Liedtka, MD., Medical Officer, DARRTS Reference ID 4148940[1]

Consult Question: "We request your help in reviewing these pregnancies and provide your comments and recommendations. Regarding labeling, historically, pregnancy has been contraindicated in weight management drugs because there is no potential benefit to a developing fetus. Please comment on whether you still think that approach is appropriate and provide any other recommendations regarding the PLLR. (For a relevant example, see Saxenda (liraglutide), NDA 206321.)"

INTRODUCTION AND BACKGROUND

On December 4, 2021, Novo Nordisk submitted a New Drug Application (215256) for semaglutide injection for the proposed indication of weight management. NDA 215256 is a 505(b)(2) application referencing IND 126360 and NDA 209637 for Ozempic (semaglutide) injection prefilled pen, also a Novo Nordisk product. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) consulted the Division of Pediatric and Maternal Health (DPMH) on March 24, 2021, to assist with the Pregnancy and Lactation subsections of labeling.

Semaglutide is currently approved for type 2 diabetes under the tradename Ozempic and Rybelsus. Ozempic is a subcutaneous injection administered at a starting dose of 0.25 mg once weekly increasing every 4 weeks by 0.5 mg once weekly to a max of 1 mg once weekly. Rybelsus is approved for oral use as a 3 mg, 7 mg and 14 mg tablet administered daily.

Table 1: Semaglutide Drug Characteristics[2]

Drug Class	Glucagon-like peptide-1 (GLP-1) receptor agonist
Mechanism of Action	Semaglutide is a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor. GLP-1 is a regulator of appetite and caloric intake.
Dose and Administration	Maintenance dose of 2.4mg once-weekly by starting with a dose of 0.25 mg following a dose escalation.
Molecular Weight	4113.5 (b) (4) g/mol
Protein Binding	>99% bound to plasma albumin
Elimination Half-Life	Approximately 1 week
Bioavailability	89%

[1] The labeling review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.
[2] NDA 209637. Semaglutide injection.

Adverse Reactions	Nausea, diarrhea, constipation, vomiting, abdominal pain, headache, fatigue, decreased appetite, dyspepsia, dizziness, eructation, abdominal distension, gastroenteritis and flatulence.

Current State of the Labeling for the relied-upon NDA 209637 (semaglutide injection)
The following labeling characteristics correspond to the relied-upon NDA 209637 semaglutide injection labeling:

- There is not a boxed warning on embryofetotoxicity.
- There is not a contraindication for pregnancy or lactation.
- Labeling notes, "There are limited human data with semaglutide use in pregnant women to inform a drug-associated risk for adverse developmental outcomes."
- Animal reproduction studies were performed in rats, rabbits and cynomolgus monkeys and are summarized in subsection 8.1 Risk Summary and described in detail in 8.1 Data.
- There are no existing pregnancy testing or contraception recommendations
- There are no known drug-drug interactions with hormonal contraceptives

REVIEW
PREGNANCY
Weight Management and Pregnancy

- Maternal and pediatric outcomes are influenced by pre-pregnancy body weight and gestational weight gain.[3,4]
- Women with a BMI greater than or equal to 30kg/m^2 are at risk for gestational diabetes, pre-eclampsia, and cesarean delivery. Likewise, women with excessive pregnancy weight gain are at risk for postpartum weight retention, obesity and type 2 diabetes.[3,4]
- Women who are underweight (BMI of <18 kg/m2) during conception or have inadequate pregnancy weight gain are at risk for a small for gestational age infant at delivery.[3,4]
- According to the American College of Obstetricians and Gynecologists (ACOG) and the Institute of Medicine (now the National Academy of Medicine), weight gain guidelines during pregnancy are based on pre-pregnancy BMI (see Table 2 below). These guidelines are independent of age, parity, smoking, race and ethnic background.[4]
- According to ACOG, it is safer to lose weight prior to becoming pregnant. There is evidence of fetal/neonatal adverse outcomes, such as fetal growth restriction, in obese women who try to lose weight during pregnancy.[4]
- Additionally, according to ACOG, obesity increases the risk of pregnancy loss (miscarriage) compared to women that are not obese, neural tube defects, macrosomia, preterm birth and stillbirth.[5]

[3] Poston L. Gestational weight gain. In UpToDate, Berghella V, X Pi-Sunyer & V Barss (Eds.), UpToDate, Waltham, MA. Accessed on April 16, 2021.
[4] Weight Gain During Pregnancy. The American College of Obstetricians and Gynecologists: Committee Opinion, Number 548, January 2013 (Reaffirmed 2016).
[5] Obesity and Pregnancy. American College of Obstetricians and Gynecologists. https://www.acog.org/womens-health/faqs/obesity-and-pregnancy. Accessed April 16, 2021.

Table 2. Weight Gain Recommendations during Pregnancy (Institute of Medicine)[4]

Prepregnancy Weight Category	Body Mass Index*	Recommended Range of Total Weight (lb)	Recommended Rates of Weight Gain† in the Second and Third Trimesters (lb) (Mean Range [lb/wk])
Underweight	Less than 18.5	28–40	1 (1–1.3)
Normal Weight	18.5–24.9	25–35	1 (0.8–1)
Overweight	25–29.9	15–25	0.6 (0.5–0.7)
Obese (includes all classes)	30 and greater	11–20	0.5 (0.4–0.6)

*Body mass index is calculated as weight in kilograms divided by height in meters squared or as weight in pounds multiplied by 703 divided by height in inches.

†Calculations assume a 1.1–4.4 lb weight gain in the first trimester.

Modified from Institute of Medicine (US). Weight gain during pregnancy: reexamining the guidelines. Washington, DC. National Academies Press; 2009. ©2009 National Academy of Sciences.

Nonclinical Experience

Embryofetal development and pre- and postnatal development studies were conducted in rats, rabbits and cynomolgus monkeys. Semaglutide caused embryotoxicity in rats exposed during organogenesis as well as structural abnormalities (heart blood vessel, cranial bones, vertebra, rib) and alterations to growth (reduced growth) at maternal doses below the MRHD based on AUC.

In rabbits, early pregnancy losses and structural abnormalities [minor visceral (kidney, liver) and skeletal (sternebra)] were observed after administration of subcutaneous semaglutide during organogenesis below the MHRD (rabbit). In cynomolgus monkeys, administered subcutaneous semaglutide during organogenesis, reduction in body weight and food consumption was observed along with sporadic abnormalities (vertebra, sternebra and ribs)and greater than or equal to 2-fold MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species. The reader is referred to the Pharmacology/Toxicology review by Elena Braithwaite, Ph.D., and Federica Basso, PhD, DARRTS.

Review of Pharmacovigilance Data

Clinical Studies

Twenty-nine pregnancies were reported in females treated with semaglutide subcutaneously across 4 clinical trials within the clinical development program for semaglutide 2.4 mg. Semaglutide was stopped as soon as pregnancy was discovered in each of the 29 cases. At the time of the report there were thirteen healthy births, one ongoing pregnancy, one ectopic pregnancy, one lost-to follow up, one congenital anomaly of the external ear (infant also positive for sickle cell trait and mother anemic), six elective abortions (unrelated to congenital anomalies) and six spontaneous abortions. See appendix A for treatment dosage and exposure for each subject. These clinical study data are also reported in the Novo Nordisk safety database described below.

Novo Nordisk safety database and data pooling

The Novo Nordisk safety database contains data from multiple sources including, clinical trials, non-interventional and observational studies, patient support programs, market research programs, literature and spontaneously reported cases. Data are also available from Ozempic (semaglutide subcutaneous injection) 2.4 mg maximum and Rybelsus (semaglutide tablets) up to 14 mg maximum, both Novo Nordisk products. A total of 107 cases were found in the Novo Nordisk safety database through October 28, 2020. These cases include exposure during pregnancy to semaglutide subcutaneous and oral formulations. With regard to the data, pregnant women and their children could account for more than 1 case; therefore, taking into account multiple cases from one pregnancy and 3 reported lactation cases there were a total of 98 pregnancies (2 of which included paternal drug exposure). Out of the 98 reported pregnancies, 86 reported exposure to semaglutide via the subcutaneous route of administration, 8 reported exposure to oral semaglutide and 4 cases remains blinded[6] from ongoing trials. Two of the 98 cases were reported as paternal drug exposure. Fetal outcomes are only known for 47 pregnancies and unknown for 51 pregnancies.

The known fetal outcomes were grouped into the following 4 categories: 1) live birth without congenital anomalies (CA); 2) live birth with CA; 3) spontaneous abortion; 4) termination without known fetal defects. None of the fetal outcomes of stillbirth or termination were noted to have a fetal defect. One congenital anomaly was reported and also discussed above in the clinical studies section includes "small left ear fold/anomaly of external ear congenital" and involved exposure to semaglutide during pregnancy at unknown gestational timing. The mother was blinded to semaglutide. Additionally, the mother was HIV positive and the pregnancy was conceived while mother had an IUD in place. The infant was born at 38 weeks and 4 days gestation and had a small left ear fold that resolved itself 4 weeks after birth. This event was categorized as "unlikely" related to study drug.

Summary of fetal loss (spontaneous abortion) cases (all patients diagnosed with obesity):

- 33-year-old female (United States) with medical history of obesity, 3 prior spontaneous abortions, current smoker, spontaneous abortion 10 weeks' gestation, first trimester semaglutide exposure;
- 32-year-old female (Germany) smoker with medical history of obesity, hypothyroidism, struma nodosa, cholecystectomy, cholelithiasis and spontaneous abortion occurred at 6 weeks' gestation, semaglutide exposure occurred prior to pregnancy;
- 43-year-old female (Japan) with type 2 diabetes, dyslipidemia, constipation, urticaria, atrophic gastritis, reflux, obesity, previous smoker and hepatic function disorder, spontaneous abortion occurred prior to gestational week 20, semaglutide exposure first trimester ;
- 22-year-old female (United States) with medical history of cocaine addiction, ADHD, asthma, intermittent sinus tachycardia, obesity, anxiety and smoker and concomitant medication use to include Advair HFA, atenolol, and hormonal birth control. Spontaneous abortion occurred during first trimester. The patient was lost-to-follow as she stopped returning phone calls from investigators, semaglutide exposure first trimester;

[6] The cases (b) (6) have not been updated correctly in Appendix 1, Section 2. They are no longer blinded, but instead belong to the 'semaglutide s.c.' category.

- 34-year-old female (United States) medical history of obesity, asthma, 2 previous pregnancies that did not result in live-birth, semaglutide exposure first trimester, spontaneous abortion occurred during 24th week of gestation due to placenta abruption and stillbirth of infant;
- 26-year-old female (Israel), spontaneous abortion at 8 weeks' gestation, no further information, diagnosed obesity, semaglutide exposure first trimester;
- 24-year-old female (Argentina), obese, spontaneous abortion 3 weeks' gestation, no concomitant medication, 1 prior healthy live-birth delivery, semaglutide exposure first trimester;
- 19-year-old female (Belgium), medical history of obesity, depression, PCOS, previous smoker, exposure to semaglutide 4 months prior to pregnancy, spontaneous abortion during first trimester (estimated 3 weeks' gestation), semaglutide exposure first trimester;
- 38-year old female (United States), HIV positive, obese, high cholesterol, hypertension, concomitant prescription medication use, spontaneous abortion at 6 weeks gestation, exposure timing to semaglutide drug unclear

Table 3. Pregnancies with fetal outcomes (corresponds to Table 3-1, page 11, applicant's supporting information for PLLR submission)

Foetal outcome	Total N (%)	Treatment		
		Semaglutide s.c. N (%)	Oral semaglutide N (%)	Blinded[a] N (%)
Total	47	38	6	3
Live birth without CA	26	19	5	2
Live birth with CA	1	1	0	0
Foetal loss (spontaneous abortion)	9	9	0	0
Termination without known foetal defects	11	9	1	1

[a]The cases (b) (6) have not been updated correctly in Appendix 1, Section 2. They are no longer blinded, and are included in the 'semaglutide s.c.' category in this table. CA: congenital anomalies; N: Number of cases.

Reviewer comments:

- *DPMH notes that one of the cases coded as a spontaneous abortion occurred at 24 weeks' gestation and according to the Centers for Disease Control and Prevention (CDC) the death of a fetus after 20 weeks gestation is considered a stillbirth.*[7]
- *DPMH notes that the reports of spontaneous abortion include women with a diagnosis of obesity and other underling conditions and smoking which carry an increased risk of spontaneous abortion.*

[7] https://www.cdc.gov/ncbddd/stillbirth/features/pregnancy-infant-loss.html, accessed April 15, 2021.

Review of Literature

Applicant's Review of Literature

The applicant conducted a review of published literature using multiple databases regarding the use of semaglutide (subcutaneous and oral formulation) and pregnancy. Refer to submission for search parameters.

Twenty-six articles were captured and categorized by the applicant as follows:

- 10 are expert opinions or overviews containing no original data
- 1 is an erratum to a previously published editorial on semaglutide
- 1 is the patent for the oral semaglutide tablet
- 5 are original publications presenting in vitro or animal data on GLP-1 analogues in the context of weight loss, pancreas histopathology or peptide delivery, i.e. not relevant to human reproduction or fertility
- 3 are original publications or conference abstracts on clinical trials using semaglutide subcutaneous (s.c.)
- 3 are original publications or conference abstracts on clinical trials with oral semaglutide
- 2 are industry newsletters with content not relevant to human reproduction or fertility
- 1 is a cost-effectiveness analysis

The applicant summarized that the articles reviewed did not contain pregnancy cases or any new information relevant for the semaglutide subcutaneous labeling.

DPMH's Review of Literature

The reader is referred to the two previous DPMH reviews for semaglutide subcutaneous and oral products.[8,9] DPMH conducted a search of published literature using PubMed and Embase regarding semaglutide subcutaneous and oral exposure during pregnancy using the following search terms, "semaglutide and fetal malformations," "semaglutide and spontaneous abortion and miscarriage," "semaglutide and embryo-fetotoxicity. In addition to the applicant's review of literature, no additional relevant data were found for review. No additional information was found for review in Micromedex[10] or *Drugs in Pregnancy and Lactation* by Briggs and Freeman.[11]

Reviewer comment:

The applicant's PLLR submission is adequate for review. There are available human data in clinical studies and the applicant's pharmacovigilance database with regard to semaglutide subcutaneous and oral formulations exposure during pregnancy. See Conclusions section at bottom for DPMH's recommendations regarding this data.

[8] September 3, 2019, DPMH consult for Rybelsus (semaglutide tablet) NDA 213051, Jane Liedtka, MD., Medical Officer, DARRTS Reference ID 4484773

[9] September 12, 2017, DPMH consult for Ozempic (semaglutide) injection NDA 209637, Jane Liedtka, MD., Medical Officer, DARRTS Reference ID 41489401

[10] Semaglutide. (b) (4) Micromedex.

[11] Briggs, GG and Freeman, R., Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk Online version: http://ovidsp.tx.ovid.com/sp-3.31.1b/ovidweb.cgi.

LACTATION

Nonclinical Experience

Semaglutide was present in the milk of lactating rats. The reader is referred to the Pharmacology/Toxicology review by Federica Basso, PhD, DARRTS.

Review of Pharmacovigilance Database

No data were found with regard to semaglutide exposure and lactation in the clinical studies. There are 3 reports of "exposure via breast milk" in the applicant's pharmacovigilance database; however, 2 of the reports were a mother/infant pair.

- 41-year-old female patient (Chile), semaglutide subcutaneous 0.25 mg weekly, indicated she was breastfeeding, no specific onset date of breastfeeding was provided, no adverse reactions reported
- 29-year-old female (United States), reported exposure during breastfeeding at the time of report child was 14 months old, no adverse reactions reported. The patient was receiving semaglutide administered subcutaneously at a dose of 0.25 mg weekly.

Review of Literature

Applicant's Review of Literature

The applicant conducted a review of published literature using multiple databases regarding the use of semaglutide (subcutaneous and oral formulation) and lactation. No data were found with regards to lactation.

DPMH's Review of Literature

DPMH conducted a search of published literature using PubMed and Embase regarding semaglutide exposure during lactation. No data were found. Also, there are no data found in *Medication and Mothers Milk,*[12] or *Drugs in Pregnancy and Lactation* by Briggs and Freeman.

According to LactMed,[13] "No information is available on the clinical use of semaglutide during breastfeeding. Because semaglutide is a peptide molecule with a molecular weight of 4113 Daltons and is over 99% protein bound, the amount in milk is likely to be very low."

Reviewer comment:
The applicant's PLLR submission is adequate for review. The reader is referred to the conclusions section for DPMH's recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

No effects were observed on male fertility in the rat. In female rats, semaglutide increased oestrus cycle length and caused a reduction in the number of corpora lutea with subsequent effect on number of implantations and litter size. These effects were considered a non-adverse adaptive response secondary to the pharmacological effect of semaglutide on food consumption and body

[12] Hale, Thomas (2017). Medications and Mother's Milk. Amarillo, Texas. Springer Publishing Company LLC.
[13] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

weight. The reader is referred to the Pharmacology/Toxicology review by Federica Basso, PhD, DARRTS.

Review of Pharmacovigilance Database

According to the applicant there were six adverse reactions related to fertility in the phase 3a clinical trials in subjects treated with 2.4 mg of semaglutide. The adverse reports consisted of five dysfunctional uterine bleeding (all resolved) and one event of polycystic ovaries. One case of dysfunctional uterine bleeding was considered serious as the subject had a past history of abnormal uterine bleeding and a hysterectomy with bilateral salpingo-oophorectomy was performed in relation to the event.

Review of Literature

Applicant's review of literature

The applicant conducted a review of published literature using multiple databases regarding the use of semaglutide (subcutaneous and oral formulation) and male or female fertility. No additional data were found.

DPMH review of literature

DPMH conducted a review of available published literature with regard to semaglutide exposure and fertility. No data were found.

Reviewer comment: The applicant's PLLR submission is adequate for review. The reader is referred to the conclusions section for DPMH's recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

According to animal reproduction studies, there may be risks to the fetus from exposure to semaglutide during pregnancy. Semaglutide was administered through organogenesis to rats, rabbits and cynomolgus monkeys at doses at or below the MRHD. Embryofetal mortality, structural abnormalities and alternations to growth were observed. During the April 29, 2021 labeling meeting the DDLO Nonclinical Team noted that the findings in animals are likely due to weight loss that occurred in the animals, and it is not clear if the findings are clinically relevant. There are limited human data available from clinical studies and the applicant's pharmacovigilance database regarding semaglutide subcutaneous and oral exposure during pregnancy. The data are insufficient to determine if there is a drug associated risk of maternal or fetal adverse reactions. Reports of exposure to semaglutide during pregnancy include pregnant females with a diagnosis of obesity and other underling conditions which carry an increased risk of spontaneous abortion.

The applicant has proposed (b) (4); however, DPMH disagrees with this approach (b) (4) (b) (4).

Due to the proposed indication of weight management and the number of cases of pregnancy in the applicant's pharmacovigilance database and clinical studies, it is possible for unintended pregnancies in females of reproductive potential who are exposed to semaglutide. DPMH

recommends issuing a postmarketing requirement (PMR) for the applicant to conduct a pregnancy exposure registry and a complementary study of a different design. Although the pregnancy registry will be an important tool for the collection of safety data in pregnant women exposed to semaglutide due to its prospective design and ability to collect detailed patient information, based on experience with other pregnancy registries, we anticipate it will take several years for a pregnancy registry to provide adequate information and may not be sufficient by itself to assess the safety of semaglutide during pregnancy. Therefore, a complementary study may provide additional understanding regarding safety in pregnancy and may address limitations inherent to a pregnancy registry providing greater confidence in the pregnancy outcomes that are observed. DPMH also recommends that language regarding the pregnancy exposure registry is included in subsection 8.1 of labeling.

The reader is referred to the FDA Draft Guidance for Industry Postapproval Pregnancy Safety Studies: Considerations for Study Design, published May 2019, for further details.

Lactation

There are no data on the presence of semaglutide in human. Semaglutide is present in the milk of lactating rats. Upon approval of Rybelsus (semaglutide tablets), Novo Nordisk was issued PMR 3692-3 to conduct a lactation study in lactating women who have received Rybelsus; therefore, DPMH does not recommend an additional lactation PMR for this product. Rybelsus is also a Novo Nordisk product. DPMH recommends that semaglutide labeling is updated once the final study results of the clinical lactation study are reviewed.

Females and Males of Reproductive Potential

In female rats, semaglutide increased oestrus cycle length and caused a reduction in the number of corpora lutea with subsequent effect on number of implantations and litter size. These effects were considered a non-adverse adaptive response secondary to the pharmacological effect of semaglutide on food consumption and body weight. No significant safety information was identified concerning fertility disorders in male and female subjects of reproductive potential associated with semaglutide use in the semaglutide development program. The current approved semaglutide labelings have the following statement that will also be included in Section 8.3 of this labeling:

(b) (4)

POSTMARKETING REQUIREMENT (PMR) RECOMMENDATIONS

1) The applicant should be required to conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to semaglutide during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

2) The applicant should be required to conduct an additional pregnancy study that uses a different design from the Pregnancy Exposure Registry (for example a case control study or a retrospective cohort study using claims or electronic medical record data with outcome validation) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to semaglutide during pregnancy compared to an unexposed control population.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

(b) (4)

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Appendix A. Pregnancies reported in semaglutide 2.4 mg clinical develop programs

Table 1. Pregnancies reported in subjects treated with semaglutide in the phase 3a trials (corresponds to Table 2-1, page 7, applicant's supporting information for PLLR submission)

Treatment	Total pregnancies	Outcome of pregnancy	Subjects	Maternal exposure during pregnancy [a]	Comment
Semaglutide 2.4 mg OW	24	Healthy child	10	~ 0–17 weeks	Birth in gestational week 32–41. Birth weight of 2265–4160 g.
		Child with malformation	1	~ 14 weeks	Birth in gestational week 38. Birth weight 2640 g.
		Ongoing pregnancy[b]	1	~ 11 weeks	
		Spontaneous abortion	4	~ 0–10 weeks	In gestational week 3, 6, 8 and 12. One subject had 3 previous spontaneous abortions.
		Elective abortion	6	~ 0–7 weeks	In gestational week 6–7. None were known to be due to congenital anomalies
		Ectopic pregnancy	1	~3 weeks and 4 days	Termination in gestational week 5 due to ectopic pregnancy.
		Lost to follow-up	1	~ 4 weeks	

[a] Approximate period of exposure includes a washout period of 7 weeks for subjects treated with semaglutide.
[b].Ongoing as per (b) (6)

Table 2. Pregnancies reported in subjects treated with semaglutide in phase 2 trial 4153 (corresponds to Table 2-2, page 8, applicant's supporting information for PLLR submission)

Treatment	Total pregnancies	Outcome of pregnancy	Subjects	Maternal exposure during pregnancy[a]	Comment
Semaglutide 0.4 mg OD	1	Healthy child	1	~ 5 weeks	Birth in gestational week 36 + 4 days. Birth weight 2640 g. APGAR score at 1 minute: 9
Semaglutide 0.4 mg OD F	1	Spontaneous abortion	1	None	Spontaneous abortion in week 5. Withdrew from trial due to wish of becoming pregnant
Semaglutide 0.2 mg OD	1	Healthy child	1	~10 weeks + 4 days	Birth in gestational week 37. Birth weight 2810 g. APGAR score at 1 minute: 9
Semaglutide 0.05 mg OD	2	Healthy child	1	~ 2 weeks + 2 days	Healthy twins. Birth in gestational week 35+5. Birth weights 2180 g and 2280 g. APGAR score at 1 min 8 for both children.
		Spontaneous abortion	1	~ 6 weeks + 0 days	Spontaneous abortion in week 8. One previous live birth

[a] Approximate period of exposure includes a washout period of 7 weeks for subjects treated with semaglutide.

F: fast dose escalation; OD: once daily.

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/

CARRIE M CERESA
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MIRIAM C DINATALE
05/03/2021 09:24:43 AM

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05/03/2021 10:52:02 AM

Clinical Inspection Summary

Date	5/03/2021
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Julie Golden, M.D., Medical Officer John Sharretts, M.D., Clinical Team Leader Division of Diabetes, Lipid Disorders, and Obesity (DDLO) Martin White, M.S., Regulatory Health Project Manager Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
NDA	215256
Applicant	Novo Nordisk Inc.
Drug	Semaglutide 2.4 mg
NME	No
Therapeutic Classification	Glucagon-like peptide-1 (GLP-1) receptor agonist
Proposed Indication	Adjunct to a reduced calorie meal plan & increased physical activity for chronic weight management (b) (4) (b) (4) in adult patients with an initial BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with weight-related comorbid condition
Consultation Request Date	1/5/2021
Summary Goal Date	5/11/2021
Action Goal Date	6/4/2021
PDUFA Date	6/4/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this new drug application (NDA) consisted of two domestic sites.

An inspection assignment was issued to the Office of Regulatory Affairs (ORA) on 1/11/2021 to conduct good clinical practice (GCP) inspections of five sites covering studies NN9536-4375 and NN9536-4376.

The ongoing COVID-19 global pandemic has significantly limited ORA's ability to conduct onsite GCP inspections. Following discussions between OSI and the Division of Diabetes, Lipid Disorders, and Obesity (DDLO), a decision was made that assessment of the application could proceed without GCP inspections if they were not possible before the action due date. Abiding by guidelines to protect the health, safety, and welfare of FDA employees and study staff, and with

repeated evaluations of the current situation and mission-critical priorities, the planned inspections of Dr. Stephen Aronoff (Site 232/Study NN9536-4375; Site 609/Study NN9536-4376), Dr. Sriram Machineni (Site 228/Study NN9536-4375) and Dr. Joseph Woolley (Site 217/Study NN9536-4375) were not able to be conducted.

In general, based on the inspections of the two clinical sites, the inspectional findings support validity of data as reported by the sponsor under this NDA.

II. BACKGROUND

Novo Nordisk has submitted an original new drug application (NDA) for semaglutide injection for the proposed indicated of weight management.

Semaglutide (NN9536) is a long-acting GLP-1 receptor agonist originally studied as an adjunct to diet and exercise for the treatment of type 2 diabetes mellitus (T2DM). Ozempic® (semaglutide) injection was originally approved on December 5, 2017 under NDA 209637. That development program is completed.

Under IND 126360, semaglutide injection is being developed for chronic weight management at a higher dose (2.4 mg once weekly). Novo Nordisk intends to launch semaglutide subcutaneous (SC) 2.4 mg with the single dose pen-injector (also referred to as DV3396 pen-injector).

There are currently four ongoing or completed phase 3 trials included in the NDA submission. Two were requested for inspection.

NN9536-4375 (STEP 3)
This was a 68-week randomized, double-blind, placebo-controlled, two-armed, parallel-group, multi-center clinical trial conducted in the US, which compared semaglutide 2.4 mg with placebo, as an adjunct to intensive behavioral therapy (IBT), in subjects overweight or with obesity. The trial consisted of a screening period of approximately 1 week, a 68-week treatment period (including 16 weeks of dose escalation and 52 weeks on maintenance dose) and a 7-week off-drug follow-up period.

The trial was conducted at 41 sites in the US. A total of 742 subjects were screened and 611 subjects were randomized 2:1 to receive either semaglutide 2.4 mg once-weekly or placebo as an adjunct to IBT; 505 subjects completed treatment.

The trial began August 1, 2018 and completed April 28, 2020. The database for this study was locked on May 19, 2020.

The primary endpoints were:

- Change from baseline at Week 0 to Week 68 in body weight (%)
- Subjects who after 68 weeks achieve (yes/no) body weight reduction ≥5% from baseline (Week 0)

The global COVID-19 pandemic occurred when almost all subjects had completed their end-of-treatment visits (last subject last treatment was March 18, 2020 and last subject last visit was April 28, 2020). Source data verification was abolished for the last part of the trial (as of March 23, 2020). All data was still entered into the electronic data capture system and checked for completeness.

NN9536-4376 (STEP 4)
This was a multinational, two-armed multi-center, randomized, double-blind, placebo-controlled, multiple-dose withdrawal trial in subjects overweight or with obesity. The trial consisted of a screening period of approximately 1 week, a 20-week run-in period (including 16 weeks of dose escalation), a 48-week period on maintenance dose and a 7-week off-drug follow-up period. Subjects were randomized after the run-in period at Week 20.

The study began June 4, 2018 and completed March 20, 2020. The database for this study was locked on April 16, 2020.

The trial was conducted in 10 countries at 73 sites. A total of 1051 subjects were screened; 902 subjects were included in the run-in period; 803 subjects were randomized 2:1 to receive either semaglutide 2.4 mg or placebo; 802 subjects received product; 741 subjects completed treatment.

The primary endpoint was change from randomization (Week 20) to Week 68 in body weight (%).

The global COID-19 pandemic occurred when almost all subjects had completed their last visits. Source data verification was abolished for the last part of the trial (as of March 23, 2020). All data was still entered into the electronic data capture system and checked for completeness.

III. RESULTS (by Site)

NOTE: Site inspections focused on review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, curricula vitae (CVs) and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1. **Domenica M. Rubino, M.D.**
   2800 S. Shirlington Rd., Suite 505
   Arlington, VA 22206-3618

   Site: 214 **Study:** NN9536-4375
   Site: 629 **Study:** NN9536-4376

Dates of inspection: March 22 – 26, 2021

For Study NN9536-4375, there were 24 subjects screened and 20 subjects enrolled into the study; 20 subjects completed the study (4 subjects discontinued study drug but continued with follow-up visits). There were 10 subject records reviewed.

For Study NN9536-4376, there were 20 subjects screened and 17 subjects enrolled into the study; 14 subjects completed the study (one subject was lost to follow-up, one death (b) (6) (b) (6) and one subject dropped out prior to randomization). There were 8 subject records reviewed.

The institutional review board of record was (b) (4) (b) (4). Subjects for both studies were recruited through advertisements and word of mouth within Dr. Rubino's current patients as well as physicians within the same field.

The inspection was conducted at Washington Center for Weight Management and Research, Inc., where the studies took place. Dr. Rubino is the sole owner of Washington Center for Weight Management and Research, Inc. since 2008 and has been at its current location for approximately five years.

On reviewing the temperature logs for the drug supply for both studies, it was noted that there were two temperature excursions. The protocol has the storage conditions for the trial product to be stored in a refrigerator (2°C-8°C/36°F-46°F). On 02/14/19, temperature reached 8.1°C and on 08/07/19, temperature reached 8.3°C. However, there was no indication or documentation of review or report of the temperature excursions. The refrigerator is configured to alarm below 1.5°C and above 8.4°C. Based on the packaging material, short spikes in temperatures (lasting 15 minutes or less) are not considered temperature excursions. Discussions with the sponsor during the inspection confirmed that the sponsor deemed the study drug acceptable.

Source records were organized, legible, and available. Electronic clinical outcome assessments (eCOA) such as the Columbia-Suicide Severity Rating Scale (C-SSRS) and Patient Health Questionaire-9 (PHQ-9) were completed via an electronic tablet and the results were sent directly to the sponsor. At the site level, the electronic clinical outcome assessments were printed with confirmed review by Dr. Rubino. The sponsor had provided the site with the final eCRF data recorded on a USB stick.

Source records were compared to the sponsor data line listings. The primary efficacy endpoints were verifiable for both studies. Of note, the Certificate of Calibration (b) (4) (b) (4) was conducted annually per the protocol on 03/19/18, 03/26/19, and 03/06/20.

There was no under-reporting of adverse events noted for Study NN9536-4375. There were a few adverse events not captured for Study NN9536-4376. *Dr. Rubino stated this*

will be corrected.

- **Subject** (b) (6) reported abnormal taste on (b) (6); however, this was not documented as an adverse event.
- **Subject** (b) (6) reported acid reflux on (b) (6); however, this was not documented as an adverse event.
- **Subject** (b) (6) reported diarrhea on (b) (6); however, this was not documented as an adverse event.
- **Subject** (b) (6) reported pelvis pain and pain in the right leg at Visit 23; however, this was not documented as an adverse event.

There were a few documentation errors noted in the source records:

- **Subject** (b) (6): At Visit 28 on (b) (6), source document states the date of the last dose was on (b) (6); however, it should be (b) (6). *Dr. Rubino stated this will be corrected.*
- **Subject** (b) (6): Subject was hospitalized on (b) (6) for an abdominal abscess, which was reported as an SAE; however, the concomitant medication log was not updated and does not include medications received while hospitalized: oxycodone-acetaminophen (Percocet) 5/325 mg, norethindrone 0.35 mg, and ibuprofen 800 mg. *Dr. Rubino stated the concomitant medications will be updated.*
- **Subject** (b) (6): Based on the dose escalation period, subject's dose increase should be 1.0 mg on (b) (6); however, the date of the next dose increase is documented as (b) (6). The study coordinator confirmed this was a transcription error and, during the inspection, it was verified on the Medication Log that the correct dose was administered on the correct date.
- **Subject** (b) (6): On (b) (6), the subject donated a kidney to her husband. Subject was prescribed oxycodone-acetaminophen (Percocet) 5/325mg, docusate sodium 100 mg, famotidine 20 mg, and fluticasone-salmeterol 250mcg/50mcg inhalation powder; however, it was not documented on the concomitant medications log. *Dr. Rubino stated the concomitant medications will be updated.*
- **Subject** (b) (6): No pregnancy test was conducted per the protocol at Visit 24 on (b) (6). This was not captured as a protocol deviation. *Dr. Rubino stated this will be corrected.*

Items related to adverse event reporting, concomitant medication, protocol deviations, investigational product storage temperature, and documentation practices were discussed verbally with Dr. Rubino.

Although there were some discussion items, the investigator plans to work with the sponsor to make corrections; the deviations should not affect overall analyses regarding safety and efficacy. The inspection revealed adequate adherence to the regulations and the investigational plan. No Form FDA-483, Inspectional Observations, was issued.

2. **Andrew P. Brockmyre, M.D.**
   240 Medical Park Blvd, Suite 2600
   Bristol, TN 37620-7352

   Site: 625
   Study: NN9536-4376

Dates of inspection: April 26 – 28 , 2021 (*Full report pending*)

There were 17 subjects screened and 17 subjects enrolled into the study; 12 subjects completed the study (Subject (b) (6) withdrew after randomization but was still included in the analysis set). There were 17 subject records reviewed.

The institutional review board of record was (b) (4). The site did not use the most recently approved informed consent form (ICF) for all subjects. A research address within the same set of suites and a phone number were added to the ICF, but the site failed to use the new form starting with Subject (b) (6). The address added did not otherwise substantively change the ICF.

Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Senior Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Min Lu, M.D., M.P.H.
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Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

cc:

DARRTS/ NDA 215256
DDLO/Director/ Lisa Yanoff
DDLO/Associate Director for Therapeutics/ Patrick Archdeacon
DDLO/Team Lead/John Sharretts
DDLO/Clinical Reviewer/ Julie Golden
DRO/Regulatory Project Manager/Martin White
OSI/DCCE/Acting Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Min Lu
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/

CYNTHIA F KLEPPINGER
05/03/2021 01:08:34 PM

MIN LU
05/03/2021 01:38:38 PM

KASSA AYALEW
05/03/2021 02:51:09 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	12/28/2020		
To:	Hamet Toure		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	Choose an item.
From	Dunya Karimi OPEQ/OHT3/DHT3C		
Through (Team)	Choose an item., Team Lead, Choose an item. OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Choose an item., Choose an item. OPEQ/OHT3/DHT3C		
Subject	NDA 215256 , Semaglutide 2001053 00044812		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☐ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 3/12/2021 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 4/21/2021 ☐ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Dunya Karimi -S	Courtney Evans -S Digitally signed by Courtney Evans -S Date: 2021.04.30 11:47:26 -04'00'	

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 215256
Sponsor	Novo Nordisk
Drug/Biologic	Semaglutide
Indications for Use	Adjunct to a reduced calorie meal plan & increased physical activity for chronic weight management (b) (4) in adult patients w/an initial BMI of 30kg/m2 or greater or 27kg/m2 or greater w/weight-related comorbid condition
Device Constituent	Auto-Injector
Related Files	

Review Team	
Lead Device Reviewer	*Dunya Karimi*

Important Dates	
Final Lead Device Review Memo Due	April 27, 2021
Interim Due Dates	**Meeting/Due Date**
Filing	2/2/2021
74-Day Letter	2/16/2021
Mid-Cycle	3/4/2021
Primary Review	5/11/2021

EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

- Approvable – the device constituent of the combination product is approvable for the proposed indication.
- Approvable with PMC or PMR, See Section 2.3
- Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation	X			
Human Factors Validation			X	

Facilities & Quality Systems	X			

1.1. Comments to the Review Team

☐ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

Comment #1: The firm FEI 1000158576 is not registered and listed. Please convey to the sponsor our suggestion that they register and list this facility.

1.2. Complete Response Deficiencies

☐ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

1.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☐

Post-Market Commitment or Requirement:

Post Approval inspections are required for FEI [redacted] (b) (4) and FEI 1000158576 because these firms are responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and a recent medical device inspection of these firms has not been performed.

TABLE OF CONTENTS

2. PURPOSE/BACKGROUND

2.1. Scope

Novo Nordisk is requesting approval of Semaglutide. The device constituent of the combination product is a Pre-Filled Syringe.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

This is a duplicate request for the facility device consult.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device Performance

This review will not cover the following review areas:

Human factors

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

2.2. Prior Interactions

IND 126360
NDA 209637

2.2.1. Related Files

2.3. Indications for Use

Combination Product	Indications for Use
Semaglutide	Adjunct to a reduced calorie meal plan & increased physical activity for chronic weight management (b) (4) in adult patients w/an initial BMI of 30kg/m2 or greater or 27kg/m2 or greater w/weight-related comorbid condition
Auto-Injector	Delivery of the Drug Product

2.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0001	1.2 1.11 1.14 3.2.P.3.3 3.2.P.3.4 3.2.P.2.7 5.3.5.4
0011	1.11
0017	1.11
0025	1.11

3. DEVICE DESCRIPTION

3.1. Device Description

The device is a single dose pen-injector for Semaglutide. It is a single patient, single dose, (b) (4) prefilled auto-injector. There are five does variants: 0.25 mg, 0.5 mg, 1 mg, 1.7 mg and 2.4 mg.

Table 1 Semaglutide drug product variants

Variant#	Dose	Concentration	Filling volume
1	0.25 mg	0.5 mg/ml	0.5 ml
2	0.5 mg	1.0 mg/ml	0.5 ml
3	1 mg	2.0 mg/ml	0.5 ml
4	1.7 mg	2.27 mg/ml	0.75 ml
5	2.4 mg	3.2 mg/ml	0.75 ml

The pen-injector components used in the variants for the three lowest concentrations are the same. The pen-injector components used in the variants for the two highest concentrations are using the same (b) (4) assembly as used for the three lowest concentration but includes another variant of the (b) (4) Assembly. For the final product the differentiation between the five variants is achieved through distinctive labelling and packaging design.

The pen-injector components are designed and supplied by (b) (4) and are customized versions of the (b) (4) auto-injector. (b) (4) contains a (b) (4) prefilled syringe (PFS) and is well-established, being used with other approved drug products such as Zembrace® Symtouch®, Brenzys®/Benepali®, Nordimet®, Benlysta®, and Eucept®/Etanercept BS.

The customization is a cosmetic change of the outer parts to give the product a Novo Nordisk appearance. The parts that are cosmetically changed are the Body, (b) (4) and Cap.

The primary container closure system for the single dose pen-injector for semaglutide is a prefillable syringe. The prefillable syringe design is made up of a (b) (4) glass syringe barrel with (b) (4) needle), (b) (4) and (b) (4). The materials and main functions of the components are summarized below:

Table 2 Materials and main functions of the prefillable syringe components

Component name	Material	Description of main functions
(b) (4)		
Syringe barrel	(b) (4)	To enclose the drug product (container closure system)
(b) (4)		To enable the administration of the drug product To enclose the drug product (container closure system)
(b) (4) needle		To enable the administration of the drug product To enclose the drug product (container closure system)
	(note: it is hidden when assembled in the pen-injector)	

The (b) (4) assembly is designed to hold the PFS. The (b) (4) assembly constituent parts are shown in Figure 6.

The functions of these parts are explained in Table 3. The (b) (4) assembly has an ergonomic design, provides an Inspection window (see further details Figure 9) and the Body provides sufficient space for affixing the appropriate labelling. The friction surface of small ribs on the Cap increases grip and facilitates removal of the Cap from the Body.

Table 3 Materials and main functions of the (b) (4) assembly components

Component name	Materials	Description of main functions
Cap	(b) (4)	To cover the Needle cover before removal
(b) (4)		(b) (4)
Needle cover		To activate the auto-injector To cause the lockout after injection To hide the needle from the user
(b) (4)		(b) (4)
Body		To hold the syringe housing; includes the Inspection window
Syringe housing		To hold the syringe inside of body

The (b) (4) assembly contains the (b) (4) components that drive (b) (4) into the Syringe and provide the Needle cover functionality. The (b) (4) assembly components are shown in Figure 7. The functions of these parts are explained in Table 4.

The components in terms of design, material and colour will be identical for all five drug concentrations, except for the (b) (4). The pictures of the components in Figure 7 is an exploded view of the components of the (b) (4) assembly.

(b) (4)

(b) (4)

Table 4 Materials and main functions of the (b) (4) Assembly components

Component name	Materials	Description of main functions
(b) (4)		

Principle of Operation

The principles of operation and features to enhance user safety for dose delivery is described in this section.

Before use (unused pen-injector)

The Inspection window on the pen-injector Body allows the user to inspect the drug. When the yellow (b) (4) (b) (4) is not visible, the Inspection window also indicates to the user that the peninjector has not been used.

Cap removal

The Cap needs to be removed prior to injection (see Figure 9). The (b) (4) in the Cap grabs (b) (4). The pen-injector is thus ready for use.

Activation and injection

The single dose pen-injector for semaglutide utilizes a proprietary design concept from (b) (4) (b) (4), whereby the pen-injector does not require pressing of a button to initiate the injection. Instead, the user holds the pen-injector and presses it against the skin. When pressure is applied on the Needle cover it enables manual needle penetration and initiation of the injection, as shown in Figure 10.

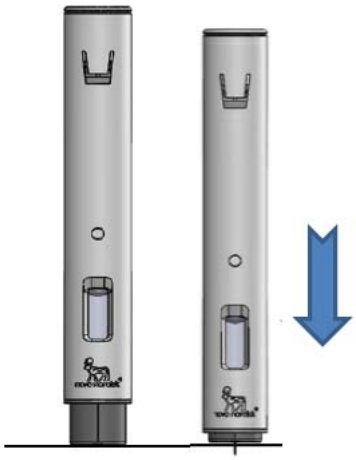


Figure 10 Activation of the single dose pen-injector for semaglutide by pressing the exposed Needle cover against the skin

(b) (4). The force required to push back the Needle cover is controlled (b) (4). Once the Needle cover is pushed for activation, the (b) (4) will flex outward and release (b) (4) (b) (4). The release will push (b) (4) towards the Needle, thus emptying the PFS.

A click sound is generated and gives the user an audible feedback that the injection has started. The injection is irreversible once activated. The pen-injector is designed to administer the full fixed dose, in order to eliminate user errors regarding dose setting and delivery.

While the injection is ongoing, the color in the Inspection window gradually turns to yellow. The movemen (b) (4) (b) (4) gives visual feedback for the user that injection is taking place. The user cannot see the needle during injection. When the (b) (4) pushes the (b) (4) in the PFS to a position nearing its end-position, the (b) (4) contact (b) (4) leads to a second click sound, providing feedback that the injection draws close to completion.

End of injection

When the injection is completed, the (b) (4) yellow (b) (4) fill the Inspection window completely (see Figure 11). At the completion of injection there is no further movement seen in Inspection window. After the injection is complete, the pen-injector can be removed from the skin.

Figure 11 Visual indication of injection and Needle cover extension

Inside the device Body, the Needle cover [redacted] (b) (4) will be irreversibly locked in the extended position. The Needle cover automatically extends over the needle as the single dose pen-injector is pulled away from the skin. In this position, the pen-injector is disabled from any subsequent injections. The concomitant action of the automatic extension of the Needle cover and its irreversible locking into this position is designed to prevent needle stick injuries.

Injection cycle feedback to the user in the single dose pen-injector for semaglutide

The design of the single dose pen-injector for semaglutide provides multimodal feedback during use (see Table 5). This feedback assists the user before, during and after the injection.

3.2. Steps for Using the Device

- Prepare for injection
  a. wash hands
  b. check device for damage etc.
- Choose injection site
  a. upper arms, upper legs (front of thighs) or lower stomach (2 in away from bellybutton)
  b. do not inject into area where the skin is tender, bruised, red, hard. Avoid areas with scars or stretchmarks
  c. may inject in same area every week but do not inject in same spot each time
  d. clean injection site
- Pull pen cap off pen
- Injection
  a. Push pen firmly against skin until the yellow bar has stopped moving
  b. If yellow bar does not start to move, press more firmly
- Disposal
  a. Throw away the pen (instructions provided)
  b. If blood appears at injection site, press lightly with gauze pad or cotton ball

Additional information included on how to dispose the pen, how to care for the pen and how to store it

3.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

4. FILING REVIEW

CDRH performed Filing Review	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

4.1. Filing Review Checklist

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability			X
	Biocompatibility	X		
	Sterility	X		
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors	X		
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		

	Control Strategy provided for EPRs	X		

Reviewer Comment

4.2. Facilities Information

Firm Name:	Novo Nordisk Pharmaceutical Industries, LP
Address:	3612 Powhatan Road Clayton North Carolina USA 27527
FEI:	1000158576
Responsibilities:	Final assembly, labeling, and packaging of finished drug product (single dose pen-injector for semaglutide) Quality control of finished drug product: Physical testing Stability testing Quality control and storage of printed packaging materials Storage of bulk product Storage of finished drug product Storage of printed packaging materials

Inspectional History
An analysis of the firm's inspection history over the past 2 years:

- Inspection was conducted 1/8/2018 to 1/12/2018. The inspection covered drug CGMP and was classified NAI.
- An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.
- N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:

- A post-approval inspection is required because:

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

- An inspection is not required because Choose an item.

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	Sub-suppliers of device components: Developing design specifications of (b) (4) assembly of finished drug product (single dose pen-injector for semaglutide) Facility maintaining the design history file for (b) (4) assembly of finished drug product

	Manufacturing of Components Pre-assembly [redacted] (b) (4) assembly Quality control of the material and components used for [redacted] (b) (4) assembly Quality control of [redacted] (b) (4) assembly: Physical testing Storage of raw materials Storage of components Storage of [redacted] (b) (4) assembly

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☐ Inspection was conducted 2/16/2016 to 2/19/2016. The inspection covered medical device QS and was classified NAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A post-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because Choose an item.

4.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☐ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☐ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☐ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☐ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☐ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☐ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☐ No ☐ UNK

cGMP Risk:
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.
☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.

Reviewer Comment

FEI 1000158576

- the facility is not registered and listed
- Since the facility has a history of getting classified as NAI and the last date of inspection was 3 years ago, post approval inspection is recommended.
- Upon review of the EIR, there were no issues. As this device is a low risk product and the facility has a history of getting NAI recommendations, we are okay with recommending post-approval inspection for this facility.

FEI (b) (4)

- While this facility hasn't been reviewed since 2016, the quality of the components from this facility is assured by facility 576 in the acceptance of the components and the release testing.

4.4. Filing Review Conclusion

FILING REVIEW CONCLUSION
Acceptable for Filing: ☐ Yes ☐ No (Convert to a RTF Memo) ☐ N/A
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☐ N/A **Site(s) needing inspection: FEI 1000158576, FEI** (b) (4)
Reviewer Comments Post-Approval inspection is needed for both indicated facilities. For FEI 1000158576, the last inspection was done 3 years ago and FEI (b) (4) the last inspection was completed 5 years ago.
Refuse to File Deficiencies: ☐ Yes ☐ No ☐ N/A **74-Day Letter Deficiencies:** ☐ Yes ☐ No ☐ N/A

5. LABELING

5.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	X		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments
Indications for use is included in "What is TRADENAME" section of (b) (4): "an injectable prescription medicine used for adults with obesity or excess weight who also have weight related medical problems to help them lose weight and keep it off. TRADENAME should be used with a reduced calorie meal plan and increased exercise"

Routes of administration for infusion: "for subcutaneous use"

Treatment population: "It is not known if TRADENAME is safe and effective for use in children under 18 years of age"

Use environment not indicated. – Storage condition is indicated but "for home or clinical use" is not noted. Resolved

5.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments CDER requested the identified IR be sent during the OND labeling team review; CDRH agreed. However, the IR was never sent and upon further discussion it was decided that the explicit indication of "home use" is not necessary. Further review of the labeling indicates that it meets the labeling requirements of the guidance document on Design Considerations for Devices Intended for Home Use.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

6. DESIGN CONTROL SUMMARY

6.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Bioequivalence Study utilized to-be-marketed device			X
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments

6.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Activation Force	(b) (4)
Needle extension	
Injection Time	
Dose Accuracy	(b) (4) for 0.5 mL volume variants for 0.75 mL volume variants

Reviewer Comments

6.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	N/A

Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Y
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

6.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

7. RISK ANALYSIS

7.1. Risk Management Plan

A Product Risk Management Summary Report was submitted. The summary report indicates the risk identification process, summaries methods of identifying error and characteristics related to safety of the device and it includes a summary of System Risk Analysis.

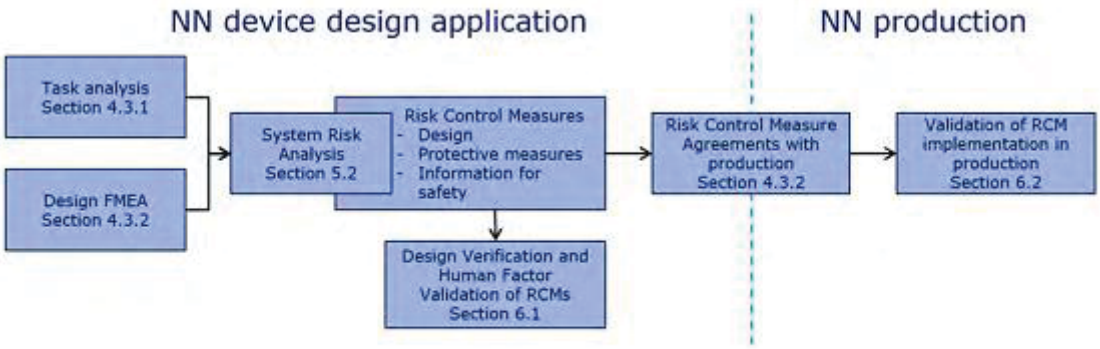


Figure 1 Novo Nordisk risk information flow from risk identification to risk control measures implemented

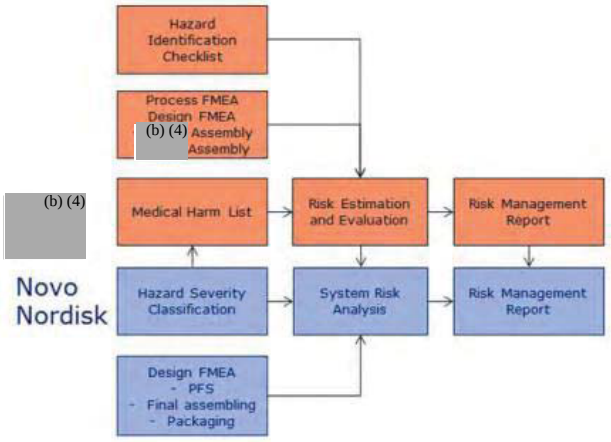


Figure 2 Overview of the safety risk management documents for (b) (4) and Novo Nordisk and their interfaces

Summary of SRA (from Summary report)

The SRA was indicated to consist of 3 parts: part one covering the inherent risks associated with using the single dose pen-injector, part two covering the use errors and part three covering the technical errors. Use error risks are indicated to be identified using the Task Analysis, a hazard and operability analysis method and an iterative usability process. The use error risks as indicated to have identified design risk control measures to the single dose pen-injector, User Communivation and Neutral Packaging. Part three covers failure risks where the failure modes identified in the design FMEAs and the Risk Estimation and Evaluation are used as causes of the risk on system level.

No SRA report was included in the submission. No analysis of actual hazardous situations is included in the report other than the list of overall residual risks included below. The report references validation reports and Human Factors reports. The HF report includes Appendix A which consists of an extract from the SRA that indicates use-related risk scenarios from the SRA.

Overall Residual Risk (from Summary report)

Overall residual risk related to the use of the single dose pen-injector is described in the following table and is based on the SRA.

Table 2 List representing overall residual risk for the single dose pen-injector

Title of risk Sequence of event	Risk Control Measures (RCMs)	Comments
User cannot differentiate pen/sales cartons User cannot differentiate between different sales cartons/single dose pen-injectors and picks up a single dose pen-injector containing wrong drug type. Root causes identified to being both use and technical related. User proceeds with the injection, even if the single dose pen-injector requires different handling steps than the intended single dose pen-injector (e.g. attachment of needle is required) OR no difference in handling, but very unlikely that the wrong drug leads to a Serious adverse event with fatal outcome. The harm is classified as a Serious adverse event with fatal outcome and the risk is found to be reduced to As Far As Possible in the System Risk Analysis.	**Design measures:** RCM1011: The device and packaging shall be designed to be differentiable **Protective Measures:** RCM2011: The production of the system shall ensure that both the device and label contain the correct differentiation features. **Information for safety:** RCM9006: The user communication shall instruct the user to check if the correct product is chosen	The Human Factors Engineering report (see 5.3.5.4 Human Factors Engineering Report (UT228)) concludes that the differentiation of the sales carton and single dose pen injector is reasonably safe and effective for the intended users.

Title of risk Sequence of event	Risk Control Measures (RCMs)	Comments
Children exposed to small loose part The single dose pen-injector Cap is a small loose part and if Cap or single dose pen-injector is left within reach of children below 3 years it can result in the Cap being swallowed. Root causes identified to be use related. Respiration is hindered, and it leads to suffocation. The harm is classified as a Serious adverse event with fatal outcome and the risk is found to be reduced to As Far As Possible in the System Risk Analysis.	**Design measures:** RCM1019: The device/sales carton shall be designed to minimize the possibility of causing suffocation **Information for safety:** RCM9014: The user communication shall instruct the user how to dispose the device RCM9018: The user communication shall instruct the user to keep the device away from children	The introduced mitigations reduce the risk as far as possible following state of art by adhering to e.g. ISO 11608-1:2014 [4]. In addition, it is generally acknowledged that medical and pharmaceutical products should be kept away from children. The risk is therefore considered to be low.
Container Closure Integrity broken prematurely The container closure integrity at the Cap is broken prematurely OR the drug is microbial contaminated prior to use. The patient is exposed to microbial contaminated drug. The root causes identified as both use and technical related. Patient receives microbial contaminated drug. This leads to a microbial infection and the harm is classified as a Serious adverse event without fatal outcome and the risk is found to be reduced to As Far As Possible in the System Risk Analysis.	**Design measures:** RCM1005: The device shall allow for visual inspection of the drug. RCM1021: The system shall be fully functional after it has been subjected to intended Novo Nordisk lifetime of system, temperatures, vibrations, transportation pressures and mechanical loads and no leakage must occur affecting the sterility of the needle/drug. RCM1029: The device shall prevent the cap from detaching when exposed to vibrations or free falls. **Protective Measures:** RCM2012: The production of the system shall ensure that the container closure integrity at the needle end will not be compromised prematurely. RCM2013: The device production shall ensure that the device is produced to contain a window as intended. RCM2022: The production of the prefilled syringe shall ensure that the drug is not bacterially contaminated. **Information for safety:** RCM9003: The user communication shall instruct the user to visually inspect the drug. RCM9026: The user communication shall inform the user to wait with removing the Cap until just before injection.	The design, production and information for safety all contain risk mitigations to minimize this risk, the risk is found to be reduced as far as possible.
Handling error of activated single dose pen-injector results in underdosing	**Design Measures:** RCM1014: The device shall be designed to have a maximum injection time of 10 seconds. **Information for safety:** RCM9012: The user communication shall instruct the user to hold the device pressed against the skin until dosing is complete.	The Human Factors Engineering report (see 5.3.5.4 Human Factors Engineering Report (UT228)) concludes that the handling of the pen injector is reasonably safe and effective.

Title of risk Sequence of event	Risk Control Measures (RCMs)	Comments
User is unable to correctly perceive the dosing feedback from the single dose pen-injector, resulting in the single dose pen-injector being lifted from the skin before dosing is complete. OR User performs the injection using a skinfold, but incorrectly, and during the single dose pen-injector activation the user loses the grip of the skinfold and the needle does not stay in skin during the entire injection. The root causes identified as use related. The single dose pen-injector expels the rest of the drug outside the skin and patient receives an underdose. The harm is classified as No medical consequence and the risk is found to be reduced to As Far As Possible in the System Risk Analysis for repeated instances.		
Needle based injection leads to injection site reactions The single dose pen-injector is used as intended and the needle is inserted into the skin. The needle induces an injection site reaction at the injection site. This is identified as an inherent risk based on the single dose pen-injector design of using a needle as route of administration. Pain, haematoma and injection site reactions is classified as a non-serious adverse event and the risk is found to be reduced to As Far As Possible in the System Risk Analysis.	**Protective measures:** RCM2020: The production of the prefilled syringe shall ensure that the shape and length of the needle is as intended and that the needle will not disengage from the prefilled syringe.	The production and design of the needle have reduced the risk as far as possible.

From the HF Report

Five levels of severity were identified to classify user tasks. A critical task is defined as a user task which, if performed incorrectly or not performed at all, would or could cause harm to the patient or user (S3, S4 or S5).

Table 6 Definition of severity class

No medical consequence		With medical consequence		
S1	S2	S3	S4	S5
Dissatisfaction of quality expectation	Discomfort or loss of non-significant functionality or quality of the device	Non-serious adverse event	Serious adverse event without fatal outcome	Serious adverse event with fatal outcome

Prioritization of critical tasks

User tasks related to use error with risk severity of S4-S5 were classified priority 1 (highest priority).
User tasks related to use error with risk severity of S3 were classified priority 2 (tasks that are required for the user to receive his/her dose)
User tasks related to use error with risk severity of S1-S2 were classified priority 3
For some tasks no system failure effect or deviation was identified for any potential use error so no severity was associated with the task (severity class N/A). This was classified priority 3

Table 7 List of steps and test priority based on severity

Condition	Step to test	Severity class* from SRA (9)	Test priority based on severity	Final test priority
Differentiation - User does not receive the correct drug due to mix up				
Steps are performed at dispensing, e.g. at the pharmacy or at home	Step 1/2: Pick the correct carton/pen-injector (Pharmacists, only carton)	S5 (S3 for mix-up of drug strengths)	1	1
	Step 3: Determine dose size (Pharmacists, only cartons)			
Handling - The user does not administer the injection as intended (all user groups except pharmacists tested)				
Steps are performed during handling at e.g. home/healthcare facilities (not pharmacies)	Step 4: Open and take out a pen-injector/the labelling	S2	3	2
	Step 5: Open and read the relevant parts of the labelling	N/A	3	3
	Step 6: Perceive used/unused pen-injector elements	S2	3	3
	Step 7: Remove cap from pen-injector	S3	2	2
	Step 8: Position needle cover against desired injection site	N/A**	3	3
	Step 9: Activate pen-injector by pressing the needle cover against injection site	S4 (cross contamination) S2 (underdose)	1	1
	Step 10: Keep pen-injector against skin with the needle inserted until dose is complete	S4 (cross contamination) S2 (underdose)	1	1
	Step 11: Retract the pen-injector	N/A	3	3
	Step 12: Dispose pen-injector	N/A	3	3

*The test priority is based on the worst-case scenario severity of the potential use errors of each task.
**Per FDA request Novo Nordisk has included the analysis of step 8 in Appendix A.

Reviewer Comments
Concerns regarding the Human Factors study were communicated from the DMEPA reviewer. The following concerns were noted from the HF Study:

- ***Increased force required to administer an injection when holding pen-injector at angle.*** *The IFU depicts an illustration of the pen-injector being injected at a 90-degree angle and does not explicitly state that users cannot administer an injection if the pen-injector is held at an angle other than 90 degrees. One participant who referenced the IFU when administering a simulated injection, held the pen-injector at a slightly less than 90-degree angle, which therefore required her to use more force to activate the injection than needed when the peninjector is held at a 90-degree angle. The additional force led her to adjust her grip, which provided a change in pressure on the pen-injector. This change in pressure resulted in an unexpected needle deployment,*

which caused the participant to lift the pen-injector from the injection cushion slightly and consequently engage the needle cover, thereby resulting in an incomplete simulated injection.

- ***Pen-injector mechanics require constant firm grip.*** *The pen-injector mechanics require users to hold the pen-injector down fully with a firm grip for the entire duration of the injection. Loosening grip on the pen-injector can cause the needle cover to engage. As such, two participants inadvertently engaged the needle cover prematurely, resulting in an underdose.*

After conversations with Rumi Young (AD) it was decided that neither concern indicated above are device design related. A 90-degree injection angle is standard and does not raise any safety concerns regarding design. Additionally, outer diameter of the device (b) (4) is reasonable and would not raise device design concerns that could relate to the HF issue indicated. The HF reviewer was notified and agreed that the labeling already indicates the 90 degree administration angle so no further interaction is needed with the sponsor.

7.2. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

8. DESIGN VERIFICATION REVIEW

8.1. Performance/Engineering Verification

8.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Accuracy	Fill Volume 0.5mL (b) (4) Fill Volume 0.75 mL: (b) (4)	95%/97.5% (Standard atmosphere, cool storage and warm atmosphere) 95%/95% (free fall and vibration tests) (See Test Method Table 1)	N	Y Accelerated shelf life to (b) (4) months (TBM formulation) Cool atmosphere: 5°C±3°C Warm Atmosphere: 40°C±2°C	Y
Cap Removal Force	(b) (4) Midcycle Deficiency #3 Resolved	95%/95%	N	N	N
Activation Force	(b) (4) Midcycle Deficiency #4 Resolved	95%/95%	N – see note Resolved Y	Y Accelerated shelf life to (b) (4) months (TBM formulation) Cool atmosphere: 5°C±3°C Warm Atmosphere: 40°C±2°C	Y
Needle Extension	(b) (4)	95%/97.5%	Y – see note	Y Accelerated shelf life to (b) (4) months (TBM formulation) Cool atmosphere: 5°C±3°C	Y

				Warm Atmosphere: 40°C±2°C	
Needle Extension at start of injection	(b) (4)	95%/95%	N	N	N
Needle Cover Override, Deflection, after Activation	(b) (4) Midcycle Deficiency #5	95%/99% Not acceptable – see notes	N	N	N
Injection Time	(b) (4)	95%/95%	Y	Y Accelerated shelf life to (b) (4) months (TBM formulation) Cool atmosphere: 5°C±3°C Warm Atmosphere: 40°C±2°C	Y

Reviewer Comment

- No audible/visual feedback requirement – necessary per ISO 11608-1. Midcycle Deficiency #2
  - Resolved Visual and audible feedback available
- Cap removal force max limit (b) (4) is too high. Midcycle Deficiency #3
  - Resolved Spec lowered (b) (4)
- Activation force max limit (b) (4) is too low. Midcycle Deficiency #4
  - Resolved Spec validated
- Needle Cover Override force (b) (4) is too low. Midcycle Deficiency #5
  - Resolved Spec raised (b) (4)
- Bracketing and bridging strategies were used for performance testing and for shelf-life testing
  - Bracketing approach – finished product variants are chosen to give evidence for performance of other variants.
    - Results from Semaglutide 2.0 mg/ml variant indicated as representative of other 0.5 ml volume variants containing Semaglutide 2.0 mg/ml and Semaglutide 1.0 mg/ml. The 2.0 mg/ml drug product is that with the highest concentration in the 0.5 ml filling volume
    - Results from Semaglutide 3.2 mg/ml variant indicated as representative of other 0.75 ml volume variants containing Semaglutide 2.27 mg/ml. The 3.2 mg/ml drug product is that with the highest concentration in the 0.75 ml filling volume
  - Bridging approach – data is leveraged from a comparable formulation "semaglutide C". The difference between semaglutide C and the to-be-marketed senaglutide devices are the (b) (4) used in each. Semaglutide C uses (b) (4) and the to-be-marketed semaglutide uses (b) (4). Justification for the use of Semaglutide C is that the density and viscosity values for the two formulations are similar.

- Design verification was conducted on the above design inputs per ISO 11608-1 and ISO 11608-5
- Needle extension was validated by literature experience for validation of depth and route of injection.
- Dose accuracy is not validated clinically but it is noted that clinical data supports that drug is being delivered, with results in circulating drug levels proportionate to the intended dose. Midcycle Deficiency #9 Resolved
- The sponsor referred to their Human Factors Study as validation for their activation force and injection time specifications. This information is not adequate to validate their specifications aside from dose accuracy since the device used in HF studies would not perform at the specification limits only at the nominal. Validation of activation force is discussed in Midcycle Deficiency #3 (Resolved). Despite the HF issues noted by DMEPA regarding the need to hold/compress the device actively, injection time is within normal limits so validation is not needed
- Stability testing and Shipping/Transportation testing are not conducted for cap removal force, needle extension or needle cover override. Midcycle Deficiency #8 Resolved
  - Accelerated shelf-life equivalent to (b) (4) months was conducted on the to-be-marketed Semaglutide formulation
- The Needle Cover Override was verified demonstrating a sample size of 60 devices met the acceptance criteria (b) (4). This method is not acceptable. Midcycle Deficiency #6
  - Resolved Updated verification analysis

8.1.2. *Evaluation of Test Methods*

Title:	Dose Accuracy
Scope/Objective & Acceptance Criteria:	Fill Volume 0.5mL 2.0mg/mL: (b) (4) (1mg, 0.5mg variants) Fill Volume 0.75 mL, 3.2 mg/mL (b) (4) (2.4mg, 1.7mg, 0.25mg variants)
Methods	Weighing was used to assess dose accuracy. Each dose was collected through a closed system that could gather and weigh the expelled drug product. The single dose pen-injector for semaglutide was fixed vertically and connected to the system where the activation and injection process could be observed. Sample size: N=60 Pre-conditions: Standard atmosphere (23°C±5°C, 50%RH ± 25%RH) – n=60 Cool atmosphere (5°C±3°C) – n=60 Warm atmosphere (40°C±2°C, 50%RH ± 10%RH) – n=60 Dry Heat Storage (5°C±3°C instead of 70°C as this is the highest acceptable storage temperature stated in IFU (b) (4) (b) (4) – n=60 storage (5°C±3°C instead of -40°C as this is the highest acceptable storage temperature stated in IFU (b) (4) (b) (4) – n=60 Free fall – n= 30-59 Vibration – n=20

Results:	Pass
Conclusions/ Reviewer Comments:	This test was conducted on Semaglutide C not on the to-be-marketed device. Performance testing was conducted in various pre-conditions listed above. Both Heat Storage and Cool Storage environments were set to the storage temperature of 5°C±3°C with the justification that this is both the highest and lowest acceptable storage conditions stated in the IFU. This is not acceptable. Midcycle Deficiency #7. Resolved Accelerated shelf-life equivalent to (b) (4) months was conducted on the to-be-marketed Semaglutide formulation. Testing was conducted for two environmental conditions: Cool atmosphere: 5°C±3°C and Warm Atmosphere: 40°C±2°C. This is not acceptable. Midcycle Deficiency #8. Resolved
Acceptable:	☐ **Yes** ☐ **No**

Title:	Performance Testing
Scope/Objective & Acceptance Criteria:	Dose Accuracy: Fill Volume 0.5mL: (b) (4) Fill Volume 0.75 mL: (b) (4) Cap Removal Force (b) (4) Activation Force: (b) (4) Needle Extension: (b) (4) Needle Extension at start of injection: (b) (4) Needle Cover Override, Deflection, after Activation: (b) (4) Injection Time: (b) (4)
Methods	Pre-conditions: Standard atmosphere (23°C±5°C, 50%RH ± 25%RH) – n=60 Cool atmosphere (5°C±3°C) – n=60 Warm atmosphere (40°C±2°C, 50%RH ± 10%RH) – n=60 Dry Heat Storage (5°C±3°C instead of 70°C as this is the highest acceptable storage temperature stated in IFU (b) (4) (b) (4)) – n=60 Cool storage (5°C±3°C instead of -40°C as this is the highest acceptable storage temperature stated in IFU (b) (4) (b) (4)) – n=60 Free fall – n= 30-59 Vibration – n= 20-30
Results:	Pass
Conclusions/ Reviewer Comments:	These tests were conducted on Semaglutide C not on the to-be-marketed device.

	Performance testing was conducted for various pre-conditions. Both Heat Storage and Cool Storage environments were set to the storage temperature of 5°C±3°C with the justification that this is both the highest and lowest acceptable storage conditions stated in the IFU. This is not acceptable. Midcycle Deficiency #7. Resolved Accelerated shelf-life equivalent to (b) (4) months was conducted on the to-be-marketed Semaglutide formulation. Testing was not conducted on all EPRs such as cap removal force, needle extension and needle cover override. This is not acceptable. Midcycle Deficiency #8. Resolved
Acceptable:	☐ **Yes** ☐ **No**

Reviewer Comment
For full comments on resolved deficiencies, see sections below.

Insert Additional Design Verification Table

8.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: 3/12/2021	**Date/Sequence Received:** 3/25/2021
Information Request #2	Device performance was evaluated per ISO 11608-1 and ISO 11608-5. The test report provided in *Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time – Single Dose Pen-Injection for Semaglutide* does not include any testing conducted on audible/visual feedback for your device. Your device should have a requirement for audible/visual feedback which indicates clear requirements regarding loudness of the audible feedback (in decibels) and accuracy (+/- x seconds) from the end of injection. Please update your performance requirements to incorporate this audible feedback and provide updated testing to verify the devices performance for these new requirements.	
Sponsor Response	Novo Nordisk has developed the single dose pen-injector with the visual parameter (i.e. a [redacted] (b) (4) filling the inspection window) as the indicator of the end of dose: • in alignment with ISO 11608-1 section 5.5h ("*The NIS shall indicate by visual, audible or tactile means, or any combination of these, that the injection stroke has been completed*"). • as the 'persistent' confirmation of completion of the automated injection, in alignment with ISO 11608-5:2015 section 4.3.4. ("*The NIS-AUTO shall provide confirmation of completion of the automated injection in an unmistakable and clear manner. Such confirmation shall be at least a persistent visual indication… Note: additional tactile and/or audible indicator(s) may be included.*"). The visual parameter has been specified in the design requirements and has been attribute verified (see Table 1). In addition to the visual feedback, audible feedback has also been implemented: a first click indicating the start of injection and a second click indicating progress of the injection. These supporting audible indicators have also been specified in the design requirements and inspected during design verification (see Table 1).	

Table 1 Requirements and results for visual and audible feedback for the single dose pen-injector

Requirement text	Purpose for the requirement	Design verification method	Design verification results
The device shall include a window allowing for visual inspection of the drug	So that the user can verify the drug quality before injection	Attribute Testing – Visual inspection of design	Pass
After injection the (b) (4) (b) (4) shall fill the inspection window	Visual confirmation of complete injection. So that the user will know when the device has been used		Pass
First click There shall be an audible click at the beginning of the injection stroke	To help ensure that the user knows when the injection begins	Attribute Testing – Audible inspection of design during functionality testing performed by a trained technician	Pass
Second click There shall be an audible click close to the end of the injection stroke	To help ensure that the user knows when the injection is close to the end		Pass

Table 2 IFU text demonstrating that the visual feedback confirms the *completion* of the injection stroke

Text on the proposed IFU	Image on the proposed IFU
	(b) (4)

Table 3 IFU text demonstrating that the audible feedback indicates beginning and progression of the injection stroke

Text on the IFU	Image on the IFU
	(b) (4)

Defining requirements for loudness of the audible feedback (in decibels) and accuracy (+/- x seconds) from the end of injection would not be aligned with the supportive function of this design feature due to the following context:

- Loudness: By verifying the detectability of the click sounds in a simulated home-use setting by trained technicians, it is documented that the design fulfils its purpose of being able to provide supporting feedback to the progress of injection.
- Accuracy of second click: since the second click is intended to support the feedback of the progress of injection, there is no added value in prescribing how accurately this sound is emitted within the course of injection.
- Accuracy of visual end of dose confirmation: (b) (4) movement stop after full injection does not have an uncertainty.

It is therefore Novo Nordisk's position that the attributive verification by inspection is appropriate.

Reviewer Comments

In accordance to ISO 11608-1-2014, either visual or audible feedback is required to indicate the completion of an injection. The subject device has the required visual feedback feature as indicated above. Concerns over possible confusion between the clicks indicating complete dose was brought up to DMEPA. The following indicates the communications with DMEPA review Jason Flint's response in red text:

> *The sponsor notes two audible clicks for the device during administration: the first click indicating the start of injection and a second click indicating progress of the injection. Our concern is that the second click may be interpreted as the end of dosing while in reality the user needs to continue holding pressure on the device until the dose is complete. The instructions indicate "* (b) (4) (b) (4) *". This leads to the visual feedback concern that the bar may not always be visible during injection.*

	Were there any HF issues with these features/ was there any discussion of this in the risk analysis for the use of the product?
	
	- *7 out of 75 users raised the AI prematurely because they thought the injection was complete.*
	  o *Confusion with first click: One user reported that they heard the *first* click and lifted the AI.*
	  o *Confusion with second click: The report does not indicate that users thought their injection was complete because of hearing a second click. Note that doesn't necessarily mean that the second click didn't play a role, but that it wasn't reported as such. I think they would have reported any issues related to the auditory feedback though (the applicant reported such instance with the first click).*
	- *4 users activated the needle safety guard prematurely, which we discussed previously.*
	- *Primary root causes identified for underdoses included test artefact (3 participants) and negative transfer (4 participants). There was one user that cited auditory feedback (as discussed above), but that was related to the first click, not the second.*
	
	Would you agree that there should be some evaluation of "time to end of dose" after the second click to mitigate possible confusion?
	
	- *We do note that the IFU includes a timing indication:*  *. The applicant included how long each participant held the AI in place, and for most of the instances of underdose, the AI was held for 2 seconds or less, and users recognized their errors. I have attached an excel file with the timing data. There appears to be a small learning effect, though we did not reference that explicitly in our final review.*
	
	Within the response, it is indicated that during all underdose scenarios, including the single instance where the first audible feedback was confused for completed dose, the user held the AI in place for less than the recommended injection time of 5-10 seconds. Given the audible feedback is an additional feature that is not required along with the feedback from DPEMA, the lack of the requirement regarding the loudness (in decibels) and accuracy (+/- x seconds) from the end of injection is acceptable.
	
	Novo Nordisk's position that the attributive verification by inspection is appropriate is acceptable.

Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #3	Performance requirements were indicated and tested in the document *Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time – Single Dose Pen-Injection for Semaglutide.* The upper limit (b) (4) for Cap Removal Force is too high. Validation testing is not performed for this specification. If the cap removal force is too high, the user cannot access their medication and deliver the dose. Please indicate how this specification was validated. If you intend to use anthropometric data to validate your specification, ensure the postures and motions are representative of cap removal force and analyze that data assuming your weakest (5th percentile females) per HE 75 to validate this upper limit specification. Alternatively, adjust your cap removal specification (b) (4). Provide updated design verification testing reports demonstrating your device meets this new specification.	
Sponsor Response	Novo Nordisk confirms that the specification limit for cap removal of the single dose pen-injector for semaglutide will be updated (b) (4) The results presented in the design verification report in 3.2.P.7 Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time – Single Dose Pen-injector for Semaglutide comply with the updated limit (b) (4). An extract of the design verification report is shown in Table 4.	

Table 4 Cap removal force according to ISO 11608-1 conditions for semaglutide C 3.2 mg/ml (0.75 ml single dose pen-injector variant)

	Sample size	Precondition[2]	Acceptance criteria[3]	Results (N)	Conclusion
Single dose pen-injector with semaglutide C[1]	60	• Standard atmosphere, 23°C ± 5°C, 50% RH ± 25% RH	(b) (4)		Pass
	60	• Cool atmosphere, 5°C ± 3°C			
	60	• Warm atmosphere, 40°C ± 2°C, 50% RH ± 10% RH			
	30	• After free fall from 1.0 m			
	20	• After vibration			

[1] Tests performed at (b) (4) on batches as reported in 3.2.P.7 Test Report According to EN ISO 11608-1, EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and Test Report for Injection Time, Table 12

[2] Preconditions based on ISO 11608-1, Table 3. Cold storage reflects the intended storage of the product. Warm storage is excluded, as the maximum storage temperature is 5°C ± 3°C.

[3]The original report has an upper limit of (b) (4) The data presented on this table uses the updated upper limit of (b) (4)

[4]Two-sided tolerance limits are described by confidence: 95%, probability content, p: 95%.

Novo Nordisk confirms that product specification for cap removal force will be implemented by change controls as part of the quality management system and that the design verification report will be updated accordingly.

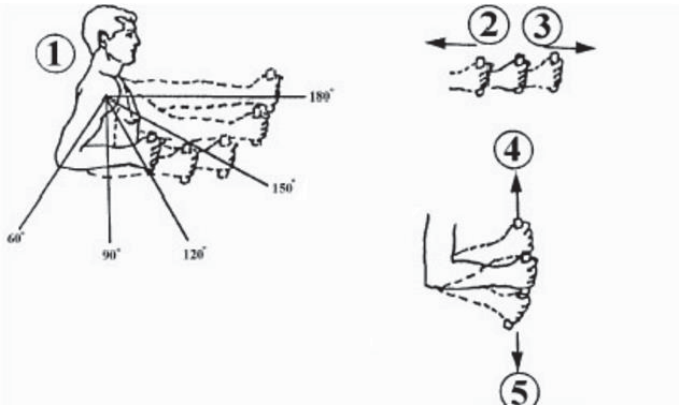
Reviewer Comments The cap removal force specification was updated to have an upper limit of (b) (4) instead of (b) (4). The response above indicates that the original verification test shows results that this the device already complies with the new force. The table above was updated to include the new (b) (4) upper limit; this is acceptable.

Response Adequate: ☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: 3/12/2021	**Date/Sequence Received: 3/25/2021**
Information Request #4	Human Factors testing was provided to validate the (b) (4) activation force upper limit. This method of validation of Essential Performance Requirements is not acceptable. Devices used in Human Factors studies would not perform at the specification limits, only at the nominal performance. Please provide data validating the limits of the proposed specifications for Activation Force. If the activation force is too high, the user cannot deliver the dose. Therefore, provide anthropometric data using postures and motions representative of activation force and analyze that data assuming your weakest (5th	

	percentile females) per HE 75. If your analysis results in a new specification, provide updated design verification testing reports demonstrating your device meets this new specification.
Sponsor Response	Novo Nordisk confirms that the upper limit of (b) (4) for activation force is validated by reference to anthropometric data according to ANSI/AAMI HE75:2009, which provides human strength data for the upper extremities. As part of the analysis performed for the use of the single dose pen-injector, a pull movement towards the upper body is considered the best representation of a typical injection. If the maximum force that can be exerted by the arm in a pull movement with a 60º elbow flexion (worst case) is (b) (4) (according to Table 7.7 in ANSI/AAMI HE75:2009), Novo Nordisk has defined the following adjustments with the purpose of accommodating for the strength of both genders and to avoid complaints (see section 7.3.5.1c and 7.3.5.2a in ANSI/AAMI HE75:2009) (b) (4) where, (b) (4) is factored into the calculations to account for the difference between males and females at the lower capabilities (5th percentile females) the additional factor (b) (4) is chosen as a safety margin to ensure even people with reduced strength may operate the pen-injector. Thus, according to the calculation, an activation force limit specified to be (b) (4) or less would be considered acceptable for the requirement. Accordingly, the selected upper limit of (b) (4) is supported by the anthropometric data according to ANSI/AAMI HE75:2009. This justification for the specification can be found in 3.2.P.7 Analysis of Functional Performance and Control Strategy, Table 2.
Reviewer Comments	A pull movement towards the upper body is not representative of activation force for a pen injector. There is no adequate justification for this be a representative motion for this force specification. This is not acceptable.
Response Adequate:	☐ **Yes** ☐ **No, See IR #13 Sent on 4/6/2021**

Follow-On Deficiency	**Date Sent: 4/6/2021**	**Date/Sequence Received: 4/9/2021**
Information Request #13	In Section 2.3.1 of *Response to FDA IR dated March 12, 2021*, the upper limit of (b) (4) for activation force is validated using pull movement towards the upper body. This is not acceptable as pull movement towards the upper body is not representation of activation force. Please provide anthropometric data using postures and motions representative of activation force. Analysis of appropriate postures and motions is necessary to adequately validate this performance requirement. Please note that if your analysis results in a new specification, you should also provide updated design verification testing reports demonstrating your device meets this new specification.	
Sponsor Response	Novo Nordisk would like to present an analysis of the appropriate postures and motions for the purpose of identifying the requirement limits for activation force for the single dose pen-injector. This analysis is done with reference to the postures presented in the human factors engineering standard ANSI/AAMI HE75:2009 [1] (Figure 1). **Figure 1 ANSI/AAMI HE75:2009, extract for arm control (section 7.3.5.3)**	



According to ANSI/AAMI HE75:2009, the upper extremity strength evaluation should account for differences in posture, especially of the elbow, shoulder and wrist. The interpretation for the motions shown in Figure 1 is as follows:

- The degree of elbow flexion (denoted by ① in Figure 1) sets the basis for the different levels of strength. Where the angle adopted for injection is between two angles in the standard, the weakest angle of the two is selected as the baseline.
- The motions pull-push (denoted by ② and ③ in Figure 1) are pictured as a movement along an imaginary horizontal axis.
- The motions up-down (denoted by ④ and ⑤ in Figure 1) are pictured as a movement along an imaginary vertical axis.

For the use of the single dose pen-injector, the wrist remains in a locked position.

Analysis of the appropriate postures and motions

To aid in the analysis of the appropriate postures and motions, the photographs in Figure 2 and Figure 3 show a person injecting with a single dose pen-injector in the stomach and upper legs. These are the two injection sites indicated in the instructions for use (IFU) that are primarily used during self-injection.

Injection into the upper arm is expected to be an injection site used by healthcare providers. Healthcare providers will use a range of positions and motions that can optimize their strength compared to self-injection. Therefore, the analysis of self-injection into the stomach and upper legs represents a more challenging use scenario.

Injection into the stomach

Figure 2 Analysis of postures and motions for using the single dose pen-injector into the stomach

Note: the single dose pen-injector is not intended to be used to inject through clothing.

The photograph on the left depicts the degree of elbow flexion of 60° (① in Figure 1). The middle and right photographs provide an example of self-injection when the pen-injector is placed at the stomach. The single dose pen-injector is activated by pulling the single dose pen-injector towards the stomach, a movement resulting from the combined rotation of the shoulder and bending of the elbow. This is therefore the primary motion denoted as a "pull" motion (② in Figure 1).

Calculations with a "② pull" motion for injection into the stomach

The calculations according to the "pull" motion (② in Figure 1) presented in the document 3.2.P.7 Analysis of Functional Performance and Control Strategy and referenced in the Novo Nordisk response submitted on March 25, 2021 to the March 12, 2021 FDA Information Request (question 3 - Device) used the lowest value for the "pull" movement at a 60° elbow flexion in HE75 as the arm strength baseline ([(b) (4)] marked with a light blue box in the ANSI/AAMI HE75:2009 extract shown in Table 1 below).

[(b) (4)]

Injection into the upper leg

Figure 3 Analysis of postures and motions for using the single dose pen-injector into the upper leg

Note: the single dose pen-injector is not intended to be used to inject through clothing.

The photograph on the left depicts the degree of elbow flexion of 90° (① in Figure 1). The middle and right photographs provide an example of self-injection when the pen-injector is placed on the upper leg. The single dose pen-injector is activated by pushing the single dose pen injector down towards the upper legs, a movement resulting from the slight increase of the elbow flexion. This is therefore the primary motion denoted as a "down" motion (⑤ in Figure 1).

Calculations with a "⑤ down" motion for injection into the upper leg

In addition to the information presented in the document 3.2.P.7 Analysis of Functional Performance and Control Strategy and referenced in the Novo Nordisk response submitted on March 25, 2021 to the March 12, 2021 FDA Information Request (question 3 - Device), Novo Nordisk would like to present calculations for the "down" motion.

These calculations are also based on the strength data according to ANSI/AAMI HE75:2009 (see Table 1). The arm strength within the degree of elbow flexion for the upper leg injection site derived from the analysis in Figure 3 is marked with a green box.

Table 1 Arm strength for "② pull" (stomach injection) and "⑤ down" (upper leg injection) motions according to ANSI/AAMI HE75:2009

Degree of elbow flexion	(2) Pull		(5) Down	
	Left	Right	Left	Right
180º	[redacted] (b) (4)			
150º				
120º				
90º				
60º				

NOTE 1—Force is given in N (pounds).

The maximum strength that can be exerted using the weakest arm when the elbow flexion is 90º (see Figure 1) when performing an "down" motion is [redacted] (b) (4) (for the worst-case 5th percentile strength to males, see Table 1). Therefore:

[redacted] (b) (4)

where,
• in accordance to the ANSI/AAMI HE75:2009, the male values should be reduced to [redacted] (b) (4) of the male strength to account for female strength values of the upper extremities (5th percentile females)
• the additional factor [redacted] (b) (4) is chosen as a safety margin to ensure even people with reduced strength may operate the pen-injector.

Conclusion
According to the calculations provided in this response, Novo Nordisk confirms that the upper limit of activation force for the single dose pen-injector of [redacted] (b) (4) is acceptable.
In the event that a user would not be able to activate the single dose pen-injector, the risk of being unable to activate the single dose pen-injector is further minimized by the user being able to optimize their strength by either choosing their dominant arm or assisting themselves with the second arm. In a real-life scenario, it is expected that users will choose the dominant arm, as well as optimize their position for strength and control.

Reviewer Comments	The response to the follow up deficiency elaborated on the representation of the pull motion for activation force – it is representative of injection into the stomach. Since there are two injection sites (stomach and thigh) for this AI, an additional analysis was provided on the injection force for the thigh. The analysis includes using down force for males at 90 degrees. According to

	ANSI/AAMI HE75:2009, to adjust the strengths to account for females the force should be reduced by 50%-60% for medical devices intended for use solely by females. The sponsor reduced the force by 43.5% (b) (4) however they also went a step further to reduce the force by an additional factor (b) (4) to ensure even people with reduced strength would be able to operate the device. With the additional reduction factor (b) (4) the down motion force equates to (b) (4). Since the sponsor performed a further reduction that was not required, this estimation to (b) (4) is acceptable; without the further reduction (b) (4). If this value were to be the maximum limit for the specification, it would exceed benchmark values therefore the (b) (4) is more appropriate. This is acceptable.
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: **4/23/2021**	**Date/Sequence Received:** **4/27/2021**
Information Request #5	Performance requirements were indicated and tested in the document *Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time – Single Dose Pen-Injection for Semaglutide.* The proposed specification of (b) (4) for Needle Cover Override appears too low to mitigate the risk of accidental needle sticks. Provide data validating this specification. If the Needle Cover Override force is too low, the user can override the safety mechanism resulting in accidental needle sticks.	
Sponsor Response	The single dose pen-injector includes a lock-out feature to prevent accidental needle sticks with a used needle. The limit of this feature is specified in accordance with ISO 11608-5:2012 section 5.1.11.2: "*it shall withstand a minimum load as determined by the risk assessment (at least two times its actuation force)*". By specifying a minimum needle cover lock force (b) (4) that is at least two times the maximum activation force (b) (4) the two forces are considered to be adequately distinguishable from one another. Two use scenarios are considered for evaluating how the needle cover override force would mitigate the risk of accidental needle sticks: • Scenario 1: A user intends to use a single dose pen-injector, however the single dose pen-injector has already been used. The user tries to activate the single dose pen-injector and experiences a higher activation force than normally experienced. • Scenario 2: A user does not intend to use a single dose pen-injector. However, they accidentally handle a used single dose pen-injector in a way that they could interact with the needle cover and thereby the needle. In both use scenarios, the needle cover lock force of (b) (4) is considered to be adequately distinguishable from the activation force. For the performance of the needle cover override force, please see the response to FDA request 5.	
Reviewer Comments	With the validation of the (b) (4) activation force, the justification of the (b) (4) needle cover lock force is not acceptable . The standard notes this spec should be "at least" two times the maximum activation force. In this case, 2x the max activation force is still within normal adult capabilities and could lead to retraction of the cover if the user is unaware the device is used. The specification should be raised.	

Response Adequate:	Yes	No, See IR # Sent on 4/23/2021

Follow-On Deficiency	Date Sent: 4/23/2021	Date/Sequence Received: 4/26/2021
Information Request #16	In section 2.4.1 of your response to our March 12, 2021 information request, you justify the (b) (4) needle cover override force by noting that ISO 11608-5:2012 states that the needle cover *"shall withstand a minimum load as determined by the risk assessment (at least two times its actuation force)"*. Please note that the standard says "at least" two times the activation force. The purpose of this specification is to mitigate the risk of accidental needle sticks. As such, the specification for this performance requirement should be determined by assuring it is higher than an adult user's strength capabilities. The current (b) (4) force specification is well within the adult populations capabilities as demonstrated by the anthropometric study used to evaluate the activation force specification. Please increase the needle cover override force specification. Provide data verifying the device performance to this new specification. If the Needle Cover Override force is too low, the user can override the safety mechanism resulting in accidental needle sticks.	
Sponsor Response	Novo Nordisk will increase the needle cover deflection specification by defining the applied force for data analysis to (b) (4) The needle cover deflection specification represents the performance of the needle cover override force, when measuring deflection at a specified applied force. This new specification limit is supported by a risk assessment, presented in section 2.2.1, which considers the user strength and pain-perception capabilities, as well as the two scenarios presented as part of a previous answer to the Agency (Response to FDA Request dated April 23, 2021, Request 4). Finally, Novo Nordisk will present the re-analysis of the provided design verification data based on the new specification limit at a confidence interval of 95% and a probability content of 99% after preconditioning according to ISO 11608-1 conditions and after accelerated aging (section 2.2.2). **Risk assessment for the choice of applied force of (b) (4)** Novo Nordisk will present different arguments supporting the acceptability of the updated applied force of (b) (4) in the needle cover deflection specification. • Section 2.2.1.1 presents the considerations that are generally applicable (user group considerations) • Section 2.2.1.2 presents the considerations that are scenario-specific. The two scenarios presented in this answer correspond to the scenarios presented as part of a previous answer to the Agency (Response to FDA Request dated April 23, 2021, Request 4). **General arguments** The following general arguments support the acceptability of the updated applied force of (b) (4) in terms of the user group's strength capabilities: • The user will not apply their maximum force As per AAMI/ANSI HE75:2009, Section 7.3.5.1 'Factors affecting strength' [1], '*It is seldom appropriate to expect people to exert their maximum strength*' in their interaction with medical devices. Additionally, a stronger user of the single dose pen-injector is expected to apply a smaller proportion of their maximum strength when operating the	

device than a weaker one, resulting in a similar absolute force being applied.

- Obesity patients are not expected to be stronger on upper extremities used for overriding a locked device
  Although there are studies proposing that the obese population is stronger than the population of healthy weight, such studies are contested and are generally associated to lower extremities [2]. The general strength of the obese user-group is therefore not expected to exceed that of the general population for the muscles needed to override the needle cover lock in the two scenarios described in section 2.2.1.2.

Scenario-specific argumentations

The following arguments support the acceptability of the updated applied force of (b) (4) in terms of specific scenarios:

1. Scenario 1: Pushing a locked device against the skin
2. Scenario 2: Handling a used single dose pen-injector and accidentally interacting with the needle cover

Scenario 1: Pushing a locked device against the skin

Table 1 shows an evaluation of the applied force limit and the resulting static pressure on the skin, when a user intends to inject with a used single dose pen-injector. The table also estimates pain perception, by calculating how a force equal to the limit specified in the needle cover deflection specification is related to pain onset for the patient.

The pressure-pain threshold is defined as the point at which a sensation of pressure changes into a sensation of pain [3]. The pressure pain threshold is typically given in kg/cm2 and in some publications, Pascals (conversion factor equivalent to the gravitational acceleration of 9.81 m/s2). Depending on the place on the body, the pressure pain threshold ranges from 2 kg/cm2 to 4.5 kg/cm2 [3][4]. The pressure pain threshold range is also dependent on the presence of other diseases, on gender [3] and, potentially, body mass index. A further assumption for pain considerations is that the user will avoid injecting into nerves/bone, associated with lower pain thresholds [5].

The assessment presented in Table 1 uses the pressure pain threshold values on healthy female subjects of Montenegro *et al.*, 2012 [6] as a reference for injections into the abdomen. The abdomen as the place for measurement is considered relevant for the intended use of the single dose pen-injector. The highest reported pressure pain threshold level for the abdomen is 2.93 kg/cm2. The value of 2.93 kg/cm2 is therefore taken as a baseline to determine the expected pain onset experienced by the patient.

For the single dose pen-injector the contact area between the skin and the device is that of the front of the needle cover. The needle cover is ring-shaped, with an outer diameter of (b) (4) and inner diameter of (b) (4) Therefore, the resulting contact area for the front of the needle cover is (b) (4). Using the contact area and the specified needle cover deflection force (both the original and the value updated as part of this response) the calculation of pressure on the skin is given in Table 1 in kg/cm2.

An example of the calculation of the pressure on the skin for an increased specification of (b) (4) is presented below:

$$Pressure\ on\ the\ skin = \frac{Increased\ specification\ in\ \mathrm{N}}{Needle\ cover\ surface\ area} \times conversion\ \mathrm{N}\ to\ \mathrm{kg}$$

(b) (4)

Table 1 Evaluation of the excess force confirmed for two proposed applied forces for the needle cover deflection test and the associated pressure on the skin and expected pain/discomfort

Condition	Comparison to the specified upper activation force limit (b) (4)	Comparison to the nominal activation force (b) (4)	Calculated pressure** on the skin from applying the specified force limit	Ratio of pressure pain threshold (baseline is 2.93 kg/cm²)***
Initial limit (b) (4)	(b) (4)			
Updated limit (b) (4)				

* In line with the minimum requirement in ISO 11608-5 ("*at least two time the actuation force*")
** Conversion factor between kg/cm² and SI pressure units (Pascal) uses the gravitational acceleration as (b) (4)
***Reported as the Pressure-Pain Threshold, based on pain perception algometry measurements on women with a healthy weight

Table 1 shows that:

- The proposed updated limit of (b) (4) will guarantee a needle cover override function that is at least (b) (4)-times higher than the activation force upper limit (around (b) (4) times higher than the nominal value of (b) (4) The updated limit of (b) (4) will therefore guarantee an additional increase in the distinguishability between the activation force and the needle cover override force, compared to the original proposed limit.
- The calculated pressure is used to determine a ratio against a described pressure-pain onset value of 2.93 kg/cm2 [6]. According to these calculations, the updated limit of (b) (4) would result in a sensation of pain that is approximately (b) (4) times higher than the reported threshold level of pressure-pain onset on the abdomen of healthy women. The conclusion from this ability to cause pain with a locked device is that the user would stop pressing in order to observe the state of the device, as a response to the unexpected pain.

Scenario 2: Handling a used single dose pen-injector and accidentally interacting with the needle cover

When analysing a scenario where a user handles a used single dose pen-injector in a way that could accidentally leads to interaction with the needle cover, these movements would be understood as clumsy/uncoordinated motions. These motions would result in lower force compared to the deliberate force that is expected when intending to activate the device.

Evaluation of the provided data to the increased specification for the needle cover override force measured as deflection

The results from measurement of the needle cover deflection have been re-analyzed for an applied force of (b) (4) The data are reported in Table 2 and Table 3. The data are reported including a full statistical summary (mean, standard deviation, min, max, *p*-value, *k*-value) and the corresponding upper tolerance value.

Therefore, the needle cover override force intended to prevent the re-use of a used single dose pen-injector (see Scenario 1) will be sufficient to mitigate the risk posed by accidental contact with the needle cover during handling.

Table 2 Needle cover override, deflection, according to ISO 11608-1 conditions for semaglutide C 3.2 mg/ml (0.75 ml single dose pen-injector variant)

Test item	Sample size	Test condition[2]	Acceptance criteria[3]	Results (mm)	Conclusion
Single dose pen-injector with semaglutide C[1,4]	60	Standard atmosphere, 23°C ± 5°C, 50% RH ± 25% RH		(b) (4)	Pass
	60	Cool atmosphere, 5°C ± 3°C			
	60	Warm atmosphere, 40°C ± 2°C, 50% RH ± 10% RH			
	60	Cold storage final device			
	30	After free fall from 1.0 m			
	20	After vibration			

[1] Tests performed at (b) (4) on batches as reported in 3.2.P.7 Test Report According to EN ISO 11608-1, EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and Test Report for Injection Time, Table 15

[2] Preconditions based on ISO 11608-1, Table 3. Cold storage reflects the intended storage of the product. Warm storage is excluded, as the maximum storage temperature is 5°C ± 3°C.

[3]One-sided tolerance limits are described by confidence: 95%, probability content, p: 99%

[4]The data generated on the 0.75 ml single dose pen-injector using the semaglutide C formulation covers both the 0.5 ml and 0.75 ml variant, as this feature is independent of the drug product formulation and fill-volume.

Table 3 Needle cover override, deflection, after accelerated shelf-life equivalent to [redacted] months for semaglutide C 3.2 mg/ml (0.75 ml single dose pen-injector variant)

Test item	Sample size	Test conditions	Acceptance criteria[3]	Results (mm)	Conclusion
Single dose pen-injector with semaglutide C[1,3]	60	Standard atmosphere, 23°C ± 5°C, 50% RH ± 25% RH after accelerated shelf-life conditions corresponding to storage at (b) (4) at 5°C ± 3°C and (b) (4) at 23°C ± 5°C, 50% RH ± 25% RH		(b) (4)	Pass

[1] Tests performed at (b) (4) on drug product batch no. HW52W68

[2]One-sided tolerance limits are described by confidence: 95%, probability content, p: 99% (k-factor: 2.807)

[3]The data generated on the 0.75 ml single dose pen-injector using the semaglutide C formulation covers both the 0.5 ml and 0.75 ml variant, as this feature is independent of the drug product formulation and fill-volume.

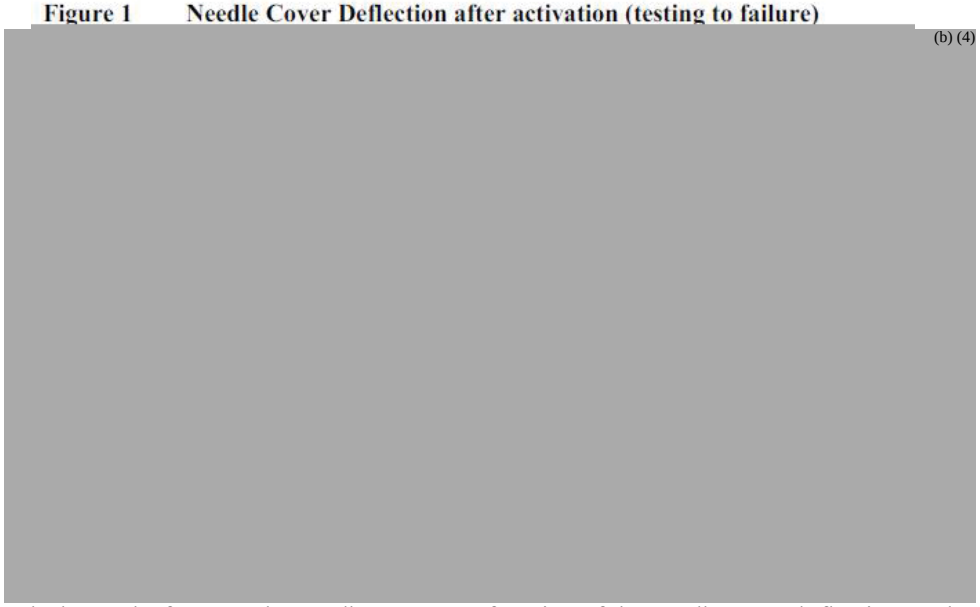
Conclusion

Novo Nordisk will increase the needle cover deflection specification by defining the applied force for data analysis to (b) (4) The needle cover deflection specification represents the performance of the needle cover override force, when measuring needle cover deflection at a specified applied force.

	The proposed updated limit of (b) (4) will guarantee a needle cover override force that is at least (b) (4) -times higher than the activation force upper limit and around (b) (4) times higher than the nominal value of (b) (4) The updated limit of (b) (4) will therefore guarantee an additional increase in the distinguishability between the activation force and the needle cover override force, compared to the original proposed limit. In addition, calculations based on a limit of performance documented at an applied force of (b) (4) indicate that pushing a locked device into the skin would likely result in pain above a pressure pain threshold. The expectation under such a scenario is that the user would stop pressing in order to observe the state of the device, as a response to the unexpected pain. The conclusion from a risk assessment regarding the use of a force of (b) (4) in the needle cover deflection test is supported by the expected intended use and users of the single dose pen-injector, including potential re-use of a locked device (Scenario 1 in 2.2.1.2) or accidental contact with the needle cover during handling (Scenario 2 in 2.2.1.2). Additionally, Novo Nordisk has re-analyzed the design verification test data based on the new specification limit of (b) (4) at a confidence interval of 95% and a probability content of 99% after preconditioning according ISO 11608-1 conditions and after accelerated aging. From the data presented, it is concluded that the single dose pen-injector complies to the new specification limit. Based on the risk assessment in 2.2.1 and the device performance during design verification shown in 2.2.2, the proposed updated specification for the needle cover deflection is adequate to additionally mitigate the risk of accidental needle sticks. Thus, Novo Nordisk confirms that the needle cover deflection specification will be implemented by change controls as part of the quality management system.
Reviewer Comments	The Needle Cover Override force was updated to (b) (4) instead of (b) (4). A risk assessment for the choice of (b) (4) was provided: General Argument Comments: The needle cover is a safety device intended to prevent patients from accidentally exposing the needle after a completed injection. The general arguments presented that the user will not apply their maximum force or the assumption that obese user-group is not expected to exceed that of the general population is not validated. Anthropometric data provided in the injection force validation indicates that adult users can exert strengths up to (b) (4). Scenario-specific Arguments Comments: Scenario 1: Pushing a locked device against the skin – pain threshold levels for the abdomen on healthy females are presented. From the data, the highest reported pressure pain threshold level of the abdomen (2.93 kg/cm^2) is taken as the baseline to determine the expected pain onset experienced by the patient. The pressure of the needle cover on the skin is calculated using the new (b) (4) specification, needle cover surface area and the conversion factor of N to kg. This is also done for the old (b) (4) specification. The conclusion is drawn that the updated limit will result in a sensation of pain approximately (b) (4) times higher than the reported threshold of pressure-pain onset on the abdomen of healthy women. A final note is made that the (b) (4) force is (b) (4) times greater than the upper limit activation force of (b) (4) and therefore there is an increased distinguishability between the activation force and the needle cover override force.

	These analyses are not appropriate validation methods of this new specification. The specification is not evaluate likelihood of a user overriding the needle cover based on the discomfort it may cause them or the notable increased force it takes compared to a normal injection; the force should be evaluated on the users ability, are users able to override the force or is it out of their strength capabilities. Scenario 2: Handling a used single dose pen-injector and accidentally interacting with the needle cover – it is noted that the scenario where a user would handle a used device in a way that could interact the needle cover is one which a user is acting clumsy/uncoordinated and that these movements would result in lower force strengths compared to deliberate forces. This is again an assumption based rational. No validating data is provided to support this claim. Despite the lack of acceptable validation for this new specification, together with reinforcements that the device is has been used by visual feedback and the acceptability of HF reports, the raised Needle Cover Override force specification to (b) (4) is acceptable. Verification: (b) (4) Though the sponsor did not provide Kact values themselves, based on my calculations the values are well within the acceptance criteria. This is acceptable.
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: **3/12/2021**	**Date/Sequence Received:** **3/25/2021**
Information Request #6	You provided performance verification data for needle cover override force demonstrating that a sample size of 60 devices met the acceptance criteria of (b) (4) needle cover deflection at an applied force of (b) (4) Your method for evaluating needle cover override force after injection is not appropriate because rather than measuring needle guard override	

	force, the specification measures and analyzes the displacement of the needle guard after (b) (4) is applied, which is a PASS/FAIL (attribute) acceptance criteria. Therefore, N=60 is an insufficient sample size to demonstrate a minimum 95%/99% confidence and reliability recommended for needle safety features per FDA guidance Medical Devices with Sharps Injury Prevention Features (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-devices-sharps-injury-prevention-features-guidance-industry-and-fda-staff) to mitigate the risk of accidental needle sticks. Provide data on an appropriate sample size, demonstrating that a minimum 95%/99% attribute sample size meets the acceptance criteria (b) (4) for needle cover override force up to the proposed shelf life real time or accelerated aging). Alternatively, you can test needle cover override force to failure and analyze the data as variable data type.
Sponsor Response	Novo Nordisk would like to elaborate on the performance verification data from needle cover deflection at an applied force of (b) (4). The test method used to generate the data in Figure 1 applies a force on the needle cover until failure (see Figure 1 for data and method description). The results in 3.2.P.7 Test Report According to EN ISO 11608-1, EN ISO 11608-5 and JIS T 3226-2 Needle Based Injection System for Medical Use and Test Report for Injection Time only report on the deflection measured a (b) (4) according to the specifications. Since the needle cover deflection reported at the applied force of (b) (4) is a data-point on the measured force curve, the data are variable. The sample size of 60 is therefore sufficient to demonstrate the needle safety feature with a minimum 95%/99% confidence and reliability. **Figure 1 Needle Cover Deflection after activation (testing to failure)**  (b) (4) The graph shows the force on the needle cover as a function of the needle cover deflection on the single dose peninjector. From the needle cover lock deflection onset the graph indicates a monotonic relation between the force applied and the deflection at or around of (b) (4) For each of the samples tested, the needle cover is compressed until the needle cover lock is overridden. Only ten samples measured from the single dose pen-injector from drug product batch HW52W68 are shown in this graph. The results reported for deflection in the design verification report are those corresponding to an applied force of (b) (4) The specification limit is shown at (b) (4). The results from measurement of the needle cover deflection distance when a force of (b) (4) is applied are reported in Table 5 and Table 6. The specified deflection distance of (b) (4) is defined to ensure that the needle tip does not come into contact with a finger covering the

shield opening. It includes an additional margin, to allow for a finger to be closer to the needle than a flat plate as described in the test method in ISO 11608-5, section 5.1.11.2: "*If the NIS-AUTO includes a lock-out feature, it shall withstand a minimum load as determined from the risk assessment (at least two times its actuation force), which shall be applied to the surface around the opening of the NISAUTO using a flat plate. The plate dimensions shall be larger than the NIS-AUTO profile so that the application of the force onto the surface around the opening is entirely within the plate. Under the application of this load, the needle tip shall not touch the flat plate*." The results in Table 5 present results at the time of initial verification testing the single dose pen-injector; Table 6 presents the results after accelerated shelf-life preconditioning. The data are reported including a full statistical summary (mean, standard deviation, min, max, *p*-value, *k*-value) and the corresponding upper tolerance value.

Table 5 Needle cover override, deflection, according to ISO 11608-1 conditions for semaglutide C 3.2 mg/ml (0.75 ml single dose pen-injector variant)

Test item	Sample size	Test condition[2]	Acceptance criteria[3]	Results (mm)	Conclusion
Single dose pen-injector with semaglutide C[1,4]	60	Standard atmosphere, 23°C ± 5°C, 50% RH ± 25% RH	(b) (4)		Pass
	60	Cool atmosphere, 5°C ± 3°C			
	60	Warm atmosphere, 40°C ± 2°C, 50% RH ± 10% RH			
	60	Cold storage final device			
	30	After free fall from 1.0 m			
	20	After vibration			

[1] Tests performed at (b) (4) on batches as reported in 3.2.P.7 Test Report According to EN ISO 11608-1, EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and Test Report for Injection Time, Table 15

[2] Preconditions based on ISO 11608-1, Table 3. Cold storage reflects the intended storage of the product. Warm storage is excluded, as the maximum storage temperature is 5°C ± 3°C.

[3] One-sided tolerance limits are described by confidence: 95%, probability content, p: 99%

[4] The data generated on the 0.75 ml single dose pen-injector using the semaglutide C formulation covers both the 0.5 ml and 0.75 ml variant, as this feature is independent of the formulation and fill-volume.

Table 6 **Needle cover override, deflection, after accelerated shelf-life equivalent to (b) (4) months for semaglutide C 3.2 mg/ml (0.75 ml single dose pen-injector variant)**

Test item	Sample size	Test conditions	Acceptance criteria[3]	Results (mm)	Conclusion
Single dose pen-injector with semaglutide C[1,3]	60	Standard atmosphere, 23°C ± 5°C, 50% RH ± 25% RH after accelerated shelf-life conditions corresponding to storage at (b) (4) at 5°C ± 3°C and (b) (4) at 23°C ± 5°C, 50% RH ± 25% RH	(b) (4)		Pass

[1] Tests performed at (b) (4) on drug product batch no. HW52W68

[2]One-sided tolerance limits are described by confidence: 95%, probability content, p: 99% (k-factor: (b) (4)

[3]The data generated on the 0.75 ml single dose pen-injector using the semaglutide C formulation covers both the 0.5 ml and 0.75 ml variant, as this feature is independent of the formulation and fill-volume.

Reviewer Comments

The sponsor elaborates on their method of analysis in the response above. They indicate that their original report did analyze the data as variable data type as they provided the mean, std, min/max and kvalue. The only data missing was the k-act calculation. The sponsor instead compared the mean to the USL which is an unclear analysis. Instead of interacting to have the sponsor provide Kact values, I completed the calculations myself below:

(b) (4)

Though the sponsor did not provide Kact values themselves, based on my calculations the values are well within the acceptance criteria.

This evaluation was redone for the higher (b) (4) spec in the Review Comments of Information Request #16.

Response Adequate: ☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: 3/12/2021	**Date/Sequence Received:** 3/25/2021

Information Request #7	Device performance was evaluated per ISO 11608-1 and ISO 11608-5. The test report provided in *Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time – Single Dose Pen-Injection for Semaglutide* indicates that the Dry Heat storage pre-condition was conducted at 5°C ± 3°C instead of 70°C and the Cool Storage Pre-Condition test was also conducted at 5°C ± 3°C instead of -40°C. Justification for these condition changes was that the storage condition of 5°C ± 3°C is proposed in the instructions for use, making it both the highest and lowest acceptable storage condition for the device. This justification is not acceptable. Per ISO 11608-1, functional testing must be conducted on the device for pre-conditions of Dry Heat Storage conditions of 70°C ± 2°C, of 50 ± 10% RH and Cool Storage conditions of -40°C ± 3°C. Please re-verify your device performance to these testing conditions and provide updated test reports.
Sponsor Response	Novo Nordisk acknowledges the reference to ISO 11608-1 and would like to clarify that the single dose pen injector for semaglutide belongs to the system designation D1 of pen-injectors ("*Needlebased injection device with an integrated non-replaceable container. Each container holds a single dose, whereby the entire deliverable volume is expelled*"). In accordance with ISO 11608-1 section 10.6, "*system designations C and D that are manufacturer-filled shall be subjected to preconditioning at the acceptable high and low storage temperatures, which shall be stated in the instructions for use*". This means that functional testing at dry-heat (70±2 °C, 50±10 % RH) and cold storage -40±3°C is not applicable for a system designation D1 device. As the single dose pen-injector is a drug-device combination product, it will follow the storage conditions of the semaglutide drug product. The drug-device combination product must comply with the drug product specification, specifying storage conditions of 5 °C ± 3 °C and in-use time of 28 days below 30 °C. On the basis of the temperature restrictions imposed by the drug product requirements, the functional testing at the conditions specified in ISO 11608-1 section 10.6 (dry-heat 70 °C ± 2 °C, 50 ± 10 % RH and cold storage -40 °C ± 3 °C) is not applicable for the single dose pen-injector for semaglutide. The dry-heat and cold-storage temperatures are replaced by the acceptable high and low temperature conditions as presented in the instructions for use. The instruction for use for the to-be-marketed single dose pen injector for semaglutide instructs the users "to store the pen injector in the refrigerator between 36°F to 46°F (2°C to 8°C)" and that the pen injector "may be stored (b) (4) 46°F to 86°F (8°C to 30°C) in the original carton for up to 28 days", see IFU extract in Figure 2. **How do I store TRADENAME?** · Store the TRADENAME pen in the refrigerator between 36°F to 46°F (2°C to 8°C). · Keep TRADENAME in the original carton to protect it from light. · If needed, TRADENAME may be stored (b) (b) (4) 46°F to 86°F (8°C to 30°C) in the original carton for up to 28 days. **Figure 2 Extract of the instruction for use stating the storage conditions of the single dose pen-injector for semaglutide.** Additionally, the single dose pen-injector has been tested after (b) (4) (b) (4) the single dose pen-injector have been

	exposed to -40°C ± 3°C and 55 ± 2°C, 50 ± 10 %RH to enhance product knowledge. After storage, the [redacted] (b) (4) assembled with syringes and tested at room temperature (23 ± 5°C) on the single dose pen injectors for semaglutide. The single dose pen-injector assembled [redacted] (b) (4) stored at these conditions complied with the requirements for activation force, needle extension, injection time, dose accuracy, cap removal force (without syringe) and needle cover override force. As part of this response, Novo Nordisk is providing additional data [redacted] (b) (4) [redacted] (b) (4) after storage at -40°C ± 3°C and 55 ± 2°C and 50 ± 10 %RH, which can be found in Table 7, Table 8, Table 9, Table 10, Table 11 and Table 12.
Reviewer Comments	The sponsors justification for evaluating device performance for cool and warm atmospheres only, not including dry-heat and cold storage pre-conditions is acceptable. Given the D1 designation of the device, these pre-conditions are not required and therefore no further data is needed.
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: 3/12/2021	**Date/Sequence Received:** 3/25/2021
Information Request #8	Stability and Shipping/Transportation testing data is provided in *Device Functional Test Report – Single Dose Pen-Injector for Semaglutide* for Activation Force, Needle Extension, Injection Time and Dose Accuracy. This testing is not conducted on Cap Removal Force or Needle Cover Override Forces. Additionally, the test conditions for this stability testing are only conducted in the following environmental conditions: Cool atmosphere: 5°C±3°C and Warm Atmosphere: 40°C±2°C. Stability and Shipping/Transportation testing needs to be conducted on all design attributes for all conditions tested in *Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time – Single Dose Pen-Injection for Semaglutide.* Please provide the following: • Stability and Shipping/Transportation Testing for all design attributes: Activation Force, Needle Extension, Injection Time, Dose Accuracy, Cap Removal and Needle Cover Override • Ensure that the testing is based all conditions outlined in ISO 11608-1 including the Dry Heat and Cool Storage Pre-Conditions as outlined in Deficiency #7.	
Sponsor Response	Novo Nordisk would like to clarify that the selection of test conditions presented in 3.2.P.7 Device Functional Test Report for Stability and for Shipping/Transportation testing are considered to comply to the current industry practice based on ISO 11608-1 and to using a risk-based approach when selecting conditions for performance testing. The single dose pen-injector demonstrated robust performance during the initial design verification and during the selected conditions under stability in terms of compliance towards the requirement. Novo Nordisk has explored some of the conditions below to enhance product knowledge. Therefore, the additional conditions tested and presented here are considered to go beyond the standard practice outlined in ISO 11608-1 for manufacturers. This response is structured around the two different types of testing requested by the Agency – stability testing (2.7.1.1) and transport/shipping testing (2.7.1.2). The summary of the data generated in the course of the development of the single dose pen-injector and of the additional data being provided as part of this response is collected in the matrix in Table 13.	

Table 13 Summary of testing for essential performance requirements and other design attributes in the single dose pen-injector

Type of precondition	Testing during initial design verification	Testing at the end of shelf life	Testing after transport simulation
Operating temperature (cool atmosphere, standard atmosphere, warm atmosphere)	All ISO 11608-1 conditions tested for essential performance requirements[1] and other design attributes[2]	All ISO 11608-1 conditions tested for essential performance requirements[1] Standard atmosphere for other design attributes[2]	Standard atmosphere tested for essential performance requirements[1]
Storage temperature	Storage defined as 5°C±3°C, according to IFU of the single dose pen-injector tested for essential performance requirements[1] Justification for the storage conditions of 5°C±3°C is presented in request 6	Storage defined as 5°C±3°C, according to IFU of the single dose pen-injector tested for essential performance requirements[1]	Justified under "Transport/shipping testing" (see 2.7.1.2)
Mechanical impact (free fall, vibration)	All ISO 11608-1 conditions tested for essential performance requirements[1] and other design attributes[2]	All ISO 11608-1 conditions tested for essential performance requirements[1]	Justified under "Transport/shipping testing" (see 2.7.1.2)

[1]Essential performance requirements: activation force, needle extension, injection time, dose accuracy

[2]Other design attributes: cap removal force, needle cover deflection after activation

Stability testing

As part of this response, Novo Nordisk is providing the additional data collected in Table 14.

Table 14 Stability data test overview for additional testing presented in this response

Design attribute	Test condition	Data location
Activation force	Standard atmosphere Free Fall Vibration Storage defined as 5°C±3°C, according to IFU	Table 15
Needle extension		Table 16
Injection time		Table 17
Dose Accuracy		Table 18
Cap removal	Standard atmosphere	Table 19
Needle cover override force		Table 20, as well as in response to request 5

All the new data presented is compliant to the requirement limits for each of the tests and confirms a performance consistent with the data presented in 3.2.P.7 Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time and 3.2.P.7 Device Functional Test Report.

Justification for the testing strategy of the cap removal force

Removing the cap from the single dose pen-injector requires interaction between two interfaces (see Figure 3):

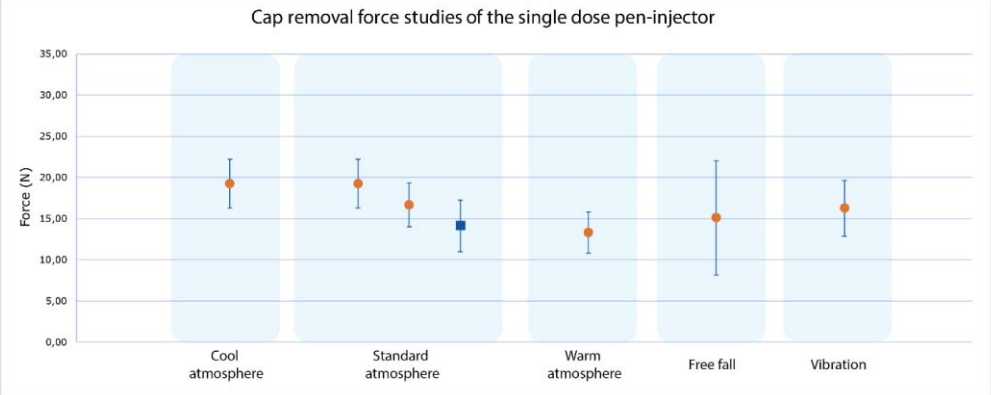
- the interface between the prefilled syringe and (b) (4)
- the interface between the body and cap.

(b) (4)

Figure 3 Interfaces contributing to the cap removal force (marked in red)

Both interfaces may be affected by changes to temperature, due to expansion-contraction of the materials. The main factor that could increase the cap removal force is the (b) (4) (b) (4), with decreased lubrication properties at low temperatures. This is supported by the performance data indicating that cool temperatures are the worst case in terms of cap removal force (see Figure 4). However, even under these conditions the force for removal of the cap is almost unaffected compared to the other temperature conditions.

Figure 4 Cap removal force



The graph shows the performance of cap removal force when tested during the verification studies (orange circles) and after shelf-life (blue square). The conditions are cool atmosphere (5°C ± 3 °C), standard atmosphere (23°C ± 5 °C, 50% ± 25% RH), warm conditions (40°C ± 2 °C, 50% ± 10% RH). The middle condition in the standard atmosphere represents testing at standard atmosphere after cold storage of the device for at least 96h.

Mechanical effects that would cause an increase in cap removal force of the single dose pen-injector will not affect the relevant interface, as supported by the data after vibration compared to standard atmosphere (see Figure 4). It can therefore be concluded that the interfaces are not functionally affected by vibrations.

As presented in 3.2.P.7 Device Functional Test Report, the evidence for cap removal force shows robust performance under the conditions of ISO 11608-1 (see Figure 4). Therefore, testing for cap removal force has been performed at the end of shelf-life at standard atmosphere (Table 19) and has been excluded from testing after transport simulation.

Justification for the testing strategy of needle cover override force, deflection after activation

The activation of the single dose pen-injector leads (b) (4) translates into (b) (4) The needle cover automatically extends to cover the needle when single

dose pen-injector is pulled away from the skin. (b) (4)

(b) (4)

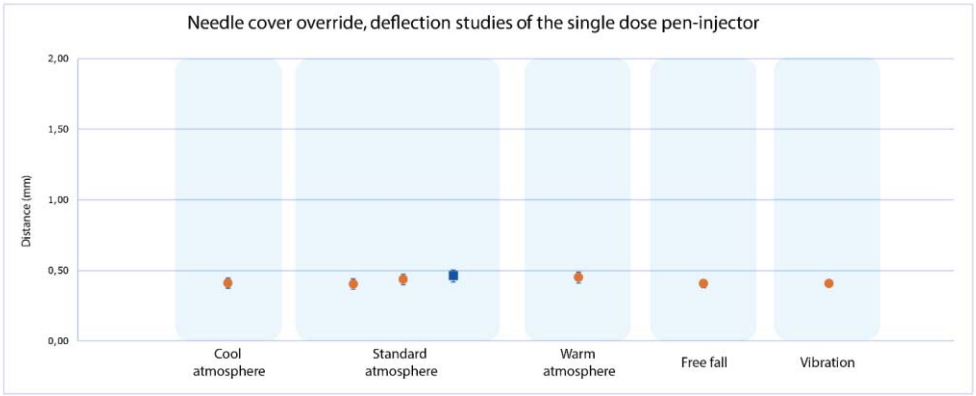
Two of the preconditions of ISO 11608-1 have been considered as potentially most challenging (b) (4) (b) (4):

Vibration: it has been assessed that the repeated impact by vibration may be associated to wear of the (b) (4) parts. However, (b) (4) (b) (4) vibrational preconditions will not cause any wear (b) (4) (b) (4).

Warm atmosphere: it was considered that operation of the device under warm conditions could potentially affect the (b) (4) parts, (b) (4) (b) (4). However, according to the results from operation of the device at warm conditions, the design of the single dose pen-injector shows no worsening in (b) (4) performance when operated up to 40°C ± 2°C, 50% ± 10% RH.

As presented in 3.2.P.7 Device Functional Test Report, the evidence for needle cover override force as measured from deflection after activation shows robust performance under the conditions of ISO 11608-1 (see Figure 6). The confirmation of performance at the end of shelf-life is restricted to one condition (Table 20) and excluded from the panel of tests after transport simulation.

Figure 6 Needle cover override force, deflection after activation



The graph shows the performance of the needle cover override force when tested during the verification studies (orange circles) and after shelf-life (blue square). The conditions are cool atmosphere (5°C ± 3 °C), standard atmosphere (23°C ± 5 °C, 50% ± 25% RH), warm conditions (40°C ± 2 °C, 50% ± 10% RH). The middle condition

in the standard atmosphere represents testing at standard atmosphere after cold storage of the device for at least 96h.

2.7.1.2 Transport/shipping testing

The single dose pen-injector has demonstrated robust performance during the design verification and during stability (see 2.7.1.1), both in terms of compliance towards the requirement and in terms of comparability of results between the conditions. On the basis of this evidence and given its risk profile, evaluation of performance after transport simulation at standard conditions for the essential performance requirements is deemed justified. The information for activation force, needle extension, injection time and dose accuracy is collected in 3.2.P.7 Device Functional Test Report.

As presented in section 2.7.1.1, the potential worst-case conditions for cap removal force and needle cover override force, deflection after activation have been shown to have no impact. Since transport simulation will not increase the potential sources of challenge to the performance of these functions, it is justified to exclude them from testing after transport simulation.

Table 15 Activation force after accelerated shelf life combined with additional ISO 11608-1 conditions

Time Point (Stage)	Pre-conditioning	Fill Volume	Sample Size[1] n	Specification	Test results				Probability Content p	K ISO k_{ISO}	Calculated Tolerance Limit(s) compared to Specification(s) (N)	Result
					Min (N)	Max (N)	Mean $\bar{x}$ (N)	Standard Deviation s (N)				
After accelerated shelf-life equivalent to (b) (4) at 5°C ±3°C and (b) (4) at 30°C ± 2°C, 50% ± 25 % RH	Standard atmosphere	0.5 ml	60	(b) (4)								PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS
	Standard atmosphere	0.75 ml	60									PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS

[1]Tests performed at (b) (4) batch: B000076115 (b) (4) 0.50 mL batch: B000076114, (b) (4) 0.75 mL batch: B000076392 with prefilled syringe batch NZJ0008 (0.50 mL PFS) and JW55R50 (0.75 mL PFS).

Table 16 Needle extension after accelerated shelf life combined with additional ISO 11608-1 conditions

Time Point (Stage)	Pre-conditioning	Fill Volume	Sample Size[1] n	Specification	Test results				Probability Content p	K ISO k_{ISO}	Calculated Tolerance Limit(s) compared to Specification(s) (mm)	Result
					Min (mm)	Max (mm)	Mean $\bar{x}$ (mm)	Standard Deviation s (mm)				
After accelerated shelf-life equivalent to (b) (4) at 5°C ±3°C and (b) (4) at 30°C ± 2°C, 50% ± 25 % RH	Standard atmosphere	0.5 ml	60	(b) (4)								PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS
	Standard atmosphere	0.75 ml	60									PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS

[1]Tests performed at (b) (4) batch: B000076115, (b) (4) 0.50 mL batch: B000076114 (b) (4) 0.75 mL batch: B000076392 with prefilled syringe batch NZJ0008 (0.50 mL PFS) and JW55R50 (0.75 mL PFS).

Table 17 Injection time after accelerated shelf life combined with additional ISO 11608-1 conditions

Time Point (Stage)	Pre-conditioning	Fill Volume	Sample Size[1] n	Specification	Test results				Probability Content p	K ISO k_{ISO}	Calculated Tolerance Limit(s) compared to Specification(s) (s)	Result
					Min (s)	Max (s)	Mean $\bar{x}$ (s)	Standard Deviation s (s)				
After accelerated shelf-life equivalent to (b) (4) at 5°C ±3°C and (b) (4) at 30°C ± 2°C, 50% ± 25 % RH	Standard atmosphere	0.5 ml	60	(b) (4)								PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS
	Standard atmosphere	0.75 ml	60									PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS

[1]Tests performed at (b) (4) batch: B000076115, (b) (4) 0.50 mL batch: B000076114, (b) (4) 0.75 mL batch: B000076392 with prefilled syringe batch NZJ0008 (0.50 mL PFS) and JW55R50 (0.75 mL PFS).

Table 18 Dose accuracy after accelerated shelf life combined with additional ISO 11608-1 conditions

Time Point (Stage)	Pre-conditioning	Fill Volume	Sample Size[1] n	Specification	Test results				Probability Content p	K ISO k_{ISO}	Calculated Tolerance Limit(s) compared to Specification(s) (mL)	Result
					Min (mL)	Max (mL)	Mean $\bar{x}$ (mL)	Standard Deviation s (mL)				
After accelerated shelf-life equivalent to (b) (4) at 5°C ±3°C and (b) (4) at 30°C ± 2°C, 50% ± 25 % RH	Standard atmosphere	0.50 ml	60	(b) (4)								PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS
	Standard atmosphere	0.75 ml	60									PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS

[1]Tests performed at (b) (4) batch: B000076115, (b) (4) 0.50 mL batch: B000076114, (b) (4) 0.75 mL batch: B000076392 with prefilled syringe batch NZJ0008 (0.50 mL PFS) and JW55R50 (0.75 mL PFS).

Table 19 Cap removal force after accelerated shelf life

Time Point (Stage)	Pre-conditioning	Fill Volume	Sample Size[1]	Specification[2]	Test results				Probability Content p	K ISO k_{ISO}	Calculated Tolerance Limit(s) compared to Specification(s) (N)	Result
					Min (N)	Max (N)	Mean $\bar{x}$ (N)	Standard Deviation s (N)				
After accelerated shelf-life (b) (4) at 5°C ±3°C and (b) (4) at 30°C ± 2°C, 50% ± 25 % RH	Standard atmosphere	0.75 ml	60								(b) (4)	PASS

[1]Tests performed (b) (4) batch: B000076115, (b) (4) 0.50 mL batch: B000076114, (b) (4) 0.75 mL batch: B000076392 with prefilled syringe batch NZJ0008 (0.50 mL PFS) and JW55R50 (0.75 mL PFS).

[2]Specification still reported as (b) (4) in the design history file documents until the change request associated to response 2 of this information request is finalized.

Table 20 Needle cover override, deflection after activation after accelerated shelf life

Time Point (Stage)	Pre-conditioning	Fill Volume	Sample Size[1] n	Specification	Test results				Probability Content p	K ISO k_{ISO}	Calculated Tolerance Limit(s) compared to Specification(s) (N)	Result
					Min (N)	Max (N)	Mean $\bar{x}$ (N)	Standard Deviation s (N)				
After accelerated shelf-life at 5°C ±3°C and at 30°C ± 2°C, 50% ± 25 % RH	Standard atmosphere	0.75 ml	60								(b) (4)	PASS

[1]Tests performed (b) (4) batch: B000076115, (b) (4) 0.50 mL batch: B000076114, (b) (4) 0.75 mL batch: B000076392 with prefilled syringe batch NZJ0008 (0.50 mL PFS) and JW55R50 (0.75 mL PFS)

Reviewer Comments

Stability/Shipping data was updated with the following changes:

Stability:

Standard Atmosphere, Vibration and Free Fall preconditions were tested after accelerated aging to (b) (4) months shelf-life (originally only warm atmosphere and cool atmosphere conditions were assessed) for:

- Activation Force
- Needle Extension
- Injection Time
- Dose Accuracy

This is acceptable.

Shipping/Transportation:

Accelerated shelf-life testing to (b) (4) months was conducted for Cap Removal and Needle Cover Override.

Cap Removal

The only pre-condition considered post accelerated aging to shelf-life was standard atmosphere. To justify this decision, the sponsor points to Figure 4 to demonstrate that cap removal is almost unaffected by cool and warm temperatures at T=0 and can be assumed as such at shelf-life as well. Since cap removal is low risk, this is acceptable. To justify the decision not to perform shipping tests the sponsor points to Figure 4 again to show how the device performance is not affected by the vibration pre-condition. Again, since cap removal is low risk, this is acceptable.

Needle Cover Override

The only pre-condition considered post accelerated aging to shelf-life was standard atmosphere. To justify this decision, the sponsor points to Figure 6 to demonstrate that the design of device shows no worsening in locking performance when operated at cool or warm temperatures. This

	is acceptable. To justify the decision not to perform shipping tests, the sponsor indicates that since the needle cover locking mechanism is not activated before use (during shipping), it wont be effected. Vibration pre-conditions were tested and support this as the device performs as expected. This is acceptable.
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: 3/12/2021	**Date/Sequence Received:** 3/25/2021
Information Request #9	In the document *Analysis of Functional Performance and Control Strategy – Single Dose Pen-Injector for Semaglutide* it is indicated that "clinical design validation of dose accuracy tolerances for the single-dose pen-injector is not performed directly, however, clinical data supports that drug is being delivered, with results in circulating drug levels proportionate to the intended dose. No further validation of the single-dose pen-injector is therefore necessary in terms of its ability to deliver an accurate dose". Based on the data provided, it is unclear if the device used during the clinical studies was the to-be-marketed autoinjector. The final finished device needs to be validated for dose accuracy to ensure that users will receive the intended dose of the drug. Please provide further information supporting the final finished product was validated for dose accuracy.	
Sponsor Response	Novo Nordisk confirms that the pen-injector used in the clinical trial NN9536-4590 BE-trial is equivalent to the to-be-marketed autoinjector: The to-be-marketed variant is identical to the clinical single dose pen-injector for semaglutide with respect to principle of operation, predefined specifications and manufacturing processes. Minor colour modification introduced does not impact device performance. The design of the BE trial including its bioequivalence limits, as agreed with the Agency during pre-approval interactions, support that the single dose pen-injector deliver an accurate dose with the intended semaglutide concentration in a clinical setting. Novo Nordisk therefore confirms that the evaluation presented in 3.2.P.7 Analysis of Functional Performance and Control Strategy regarding dose accuracy performance is also applicable to the final finished product. The comparison between the clinical single dose pen-injector for semaglutide and the to-bemarketed single dose pen-injector for semaglutide can be seen in Table 21 (presented as Table 2, 3.2.P.7 Comparison to the approved Ozempic® Pen-Injector).	

Table 21 Comparison of single dose pen-injector for semaglutide used in clinical studies and to-be marketed single dose pen-injector for semaglutide1

Feature	Single dose pen-injector for semaglutide (Clinical version)				Single dose pen-injector for semaglutide (To-be-marketed version)
Appearance (graphics are for illustration purpose only)	(b) (4)				
Labelling	For clinical use only				Approved Tradename
Product type	Pre-filled single dose disposable pen containing a 0.5 ml or 0.75 ml prefilled syringe with semaglutide				The launch version's features and materials are identical to the clinical version, the only difference is the modification made to white color grade chosen for the body of the pen.
Intended use	Once weekly subcutaneous injection of semaglutide				
Indication for use	Incorporates a design containing a 0.5 ml or 0.75 ml syringe to assist in the subcutaneous injection of semaglutide for weight management.				
Where used	Home or in hospital				
Energy used and/or delivered	Manual				
Needle	Integrated hidden (b) (4) needle				
Target population	Adult				
Pen type	Escalation				Maintenance
Dose size	0.25 mg	0.5 mg	1 mg	1.7 mg	2.4 mg
Concentration	0.5 mg/ml	1.0 mg/ml	2.0 mg/ml	2.27 mg/ml	3.2 mg/ml
Dose volume	0.5 ml			0.75 ml	
Primary packaging	Prefillable syringe				
Activation profile	(b) (4) activated				
Click at activation	Yes				
Click during dosing	Yes				
Click at end of dose	No				
Materials (prefillable syringe excluded)	Cap, needle cover and pen body: (b) (4) (b) (4)				
Biocompatibility	ISO 10993-1 Contact with intact skin during handling only				
Number of components	12 (pre-filled syringe with needle excluded)				
Housing colour	White				
Cap colour	Grey				
Functional testing and dose accuracy	According to EN ISO 11608-1:2015 and EN ISO 11608-5:2012.				
Length with cap	(b) (4)				
Diameter					
Anatomical sites for injection	As recommended in the Directions for Use				As recommended in the Instruction for use

Reviewer Comments	It is confirmed that the device used during the clinical study is identical to the final finished product except for the color change made to the body of the pen. This change would not affect device performance. This is acceptable.
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Design Verification Review Section**

8.3. Discipline Specific Sub-Consulted Review Summary

No Additional Discipline Specific Sub-Consults were requested
The following additional Discipline Specific Sub-Consults were requested:

Study Name	Biocompatibility Evaluation Report for (b) (4)
Study Type	Cytotoxicity, Sensitization, Irritation
Objectives/Endpoints	Surface device with prolonged (>24 hrs. to 30 days) intact skin contact
Drug/Device Studied	(b) (4) Clinical Autoinjector (Sensitization and irritation) Commercial Autoinjector (Cytotoxicity)
Number and Type of Subjects	*Cytotoxicity* – n/a *Sensitization* – 34 guinea pigs (11 test, 6 negative control – one set for polar and another for non polar test) *Irritation* – 3 New Zealand White Rabbits
Brief description of protocol	*Cytotoxicity* – MEM method of testing used *Sensitization* – Guinea Pig Maximization Test - polar and non polar extraction (physiological saline and cottonseed oil) – 2 Phases (Induction and challenge) - Magnusson and Kligman scoring system at 24 and 48 hours after the removal of the test article *Irritation* – Intradermal Reactivity Test - polar and non polar extraction (physiological saline and cottonseed oil) – 0.2 mL of test article extract in saline injected at 5 sites anterior to the midline on one side of the spinal column, 0.2 mL of corresponding control injected at 5 sites on other side of spinal column (same process for cottonseed oil but posterior to dorsal midline) – scored at 24 hours, 28 hours, and 72 hours
Results	*Cytotoxicity* (Commercial (b) (4)) – test article showed grade 0 at 24 and 48 hours – no reactivity *Sensitization* (Clinical (b) (4)) – all animals appeared heathy, no sensitization reactions or patterns noted, test animals did not receive scores higher than negative control animals, positive control animals exhibited strong sensitization *Irritation* (Clinical (b) (4)) – saline extract: all animals appeared healthy, overall mean score of test site 0 & control site = 0 ; cottonseed oil extract: all animals appeared healthy, all animals exhibited slight erythema (score of 1) , overall mean score of test site = 1.0 & control site = 1.0 ; all positive control animals exhibited a strong irritation response
Device Related Comments	Clinical and Commercial (b) (4) devices share identical materials, design, and manufacturing processes except the white color of the body and (b) (4) cap. Full CSI tests were conducted on the Clinical (b) (4) device and showed no adverse biological effects An additional cytotoxicity test was conducted on the Commercial (b) (4) device due to the slight difference of white color between the two devices.
Reviewer Comments	Only a summary of the cytotoxicity testing performed on Commercial (b) (4) was provided indicating no reactivity (0 grade at 24 and 48 hours) results. The methods and results of the test are acceptable.
Reviewer Conclusion	Biocompatibility reports from (b) (4) indicate two different devices were used for testing: Clinical (b) (4) and Commercial (b) (4) (cytotoxicity only), with the differences between the two being the white color of the body and (b) (4) cap. Commercial (b) (4) has "*two additional chemicals which only constitute small amounts* (b) (4) *%)*". After communicating this difference with a biocompatibility focal point, Gang Peng, it was

	determined that without knowing the compounds and the quantity of the compounds added, we cannot determine that the addition would not introduce a new biocompatibility risk. Points brought up by Gang: 1) *Even though it's a small ratio, the new chemical may still be toxicologically potent.* 2) *Even if the new chemical itself is not toxicologically potent, it in combination with the rest of the color/device may create new compounds which would be of biocompatibility concern.* **Midcycle Deficiency #10.** Resolved

	Date Sent: Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #10	Biocompatibility of the cap, (b) (4) needle cover, body, and (b) (4) cap components of the pen-injector was assess by (b) (4). and provided in *Biological Evaluation Report – Single Dose Pen-Injector for Semaglutide*. In the summary of the report on page 14 section 8.2 and in the test reports provided by (b) (4) (Appendix H), it is indicated that two different devices were used for testing: Clinical (b) (4) and Commercial (b) (4) (cytotoxicity only), with the differences between the two being the white color of the body and (b) (4) cap. Commercial (b) (4) has "*two additional chemicals which only constitute small amounts (* (b) (4) *%)*". The justification provided that the difference between (b) (4) (b) (4) the white used in the body and (b) (4) cap components of the device being (b) (4) % and therefore insignificant is not acceptable. Even though it's a small ratio, (b) (4) (b) (4) may still be toxicologically potent. Additionally, even if the new chemical itself is not toxicologically potent, it in combination with the rest of the color/device may create new compounds which would be of biocompatibility concern. Please provide the compounds that are additional in the new device and a quantity for each compound added.	
Sponsor Response	Novo Nordisk would like to clarify, which compounds have been added in the device constituent part of the single dose pen-injector for semaglutide (designated "Commercial (b) (4)" by the supplier). For the (b) (4) cap component there are no added compounds. For the body component two compounds are added: (b) (4) The compounds and the exact quantity (given in parentheses) used in the body and (b) (4) cap are presented in Table 22.	

	Table 22 Compounds in the body and (b) (4) cap (b) (4)  With the exception of the specific quantities, this information can be found in the (b) (4). biocompatibility test report presented in appendix H of the 3.2.P.7 Biological Evaluation Report.
Reviewer Comments	Toxicologist Alan Hood was consulted regarding the response from the sponsor to determine acceptability of leveraging Clinical (b) (4) biocompatibility data for Commercial (b) (4) biocompatibility. His response indicated that information provided by the sponsor is still insufficient to determine if the material change could raise irritation or sensitization concerns: *Sure thing. Just for clarification, are Clinical (b) (4) and Commercial (b) (4) the subject device of the NDA or just one of these?* *The percentage information in the table below is unclear because I cannot confirm that the percentages represent the (b) (4) material.* *In general, it is unlikely the chemicals below raise an irritancy or sensitization concern for the following reasons.* *The substances in the table below (b) (4) do not raise a toxicological concern when used (b) (4) (b) (4).* (b) (4) *(b) (4) the concentration (b) (4) is too low to be a concern if the amount of it in the product is also small or if the subject device is Clinical (b) (4) (b) (4).* *Note: There is insufficient information below to calculate an amount of the chemicals in the table below.* A follow-up IR was sent to the sponsor based on Alan's recommendation. See below.
Response Adequate:	☐ **Yes** ☐ **No, See IR #14 Sent on 4/14/2021**

Follow-On Deficiency	Date Sent: 4/15/2021	Date/Sequence Received: 4/16/2021
Information Request #14	Based on the information provided to FDA Device Request 9 regarding biocompatibility of Commercial (b) (4) additional information is needed on the chemicals presented in Table 22. Please report the quantity in nanograms or micrograms per device for each chemical in the table. This information is necessary to confirm worst-case exposure will be small to support the decision to leverage Clinical (b) (4) biocompatibility for Commercial (b) (4).	
Sponsor Response	Novo Nordisk would like to report the quantity in micrograms per device for each chemical presented in Table 22 in the response to Device Request 9 dated March 25, 2021. The requested information is provided in Table 1 and Table 2 below. **Table 1 Components in Clinical** (b) (4) (b) (4) **Table 2 Components in Commercial** (b) (4) (b) (4)	
Reviewer Comments	Alan Hood was consulted again and raised concerns regarding weight and the lack of a toxicological risk assessment. He also pointed me to the CDRH (b) (4) webinar. See his comments regarding the response:	

Strange. The (b) (4) *ug indicates the quantity is in the hundreds of milligram quantity, which is not small. Of course, small is relative; however,* (b) (4) (b) (4) *are present in a medical device* (b) (4) *at much lower quantities due to (a) low percentage, (b) low* (b) (4) *density, and (3) small surface area. The information below indicates that the body and cap are relatively large* (b) (4) (b) (4)*. Is this true? Does the entire* (b) (4) *contact the body?*

Of these (b) (4) *and quantities, the* (b) (4) *that raises the greatest toxicity concern are* (b) (4)*; however, the quantities of these* (b) (4) *appear to be small if the quantity represents the total amount present. Although the other* (b) (4) *are relatively lower toxicity, the quantities of these* (b) (4) *appear quite high. To verify the reported total quantities of the* (b) (4) *in Commercial* (b) (4) *represent the total present, the Sponsor could provide documentation of the percentages* (b) (4)*.*

Because the Sponsor appears to be stating that the total quantity (b) (4) (b) (4) *are known, it is unclear why the Sponsor has not conducted a toxicological risk assessment (i.e., reported a margin of safety) of these* (b) (4) (b) (4)*. Are we not requesting a toxicological risk assessment* (b) (4) (b) (4)

With Alan's response, watched the webinar and decided to contact Rong Guo, biocompatibility focal point, for recommendation on if full biocom data would be needed based on this change. See her comments:

It would be ideal to test the final finished device component. Ask sponsor to provide a risk analysis.

What is the device to be used for? If per injector, or syringes, we evaluate the non-fluid pathway, which is the intact skin contact part. Based on the low risk of intact skin contact and the ratio of these (b) (4) *in the final device, I think it's reasonable to accept sponsor's risk analysis or justification for not performing CSI on the final finished device component. These* (b) (4) *are commonly used in food or cosmetics:*

(b) (4)

	(b) (4) [redacted] Based on her recommendation, the follow up deficiency below was sent.
Response Adequate:	**Yes** **No, See IR # Sent on 4/19/2021**

Follow-On Deficiency	**Date Sent: 4/15/2021**	**Date/Sequence Received: 4/16/2021**
Information Request #15	We refer to your submission dated April 16, 2021, and your response to FDA Request 1. Based on the quantities of the chemical additives to the Commercial (b) (4) presentation of the device, please provide a Risk Assessment for the change to justify the (b) (4) is biocompatible and will not interact with the rest of the raw materials causing new irritants. Please note that this risk assessment will be sufficient justification for now; however, biocompatibility testing for the Final Finished Product is still necessary. Since Cytotoxicity testing has already been conducted, Irritation and Sensitization testing is still needed. Once completed, please file the updated biocompatibility report in the Design History File.	
Sponsor Response	As requested, Novo Nordisk is hereby providing a Risk Assessment for the change of the chemical additives in the Commercial (b) (4) presentation of the device that is used for the single dose pen-injector for semaglutide. This Risk Assessment is based on the results from cytotoxicity, irritation and sensitization test data from related autoinjectors. A summary of the biological evaluation report for the related autoinjector "(b) (4) Autoinjector" is presented in Appendix A. The (b) (4) Autoinjector is commercialized by Novo Nordisk in Japan with a semaglutide drug product for the treatment of Type 2 Diabetes Mellitus. Appendix A also shows a comparison between the (b) (4) Autoinjector and the Commercial (b) (4). The biological evaluation report summary for the (b) (4) Autoinjector presents the tests and results relevant to support the risk assessment for irritation and sensitization for the Commercial (b) (4). (b) (4) [redacted] Finally, Novo Nordisk would like to confirm that irritation and sensitization testing will be performed on the Final Finished Product and that the updated biocompatibility report will be filed in the Design History File.	

Risk assessment for the change of the chemical additives in the Commercial (b) (4) presentation of the single dose pen-injector

The Risk Assessment presented here is based on the results from cytotoxicity, irritation and sensitization test data from related autoinjectors.

The same materials, (b) (4) are used in the related autoinjectors to which reference is being made (see Table 1 for comparisons to the Commercial (b) (4)). It is for these related autoinjectors ((b) (4) Autoinjector and "Similar Autoinjector", an (b) (4) device approved in the US under the responsibility of another manufacturer) that cytotoxicity, sensitization and irritation testing was performed.

All three autoinjectors are fixed-dose autoinjectors for single use, with a prefilled syringe, for once-weekly use, with a comparable maximal injection time.

Table 1 Material comparison between related autoinjectors

Device	Commercial (b) (4) (for the single dose pen-injector for semaglutide)	(b) (4) Autoinjector (clinical and marketed versions, commercialized by Novo Nordisk)		Similar Autoinjector (designed and manufactured by (b) (4) for another manufacturer)
Biological evaluation tests performed	• Cytotoxicity	• Cytotoxicity • Sensitization • Irritation		• Cytotoxicity • Sensitization • Irritation
Component	Body	Needle Cover	Cap	Front Shell, Rear Cover and Housing Connector
(b) (4)				

The Body of the Commercial (b) (4), the Needle Cover and Cap of the (b) (4) Autoinjector and the (b) (4) of a Similar Autoinjector shown in Table 1 are supplied by the same (b) (4) (b) (4) supplier.

A higher quantity (w/w%) of [(b) (4)] is presented in the [(b) (4)] Autoinjector and the Similar Autoinjector compared to Commercial [(b) (4)].

The Similar Autoinjector contains a higher quantity (w/w%) of [(b) (4)] compared to Commercial [(b) (4)]

The autoinjectors are manufactured with the same manufacturing process, [(b) (4)]

The Commercial [(b) (4)], the [(b) (4)] Autoinjector and the Similar Autoinjector are classified as a surface device (contact to intact-skin). All three devices share the same [(b) (4)] material. In addition, both the [(b) (4)] Autoinjector and the Similar Autoinjector also contain the other compounds found in Commercial [(b) (4)] [(b) (4)]

A summary of test results for the [(b) (4)] Autoinjector and the Similar Autoinjector for the endpoints of cytotoxicity, sensitization and irritation are shown in Table 2 and Table 3. All results were negative for cytotoxicity, sensitization and irritation.

Table 2 Summary of Biocompatibility Testing Conducted on [(b) (4)] Autoinjector

ISO Standard	Test	Results
10993-5	Cytotoxicity- MEM Elution Test in L-929 Mouse Fibroblast Cells	No reactivity at 24 and 48 hours
10993-10	Maximization Test for Delayed-Type Hypersensitivity in Hartley Guinea Pigs	Non-sensitizer
10993-10	Intracutaneous (Intradermal) Reactivity Test in New Zealand White Rabbits	Non-irritant

Table 3 Summary of Biocompatibility Testing Conducted on Similar Autoinjector

ISO Standard	Test	Results
10993-5	Cytotoxicity- MEM Elution Test in L-929 Mouse Fibroblast Cells	No reactivity at 24 and 48 hours
10993-10	Maximization Test for Delayed-Type Hypersensitivity in Hartley Guinea Pigs	Non-sensitizer
10993-10	Intracutaneous (Intradermal) Reactivity Test in New Zealand White Rabbits	Non-irritant

Previous biocompatibility test results from autoinjectors comparable to the Commercial [(b) (4)] passed the endpoints of cytotoxicity, sensitization and irritation. The comparable autoinjectors and the Commercial [(b) (4)] use the same suppliers [(b) (4)]. The comparable autoinjectors and the Commercial [(b) (4)] have the same manufacturing process at [(b) (4)].

The following points are considered crucial to provide a basis for the risk assessment for irritation and sensitization for the Commercial [(b) (4)]:

- The material composition of the [(b) (4)] Commercial, [(b) (4)] Autoinjector and the Similar Autoinjector show that the [(b) (4)] is the same.

	• The (b) (4) Autoinjector and the Similar Autoinjector both contain (b) (4) at a higher quantity (w/w %) than Commercial (b) (4) • The (b) (4) Autoinjector and the similar autoinjector both contain (b) (4) where the (b) (4) Autoinjector contains a slightly lower quantity (w/w %) and the Similar Autoinjector contains a higher quantity (w/w %) than Commercial (b) (4). • In addition, both the (b) (4) Autoinjector and the Similar Autoinjector also contain the other compounds found in Commercial (b) (4) (b) (4) The test results for irritation and sensitization for the two comparable autoinjectors are considered to represent equal or worst-case scenarios for evaluating the biocompatibility of the Commercial (b) (4). The passed endpoints for the comparable autoinjectors for irritation and sensitization are therefore seen as evidence for the biocompatibility (b) (4) (b) (4) as well as of the biocompatibility in the event of their potential interaction (b) (4) in the Final Finished Product of the Commercial (b) (4). In conclusion, exposure to any or all of the constituents in the Commercial (b) (4) via intact dermal contact during use of the autoinjectors is considered to be of no safety concern/negligible risk for the user from a toxicological perspective. Therefore, this risk assessment, based on the comparable autoinjectors justify the (b) (4) is biocompatible and will not interact with the rest of the raw materials causing new irritants. Furthermore, Novo Nordisk will ensure that irritation and sensitization testing is conducted for the Final Finished Product of Commercial (b) (4). The updated biocompatibility report will be filed in the Design History File.

Table 4 Comparison of Commercial (b) (4) with (b) (4) Autoinjector for biocompatibility purposes

	Commercial (b) (4) (for the single dose pen-injector for semaglutide)	(b) (4) Autoinjector (clinical and marketed versions, commercialized by Novo Nordisk)	Comparability for biocompatibility
Intended use / Indication for use	A single dose single patient pre-filled pen-injector to be used for subcutaneous injection of the glucagon-like-peptide-1 (GLP-1) analogue semaglutide as an adjunct to a reduced-calorie diet and increased physical activity for weight management.	A single dose, single patient, pre-filled pen-injector intended for once weekly subcutaneous injection of GLP-1 analogue semaglutide for the treatment of T2DM in patients.	The frequency of use is identical (once weekly). The duration of therapy is assumed to be life-long treatment in both indications, as this is the worst-case scenario. From the comparison of the intended user groups in both indications, there are no expected differences with regard to handling of the device (see handling steps).
Handling steps (Human factors)	Key steps include removing cap, injecting dose by pressing the pen-injector against the injection site, 5-10 seconds injection time while a yellow bar progressively blocks the window, removal and disposal of pen-injector	Key steps include removing cap, injecting dose by pressing the pen-injector against the injection site, 5-10 seconds injection time while a yellow bar progressively blocks the window, removal and disposal of pen-injector	No difference in handling steps
Length with the Cap (approximately)	(b) (4)		No difference in dimension and form
Diameter (approximately)			No difference in dimension and form

Reviewer Comments

The risk assessment compared the to be marketed device (Commercial (b) (4)) to two related autoinjectors with the similar intended uses, handling steps and dimensions. The chemical make-up of all three devices were provided. (b) (4) (b) (4) (b) (4) The results in the analysis show that the (b) (4) Autoinjector and the Similar Autoinjector both have higher concentrations (b) (4) in their devices compared to the subject Commercial (b) (4) device. It is also confirmed that the autoinjectors are manufactured with the same manufacturing process. Biocompatibility summaries for the (b) (4) Autoinjector and Similar Autoinjector show that all results were negative for cytotoxicity, sensitization and irritation.

This risk assessment along with the sponsors agreement to providing irritation and sensitization testing for the final finished combination product (Commercial (b) (4) a) in the Design History File, this response is acceptable. (please note that cytotoxicity testing for Commercial (b) (4) was already provided which is why only irritation and sensitization are being indicated in the response).

Response Adequate: ☐ **Yes** ☐ **No, See IR # Sent on**

9. CLINICAL VALIDATION REVIEW

9.1. Review of Clinical Studies Clinical Studies

There is no device related clinical studies for review
There are clinical studies for review
This information was obtained from the following documents:

Reviewer Comment

9.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: Yes No N/A	**Mid-Cycle Deficiencies:** Yes No N/A	**Final Deficiencies:** Yes No N/A
Reviewer Comments		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: Yes No		

10. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	
Human Factors deferred to DMEPA	

11.FACILITIES & QUALITY SYSTEMS

11.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	
CDRH Facilities Inspection Review was not conducted	

Reviewer Comments
See facilities review above.

Facilities Review Conclusion		
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	Yes	No

11.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	
CDRH Quality Systems Documentation Review was not conducted	

11.2.1. Description of the Device Manufacturing Process

(b) (4)

[redacted]

12 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

(b) (4)

[redacted]

Add Additional Information Request

No Additional Information Requests – Finalize Facilities & QS Review Section

<<END OF REVIEW>>

12. APPENDIX A (INFORMATION REQUESTS)

12.1. Mid-Cycle Information Requests

Information Request #2

Device performance was evaluated per ISO 11608-1 and ISO 11608-5. The test report provided in *Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time – Single Dose Pen-Injection for Semaglutide* does not include any testing conducted on audible/visual feedback for your device. Your device should have a requirement for audible/visual feedback which indicates clear requirements regarding loudness of the audible feedback (in decibels) and accuracy (+/- x seconds) from the end of injection. Please update your performance requirements to incorporate this audible feedback and provide updated testing to verify the devices performance for these new requirements.

Sponsor Response

Novo Nordisk has developed the single dose pen-injector with the visual parameter (i.e. (b) (4) filling the inspection window) as the indicator of the end of dose:

- in alignment with ISO 11608-1 section 5.5h ("*The NIS shall indicate by visual, audible or tactile means, or any combination of these, that the injection stroke has been completed*").
- as the 'persistent' confirmation of completion of the automated injection, in alignment with ISO 11608-5:2015 section 4.3.4. ("*The NIS-AUTO shall provide confirmation of completion of the automated injection in an unmistakable and clear manner. Such confirmation shall be at least a persistent visual indication… Note: additional tactile and/or audible indicator(s) may be included.*").

The visual parameter has been specified in the design requirements and has been attribute verified (see Table 1).

In addition to the visual feedback, audible feedback has also been implemented: a first click indicating the start of injection and a second click indicating progress of the injection. These supporting audible indicators have also been specified in the design requirements and inspected during design verification (see Table 1).

Table 1 Requirements and results for visual and audible feedback for the single dose pen-injector

Requirement text	Purpose for the requirement	Design verification method	Design verification results
The device shall include a window allowing for visual inspection of the drug	So that the user can verify the drug quality before injection	Attribute Testing – Visual inspection of design	Pass
After injection the (b) (4) (b) (4) shall fill the inspection window	Visual confirmation of complete injection. So that the user will know when the device has been used		Pass
First click There shall be an audible click at the beginning of the injection stroke	To help ensure that the user knows when the injection begins	Attribute Testing – Audible inspection of design during functionality testing performed by a trained technician	Pass
Second click There shall be an audible click close to the end of the injection stroke	To help ensure that the user knows when the injection is close to the end		Pass

Table 2 **IFU text demonstrating that the visual feedback confirms the *completion* of the injection stroke**

Text on the proposed IFU	Image on the proposed IFU
	(b) (4)

Table 3 **IFU text demonstrating that the audible feedback indicates beginning and progression of the injection stroke**

Text on the IFU	Image on the IFU
	(b) (4)

Defining requirements for loudness of the audible feedback (in decibels) and accuracy (+/- x seconds) from the end of injection would not be aligned with the supportive function of this design feature due to the following context:

- Loudness: By verifying the detectability of the click sounds in a simulated home-use setting by trained technicians, it is documented that the design fulfils its purpose of being able to provide supporting feedback to the progress of injection.
- Accuracy of second click: since the second click is intended to support the feedback of the progress of injection, there is no added value in prescribing how accurately this sound is emitted within the course of injection.

- Accuracy of visual end of dose confirmation: the (b) (4) movement stop after full injection does not have an uncertainty.

It is therefore Novo Nordisk's position that the attributive verification by inspection is appropriate.

Reviewer Comments

In accordance to ISO 11608-1-2014, either visual or audible feedback is required to indicate the completion of an injection. The subject device has the required visual feedback feature as indicated above. Given the audible feedback an additional feature that is not required, the lack of the requirement regarding the loudness (in decibels) and accuracy (+/- x seconds) from the end of injection is acceptable. Novo Nordisk's position that the attributive verification by inspection is appropriate is acceptable.

Information Request #3

Performance requirements were indicated and tested in the document *Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time – Single Dose Pen-Injection for Semaglutide.* The upper limit (b) (4) for Cap Removal Force is too high. Validation testing is not performed for this specification. If the cap removal force is too high, the user cannot access their medication and deliver the dose. Please indicate how this specification was validated. If you intend to use anthropometric data to validate your specification, ensure the postures and motions are representative of cap removal force and analyze that data assuming your weakest (5th percentile females) per HE 75 to validate this upper limit specification. Alternatively, adjust your cap removal specification to (b) (4). Provide updated design verification testing reports demonstrating your device meets this new specification.

Sponsor Response

Novo Nordisk confirms that the specification limit for cap removal of the single dose pen-injector for semaglutide will be updated to (b) (4)

The results presented in the design verification report in 3.2.P.7 Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time – Single Dose Pen-injector for Semaglutide comply with the updated limit of (b) (4) An extract of the design verification report is shown in Table 4.

Table 4 Cap removal force according to ISO 11608-1 conditions for semaglutide C 3.2 mg/ml (0.75 ml single dose pen-injector variant)

	Sample size	Precondition[2]	Acceptance criteria[3]	Results (N)	Conclusion
Single dose pen-injector with semaglutide C[1]	60	• Standard atmosphere, 23°C ± 5°C, 50% RH ± 25% RH	(b) (4)	(b) (4)	Pass
	60	• Cool atmosphere, 5°C ± 3°C			
	60	• Warm atmosphere, 40°C ± 2°C, 50% RH ± 10% RH			
	30	• After free fall from 1.0 m			
	20	• After vibration			

[1] Tests performed at (b) (4) on batches as reported in 3.2.P.7 Test Report According to EN ISO 11608-1, EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and Test Report for Injection Time, Table 12

[2] Preconditions based on ISO 11608-1, Table 3. Cold storage reflects the intended storage of the product. Warm storage is excluded, as the maximum storage temperature is 5°C ± 3°C.

[3]The original report has an upper limit of (b) (4). The data presented on this table uses the updated upper limit of (b) (4)

[4]Two-sided tolerance limits are described by confidence: 95%, probability content, p: 95%.

Novo Nordisk confirms that product specification for cap removal force will be implemented by change controls as part of the quality management system and that the design verification report will be updated accordingly.

Reviewer Comments

The cap removal force specification was updated to have an upper limit of (b) (4) instead of (b) (4). The response above indicates that the original verification test shows results that this the device already complies with the new force. The table above was updated to include the new (b) (4) upper limit; this is acceptable.

Information Request #4

Human Factors testing was provided to validate the (b) (4) activation force upper limit. This method of validation of Essential Performance Requirements is not acceptable. Devices used in Human Factors studies would not perform at the specification limits, only at the nominal performance. Please provide data validating the limits of the proposed specifications for Activation Force. If the activation force is too high, the user cannot deliver the dose. Therefore, provide anthropometric data using postures and motions representative of activation force and analyze that data assuming your weakest (5th percentile females) per HE 75. If your analysis results in a new specification, provide updated design verification testing reports demonstrating your device meets this new specification.

Sponsor Response

Novo Nordisk confirms that the upper limit of (b) (4) for activation force is validated by reference to anthropometric data according to ANSI/AAMI HE75:2009, which provides human strength data for the upper extremities.

As part of the analysis performed for the use of the single dose pen-injector, a pull movement towards the upper body is considered the best representation of a typical injection.

If the maximum force that can be exerted by the arm in a pull movement with a 60º elbow flexion (worst case) is (b) (4) (according to Table 7.7 in ANSI/AAMI HE75:2009), Novo Nordisk has defined the following adjustments with the purpose of accommodating for the strength of both genders and to avoid complaints (see section 7.3.5.1c and 7.3.5.2a in ANSI/AAMI HE75:2009)
(b) (4)
where,
(b) (4) is factored into the calculations to account for the difference between males and females at the lower capabilities (5th percentile females)
the additional factor (b) (4) is chosen as a safety margin to ensure even people with reduced strength may operate the pen-injector.

Thus, according to the calculation, an activation force limit specified to be (b) (4) or less would be considered acceptable for the requirement. Accordingly, the selected upper limit of (b) (4) is supported by the anthropometric data according to ANSI/AAMI HE75:2009. This justification for the specification can be found in 3.2.P.7 Analysis of Functional Performance and Control Strategy, Table 2.

Reviewer Comments

A pull movement towards the upper body is not representative of activation force for a pen injector. There is no adequate justification for this be a representative motion for this force specification. This is not acceptable.

See Section 12.2 Interactive Review below.

Information Request #5

Performance requirements were indicated and tested in the document *Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time – Single Dose Pen-Injection for Semaglutide.* The proposed specification of (b) (4) for Needle Cover Override appears too low to mitigate the risk of accidental needle sticks. Provide data validating this specification. If the Needle Cover Override force is too low, the user can override the safety mechanism resulting in accidental needle sticks.

Sponsor Response

The single dose pen-injector includes a lock-out feature to prevent accidental needle sticks with a used needle. The limit of this feature is specified in accordance with ISO 11608-5:2012 section 5.1.11.2: "*it shall withstand a minimum load as determined by the risk assessment (at least two times its actuation force)*". By specifying a minimum needle cover lock force (b) (4) that is at least two times the maximum activation force (b) (4) the two forces are considered to be adequately distinguishable from one another.

Two use scenarios are considered for evaluating how the needle cover override force would mitigate the risk of accidental needle sticks:

- Scenario 1: A user intends to use a single dose pen-injector, however the single dose pen-injector has already been used. The user tries to activate the single dose pen-injector and experiences a higher activation force than normally experienced.
- Scenario 2: A user does not intend to use a single dose pen-injector. However, they accidentally handle a used single dose pen-injector in a way that they could interact with the needle cover and thereby the needle.

In both use scenarios, the needle cover lock force of (b) (4) is considered to be adequately distinguishable from the activation force. For the performance of the needle cover override force, please see the response to FDA request 5.

Reviewer Comments

With the validation of the (b) (4) activation force, the justification of the (b) (4) needle cover lock force is acceptable as it is two times the maximum activation force.

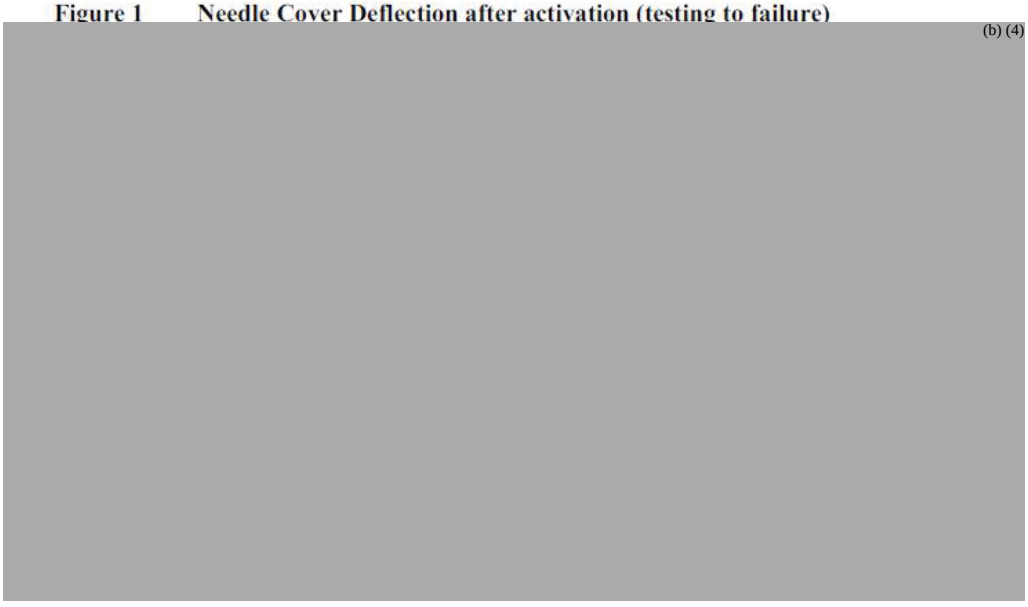
Information Request #6

You provided performance verification data for needle cover override force demonstrating that a sample size of 60 devices met the acceptance criteria of (b) (4) needle cover deflection at an applied force of (b) (4) Your method for evaluating needle cover override force after injection is not appropriate because rather than measuring needle guard override force, the specification measures and analyzes the displacement of the needle guard after (b) (4) is applied, which is a PASS/FAIL (attribute) acceptance criteria. Therefore, N=60 is an insufficient sample size to demonstrate a minimum 95%/99% confidence and reliability recommended for needle safety features per FDA guidance Medical Devices with Sharps Injury Prevention Features (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-devices-sharps-injury-prevention-features-guidance-industry-and-fda-staff) to mitigate the risk of accidental needle sticks. Provide data on an appropriate sample size, demonstrating that a minimum 95%/99% attribute sample size meets the acceptance criteria (b) (4) is (b) (4) for needle cover override force up to the proposed shelf life real time or accelerated aging). Alternatively, you can test needle cover override force to failure and analyze the data as variable data type.

Sponsor Response

Novo Nordisk would like to elaborate on the performance verification data from needle cover deflection at an applied force of (b) (4) The test method used to generate the data in Figure 1 applies a force on the needle cover until failure (see Figure 1 for data and method description). The results in 3.2.P.7 Test Report According to EN ISO 11608-1, EN ISO 11608-5 and JIS T 3226-2 Needle Based Injection System for Medical Use and Test Report for Injection Time only report on the deflection measured at (b) (4), according to the specifications. Since the needle cover deflection reported at the applied force of (b) (4) is a data-point on the measured force curve, the data are variable. The sample size of 60 is therefore sufficient to demonstrate the needle safety feature with a minimum 95%/99% confidence and reliability.

Figure 1 Needle Cover Deflection after activation (testing to failure)



The graph shows the force on the needle cover as a function of the needle cover deflection on the single dose peninjector. From the needle cover lock deflection onset the graph indicates a monotonic relation between the force applied and the deflection at or around of (b) (4) For each of the samples tested, the needle cover is compressed until the needle cover lock is overridden. Only ten samples measured from the single dose pen-injector from drug product batch HW52W68 are shown in this graph. The results reported for deflection in the

design verification report are those corresponding to an applied force of (b) (4) The specification limit is shown at 2 mm.

The results from measurement of the needle cover deflection distance when a force of (b) (4) is applied are reported in Table 5 and Table 6. The specified deflection distance of (b) (4) is defined to ensure that the needle tip does not come into contact with a finger covering the shield opening. It includes an additional margin, to allow for a finger to be closer to the needle than a flat plate as described in the test method in ISO 11608-5, section 5.1.11.2: "*If the NIS-AUTO includes a lock-out feature, it shall withstand a minimum load as determined from the risk assessment (at least two times its actuation force), which shall be applied to the surface around the opening of the NISAUTO using a flat plate. The plate dimensions shall be larger than the NIS-AUTO profile so that the application of the force onto the surface around the opening is entirely within the plate. Under the application of this load, the needle tip shall not touch the flat plate.*" The results in Table 5 present results at the time of initial verification testing the single dose pen-injector; Table 6 presents the results after accelerated shelf-life preconditioning. The data are reported including a full statistical summary (mean, standard deviation, min, max, *p*-value, *k*-value) and the corresponding upper tolerance value.

Table 5 Needle cover override, deflection, according to ISO 11608-1 conditions for semaglutide C 3.2 mg/ml (0.75 ml single dose pen-injector variant)

Test item	Sample size	Test condition[2]	Acceptance criteria[3]	Results (mm)	Conclusion
Single dose pen-injector with semaglutide C[1,4]	60	Standard atmosphere, 23°C ± 5°C, 50% RH ± 25% RH	(b) (4)	(b) (4)	Pass
	60	Cool atmosphere, 5°C ± 3°C			
	60	Warm atmosphere, 40°C ± 2°C, 50% RH ± 10% RH			
	60	Cold storage final device			
	30	After free fall from 1.0 m			
	20	After vibration			

[1] Tests performed at (b) (4) on batches as reported in 3.2.P.7 Test Report According to EN ISO 11608-1, EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and Test Report for Injection Time, Table 15

[2] Preconditions based on ISO 11608-1, Table 3. Cold storage reflects the intended storage of the product. Warm storage is excluded, as the maximum storage temperature is 5°C ± 3°C.

[3] One-sided tolerance limits are described by confidence: 95%, probability content, p: 99%

[4] The data generated on the 0.75 ml single dose pen-injector using the semaglutide C formulation covers both the 0.5 ml and 0.75 ml variant, as this feature is independent of the formulation and fill-volume.

Table 6 Needle cover override, deflection, after accelerated shelf-life equivalent to (b) (4) months for semaglutide C 3.2 mg/ml (0.75 ml single dose pen-injector variant)

Test item	Sample size	Test conditions	Acceptance criteria[3]	Results (mm)	Conclusion
Single dose pen-injector with semaglutide C[1,3]	60	Standard atmosphere, 23°C ± 5°C, 50% RH ± 25% RH after accelerated shelf-life conditions corresponding to storage at (b) (4) (b) (4) at 5°C ± 3°C and (b) (4) at 23°C ± 5°C, 50% RH ± 25% RH	(b) (4)		Pass

[1] Tests performed at (b) (4) on drug product batch no. HW52W68

[2]One-sided tolerance limits are described by confidence: 95%, probability content, p: 99% (k-factor:)

[3]The data generated on the 0.75 ml single dose pen-injector using the semaglutide C formulation covers both the 0.5 ml and 0.75 ml variant, as this feature is independent of the formulation and fill-volume.

Reviewer Comments

The sponsor elaborates on their method of analysis in the response above. They indicate that their original report did analyze the data as variable data type as they provided the mean, std, min/max and kvalue. The only data missing was the k-act calculation. The sponsor instead compared the mean to the USL which is an unclear analysis. Instead of interacting to have the sponsor provide Kact values, I completed the calculations myself below:

(b) (4)

Though the sponsor did not provide Kact values themselves, based on my calculations the values are well within the acceptance criteria.

Information Request #7

Device performance was evaluated per ISO 11608-1 and ISO 11608-5. The test report provided in *Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time – Single Dose Pen-Injection for Semaglutide* indicates that the Dry Heat storage pre-condition was conducted at 5°C ± 3°C instead of 70°C and the Cool Storage Pre-Condition test was also conducted at 5°C ± 3°C instead of -40°C. Justification for these condition changes was that the storage condition of 5°C ± 3°C is proposed in the instructions for use, making it both the highest and lowest acceptable

storage condition for the device. This justification is not acceptable. Per ISO 11608-1, functional testing must be conducted on the device for pre-conditions of Dry Heat Storage conditions of 70°C ± 2°C, of 50 ± 10% RH and Cool Storage conditions of -40°C ± 3°C. Please re-verify your device performance to these testing conditions and provide updated test reports.

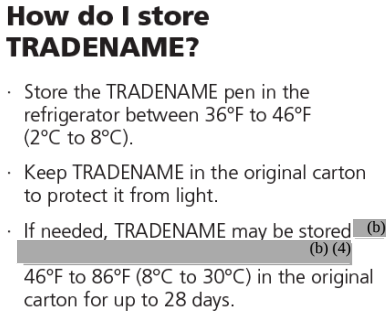
Sponsor Response

Novo Nordisk acknowledges the reference to ISO 11608-1 and would like to clarify that the single dose pen injector for semaglutide belongs to the system designation D1 of pen-injectors ("*Needlebased injection device with an integrated non-replaceable container. Each container holds a single dose, whereby the entire deliverable volume is expelled*"). In accordance with ISO 11608-1 section 10.6, "*system designations C and D that are manufacturer-filled shall be subjected to preconditioning at the acceptable high and low storage temperatures, which shall be stated in the instructions for use*". This means that functional testing at dry-heat (70±2 °C, 50±10 % RH) and cold storage -40±3°C is not applicable for a system designation D1 device.

As the single dose pen-injector is a drug-device combination product, it will follow the storage conditions of the semaglutide drug product. The drug-device combination product must comply with the drug product specification, specifying storage conditions of 5 °C ± 3 °C and in-use time of 28 days below 30 °C.

On the basis of the temperature restrictions imposed by the drug product requirements, the functional testing at the conditions specified in ISO 11608-1 section 10.6 (dry-heat 70 °C ± 2 °C, 50 ± 10 % RH and cold storage -40 °C ± 3 °C) is not applicable for the single dose pen-injector for semaglutide. The dry-heat and cold-storage temperatures are replaced by the acceptable high and low temperature conditions as presented in the instructions for use.

The instruction for use for the to-be-marketed single dose pen injector for semaglutide instructs the users "to store the pen injector in the refrigerator between 36°F to 46°F (2°C to 8°C)" and that the pen injector "may be stored (b) (4) (b) (4) 46°F to 86°F (8°C to 30°C) in the original carton for up to 28 days", see IFU extract in Figure 2.



How do I store TRADENAME?

- Store the TRADENAME pen in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep TRADENAME in the original carton to protect it from light.
- If needed, TRADENAME may be stored (b) (b) (4) 46°F to 86°F (8°C to 30°C) in the original carton for up to 28 days.

Figure 2 Extract of the instruction for use stating the storage conditions of the single dose pen-injector for semaglutide.

Additionally, the single dose pen-injector has been tested after the (b) (4) - assemblies of the single dose pen-injector have been exposed to -40°C ± 3°C and 55 ± 2°C, 50 ± 10 %RH to enhance product knowledge. After storage, the (b) (4) are assembled with syringes and tested at room temperature (23 ± 5°C) on the single dose pen injectors for semaglutide. The single dose pen-injector assembled from the sub-assemblies stored at these conditions complied with the requirements for activation force, needle extension, injection time, dose accuracy, cap removal force (without syringe) and needle cover override force. As part of this response, Novo Nordisk is providing additional data on sub-assemblies after storage at -40°C ± 3°C and 55 ± 2°C and 50 ± 10 %RH, which can be found in Table 7, Table 8, Table 9, Table 10, Table 11 and Table 12.

Reviewer Comments

The sponsors justification for evaluating device performance for cool and warm atmospheres only, not including dry-heat and cold storage pre-conditions is acceptable. Given the D1 designation of the device, these pre-conditions are not required and therefore no further data is needed.

Information Request #8

Stability and Shipping/Transportation testing data is provided in *Device Functional Test Report – Single Dose Pen-Injector for Semaglutide* for Activation Force, Needle Extension, Injection Time and Dose Accuracy. This testing is not conducted on Cap Removal Force or Needle Cover Override Forces. Additionally, the test conditions for this stability testing are only conducted in the following environmental conditions: Cool atmosphere: 5°C±3°C and Warm Atmosphere: 40°C±2°C. Stability and Shipping/Transportation testing needs to be conducted on all design attributes for all conditions tested in *Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time – Single Dose Pen-Injection for Semaglutide.* Please provide the following:

- Stability and Shipping/Transportation Testing for all design attributes: Activation Force, Needle Extension, Injection Time, Dose Accuracy, Cap Removal and Needle Cover Override
- Ensure that the testing is based all conditions outlined in ISO 11608-1 including the Dry Heat and Cool Storage Pre-Conditions as outlined in Deficiency #7.

Sponsor Response

Novo Nordisk would like to clarify that the selection of test conditions presented in 3.2.P.7 Device Functional Test Report for Stability and for Shipping/Transportation testing are considered to comply to the current industry practice based on ISO 11608-1 and to using a risk-based approach when selecting conditions for performance testing. The single dose pen-injector demonstrated robust performance during the initial design verification and during the selected conditions under stability in terms of compliance towards the requirement. Novo Nordisk has explored some of the conditions below to enhance product knowledge. Therefore, the additional conditions tested and presented here are considered to go beyond the standard practice outlined in ISO 11608-1 for manufacturers.

This response is structured around the two different types of testing requested by the Agency – stability testing (2.7.1.1) and transport/shipping testing (2.7.1.2). The summary of the data generated in the course of the development of the single dose pen-injector and of the additional data being provided as part of this response is collected in the matrix in Table 13.

Table 13 Summary of testing for essential performance requirements and other design attributes in the single dose pen-injector

Type of precondition	Testing during initial design verification	Testing at the end of shelf life	Testing after transport simulation
Operating temperature (cool atmosphere, standard atmosphere, warm atmosphere)	All ISO 11608-1 conditions tested for essential performance requirements[1] and other design attributes[2]	All ISO 11608-1 conditions tested for essential performance requirements[1] Standard atmosphere for other design attributes[2]	Standard atmosphere tested for essential performance requirements[1]
Storage temperature	Storage defined as 5°C±3°C, according to IFU of the single dose pen-injector tested for essential performance requirements[1] Justification for the storage conditions of 5°C±3°C is presented in request 6	Storage defined as 5°C±3°C, according to IFU of the single dose pen-injector tested for essential performance requirements[1]	Justified under "Transport/shipping testing" (see 2.7.1.2)
Mechanical impact (free fall, vibration)	All ISO 11608-1 conditions tested for essential performance requirements[1] and other design attributes[2]	All ISO 11608-1 conditions tested for essential performance requirements[1]	Justified under "Transport/shipping testing" (see 2.7.1.2)

[1]Essential performance requirements: activation force, needle extension, injection time, dose accuracy
[2]Other design attributes: cap removal force, needle cover deflection after activation

Stability testing

As part of this response, Novo Nordisk is providing the additional data collected in Table 14.

Table 14 Stability data test overview for additional testing presented in this response

Design attribute	Test condition	Data location
Activation force	Standard atmosphere Free Fall Vibration Storage defined as 5°C±3°C, according to IFU	Table 15
Needle extension		Table 16
Injection time		Table 17
Dose Accuracy		Table 18
Cap removal	Standard atmosphere	Table 19
Needle cover override force		Table 20, as well as in response to request 5

All the new data presented is compliant to the requirement limits for each of the tests and confirms a performance consistent with the data presented in 3.2.P.7 Test Report According to EN ISO 11608-1 and EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and test report for injection time and 3.2.P.7 Device Functional Test Report.

Justification for the testing strategy of the cap removal force

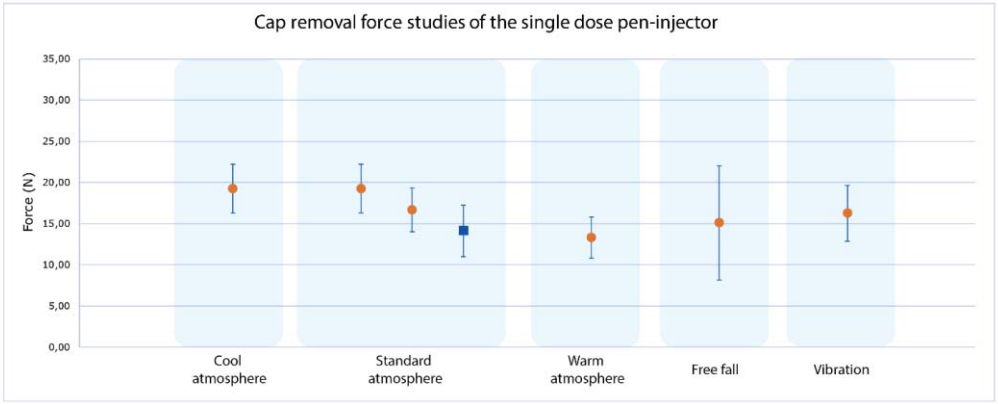
Removing the cap from the single dose pen-injector requires interaction between two interfaces (see Figure 3):

- the interface between the prefilled syringe and (b) (4)
- the interface between the body and cap.

Figure 3 Interfaces contributing to the cap removal force (marked in red)

Both interfaces may be affected by changes to temperature, due to expansion-contraction of the materials. The main factor that could increase the cap removal force is the (b) (4) decreased lubrication properties at low temperatures. This is supported by the performance data indicating that cool temperatures are the worst case in terms of cap removal force (see Figure 4). However, even under these conditions the force for removal of the cap is almost unaffected compared to the other temperature conditions.

Figure 4 Cap removal force



The graph shows the performance of cap removal force when tested during the verification studies (orange circles) and after shelf-life (blue square). The conditions are cool atmosphere (5°C ± 3 °C), standard atmosphere (23°C ± 5 °C, 50% ± 25% RH), warm conditions (40°C ± 2 °C, 50% ± 10% RH). The middle condition in the standard atmosphere represents testing at standard atmosphere after cold storage of the device for at least 96h.

Mechanical effects that would cause an increase in cap removal force of the single dose pen-injector will not affect the relevant interface, as supported by the data after vibration compared to standard atmosphere (see Figure 4). It can therefore be concluded that the interfaces are not functionally affected by vibrations.

As presented in 3.2.P.7 Device Functional Test Report, the evidence for cap removal force shows robust performance under the conditions of ISO 11608-1 (see Figure 4). Therefore, testing for cap removal force has been performed at the end of shelf-life at standard atmosphere (Table 19) and has been excluded from testing after transport simulation.

Justification for the testing strategy of needle cover override force, deflection after activation

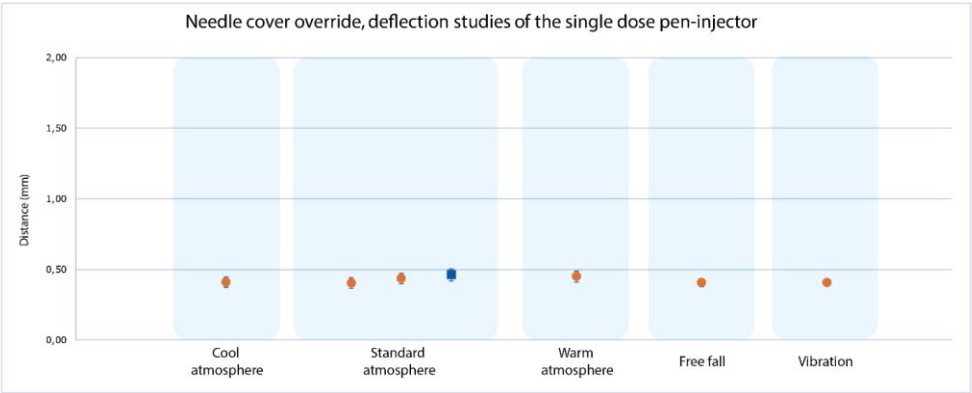
The activation of the single dose pen-injector (b) (4) translates into a (b) (4) needle cover automatically extends to cover the needle when single dose pen-injector is pulled away from the skin. (b) (4)

(b) (4)

Two of the preconditions of ISO 11608-1 have been considered as potentially most challenging (b) (4) (b) (4):
Vibration: it has been assessed that the repeated impact by vibration may be associated to wear of the (b) (4) parts. However, (b) (4), vibrational preconditions will not cause any wear (b) (4).
Warm atmosphere: it was considered that operation of the device under warm conditions could potentially affect the (b) (4) parts, (b) (4).
However, according to the results from operation of the device at warm conditions, the design of the single dose pen-injector shows no worsening in (b) (4) performance when operated up to 40°C ± 2°C, 50% ± 10% RH.

As presented in 3.2.P.7 Device Functional Test Report, the evidence for needle cover override force as measured from deflection after activation shows robust performance under the conditions of ISO 11608-1 (see Figure 6). The confirmation of performance at the end of shelf-life is restricted to one condition (Table 20) and excluded from the panel of tests after transport simulation.

Figure 6 Needle cover override force, deflection after activation



The graph shows the performance of the needle cover override force when tested during the verification studies (orange circles) and after shelf-life (blue square). The conditions are cool atmosphere (5°C ± 3 °C), standard atmosphere (23°C ± 5 °C, 50% ± 25% RH), warm conditions (40°C ± 2 °C, 50% ± 10% RH). The middle condition in the standard atmosphere represents testing at standard atmosphere after cold storage of the device for at least 96h.

2.7.1.2 Transport/shipping testing

The single dose pen-injector has demonstrated robust performance during the design verification and during stability (see 2.7.1.1), both in terms of compliance towards the requirement and in terms of comparability of results between the conditions. On the basis of this evidence and given its risk profile, evaluation of performance after transport simulation at standard conditions for the essential performance requirements is deemed justified. The information for activation force, needle extension, injection time and dose accuracy is collected in 3.2.P.7 Device Functional Test Report.

As presented in section 2.7.1.1, the potential worst-case conditions for cap removal force and needle cover override force, deflection after activation have been shown to have no impact. Since transport simulation will not increase the potential sources of challenge to the performance of these functions, it is justified to exclude them from testing after transport simulation.

Table 15 Activation force after accelerated shelf life combined with additional ISO 11608-1 conditions

Time Point (Stage)	Pre-conditioning	Fill Volume	Sample Size[1] n	Specification	Test results				Probability Content p	K ISO k_{ISO}	Calculated Tolerance Limit(s) compared to Specification(s) (N)	Result
					Min (N)	Max (N)	Mean $\bar{x}$ (N)	Standard Deviation s (N)				
After accelerated shelf-life equivalent to (b) (4) at 5°C ±3°C and (b) (4) at 30°C ± 2°C, 50% ± 25 % RH	Standard atmosphere	0.5 ml	60	(b) (4)							(b) (4)	PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS
	Standard atmosphere	0.75 ml	60									PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS

[1]Tests performed at (b) (4) batch: B000076115, (b) (4) 0.50 mL batch: B000076114, (b) (4) 0.75 mL batch: B000076392 with prefilled syringe batch NZJ0008 (0.50 mL PFS) and JW55R50 (0.75 mL PFS).

Table 16 Needle extension after accelerated shelf life combined with additional ISO 11608-1 conditions

Time Point (Stage)	Pre-conditioning	Fill Volume	Sample Size[1] n	Specification	Test results				Probability Content p	K ISO k_{ISO}	Calculated Tolerance Limit(s) compared to Specification(s) (mm)	Result
					Min (mm)	Max (mm)	Mean $\bar{x}$ (mm)	Standard Deviation s (mm)				
After accelerated shelf-life equivalent to (b) (4) at 5°C ±3°C and (b) (4) at 30°C ± 2°C, 50% ± 25 % RH	Standard atmosphere	0.5 ml	60	(b) (4)							(b) (4)	PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS
	Standard atmosphere	0.75 ml	60									PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS

[1]Tests performed at (b) (4) batch: B000076115, (b) (4) 0.50 mL batch: B000076114, (b) (4) 0.75 mL batch: B000076392 with prefilled syringe batch NZJ0008 (0.50 mL PFS) and JW55R50 (0.75 mL PFS).

Table 17 Injection time after accelerated shelf life combined with additional ISO 11608-1 conditions

Time Point (Stage)	Pre-conditioning	Fill Volume	Sample Size[1] n	Specification	Test results				Probability Content p	K ISO k_{ISO}	Calculated Tolerance Limit(s) compared to Specification(s) (s)	Result
					Min (s)	Max (s)	Mean $\bar{x}$ (s)	Standard Deviation s (s)				
After accelerated shelf-life equivalent to (b) (4) at 5°C ±3°C and (b) (4) at 30°C ± 2°C, 50% ± 25 % RH	Standard atmosphere	0.5 ml	60	(b) (4)							(b) (4)	PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS
	Standard atmosphere	0.75 ml	60									PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS

[1]Tests performed at (b) (4) batch: B000076115, (b) (4) 0.50 mL batch: B000076114, (b) (4) 0.75 mL batch: B000076392 with prefilled syringe batch NZJ0008 (0.50 mL PFS) and JW55R50 (0.75 mL PFS).

Table 18 Dose accuracy after accelerated shelf life combined with additional ISO 11608-1 conditions

Time Point (Stage)	Pre-conditioning	Fill Volume	Sample Size[1] n	Specification	Test results				Probability Content p	K ISO k_{ISO}	Calculated Tolerance Limit(s) compared to Specification(s) (mL)	Result
					Min (mL)	Max (mL)	Mean $\bar{x}$ (mL)	Standard Deviation s (mL)				
After accelerated shelf-life equivalent to (b) (4) at 5°C ±3°C and (b) (4) at 30°C ± 2°C, 50% ± 25 % RH	Standard atmosphere	0.50 ml	60	(b) (4)							(b) (4)	PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS
	Standard atmosphere	0.75 ml	60									PASS
	Cold Storage		60									PASS
	Vibration		20									PASS
	Free Fall		30									PASS

[1]Tests performed at (b) (4) batch: B000076115, (b) (4) 0.50 mL batch: B000076114, (b) (4) 0.75 mL batch: B000076392 with prefilled syringe batch NZJ0008 (0.50 mL PFS) and JW55R50 (0.75 mL PFS).

Table 19 Cap removal force after accelerated shelf life

Time Point (Stage)	Pre-conditioning	Fill Volume	Sample Size[1]	Specification[2]	Test results				Probability Content p	K ISO k_{ISO}	Calculated Tolerance Limit(s) compared to Specification(s) (N)	Result
					Min (N)	Max (N)	Mean $\bar{x}$ (N)	Standard Deviation s (N)				
After accelerated (b) (4) (b) (4) at 5°C ±3°C and (b) (4) at 30°C ± 2°C, 50% ± 25 % RH	Standard atmosphere	0.75 ml	60	(b) (4)							(b) (4)	PASS

[1]Tests performed (b) (4) batch: B000076115, (b) (4) 0.50 mL batch: B000076114, (b) (4) 0.75 mL batch: B000076392 with prefilled syringe batch NZJ0008 (0.50 mL PFS) and JW55R50 (0.75 mL PFS).
[2]Specification still reported as (b) (4) in the design history file documents until the change request associated to response 2 of this information request is finalized.

Table 20 Needle cover override, deflection after activation after accelerated shelf life

Time Point (Stage)	Pre-conditioning	Fill Volume	Sample Size[1] n	Specification	Test results				Probability Content p	K ISO k_{ISO}	Calculated Tolerance Limit(s) compared to Specification(s) (N)	Result
					Min (N)	Max (N)	Mean $\bar{x}$ (N)	Standard Deviation s (N)				
After accelerated shelf-life (b) (4) (b) (4) at 5°C ±3°C and (b) (4) at 30°C ± 2°C, 50% ± 25 % RH	Standard atmosphere	0.75 ml	60	(b) (4)							(b) (4)	PASS

[1]Tests performed (b) (4) batch: B000076115, (b) (4) 0.50 mL batch: B000076114, (b) (4) 0.75 mL batch: B000076392 with prefilled syringe batch NZJ0008 (0.50 mL PFS) and JW55R50 (0.75 mL PFS)

Reviewer Comments

Stability/Shipping data was updated with the following changes:

Stability:

Standard Atmosphere, Vibration and Free Fall preconditions were tested after accelerated aging to (b) (4) months shelf-life (originally only warm atmosphere and cool atmosphere conditions were assessed) for:

- Activation Force
- Needle Extension
- Injection Time
- Dose Accuracy

This is acceptable.

Shipping/Transportation:

Accelerated shelf-life testing to (b) (4) months was conducted for Cap Removal and Needle Cover Override.

Cap Removal

The only pre-condition considered post accelerated aging to shelf-life was standard atmosphere. To justify this decision, the sponsor points to Figure 4 to demonstrate that cap removal is almost unaffected by cool and warm temperatures at T=0 and can be assumed as such at shelf-life as well. Since cap removal is low risk, this is acceptable. To justify the decision not to perform shipping tests the sponsor points to Figure 4 again to show how the device performance is not affected by the vibration pre-condition. Again, since cap removal is low risk, this is acceptable.

Needle Cover Override

The only pre-condition considered post accelerated aging to shelf-life was standard atmosphere. To justify this decision, the sponsor points to Figure 6 to demonstrate that the design of device shows no worsening in locking performance when operated at cool or warm temperatures. This is acceptable. To justify the decision not to perform shipping tests, the sponsor indicates that since the needle cover locking mechanism is not activated before use (during shipping), it wont be effected. Vibration pre-conditions were tested and support this as the device performs as expected. This is acceptable.

Information Request #9

In the document *Analysis of Functional Performance and Control Strategy – Single Dose Pen-Injector for Semaglutide* it is indicated that "clinical design validation of dose accuracy tolerances for the single-dose pen-injector is not performed directly, however, clinical data supports that drug is being delivered, with results in circulating drug levels proportionate to the intended dose. No further validation of the single-dose pen-injector is therefore necessary in terms of its ability to deliver an accurate dose". Based on the data provided, it is unclear if the device used during the clinical studies was the to-be-marketed autoinjector. The final finished device needs to be validated for dose accuracy to ensure that users will receive the intended dose of the drug. Please provide further information supporting the final finished product was validated for dose accuracy.

Sponsor Response

Novo Nordisk confirms that the pen-injector used in the clinical trial NN9536-4590 BE-trial is equivalent to the to-be-marketed autoinjector:
The to-be-marketed variant is identical to the clinical single dose pen-injector for semaglutide with respect to principle of operation, predefined specifications and manufacturing processes.
Minor colour modification introduced does not impact device performance.

The design of the BE trial including its bioequivalence limits, as agreed with the Agency during pre-approval interactions, support that the single dose pen-injector deliver an accurate dose with the intended semaglutide concentration in a clinical setting.

Novo Nordisk therefore confirms that the evaluation presented in 3.2.P.7 Analysis of Functional Performance and Control Strategy regarding dose accuracy performance is also applicable to the final finished product.

The comparison between the clinical single dose pen-injector for semaglutide and the to-bemarketed single dose pen-injector for semaglutide can be seen in Table 21 (presented as Table 2, 3.2.P.7 Comparison to the approved Ozempic® Pen-Injector).

Table 21 Comparison of single dose pen-injector for semaglutide used in clinical studies and to-be marketed single dose pen-injector for semaglutide1

Feature	Single dose pen-injector for semaglutide (Clinical version)					Single dose pen-injector for semaglutide (To-be-marketed version)
Appearance (graphics are for illustration purpose only)	(b) (4)					
Labelling	For clinical use only					Approved Tradename
Product type	Pre-filled single dose disposable pen containing a 0.5 ml or 0.75 ml prefilled syringe with semaglutide					The launch version's features and materials are identical to the clinical version, the only difference is the modification made to white color grade chosen for the body of the pen.
Intended use	Once weekly subcutaneous injection of semaglutide					
Indication for use	Incorporates a design containing a 0.5 ml or 0.75 ml syringe to assist in the subcutaneous injection of semaglutide for weight management.					
Where used	Home or in hospital					
Energy used and/or delivered	Manual					
Needle	Integrated hidden (b) (4) needle					
Target population	Adult					
Pen type	Escalation				Maintenance	
Dose size	0.25 mg	0.5 mg	1 mg	1.7 mg	2.4 mg	
Concentration	0.5 mg/ml	1.0 mg/ml	2.0 mg/ml	2.27 mg/ml	3.2 mg/ml	
Dose volume	0.5 ml			0.75 ml		
Primary packaging	Prefillable syringe					
Activation profile	(b) (4) activated					
Click at activation	Yes					
Click during dosing	Yes					
Click at end of dose	No					
Materials (prefillable syringe excluded)	Cap, needle cover and pen body: (b) (4) (b) (4)					
Biocompatibility	ISO 10993-1 Contact with intact skin during handling only					
Number of components	12 (pre-filled syringe with needle excluded)					
Housing colour	White					
Cap colour	Grey					
Functional testing and dose accuracy	According to EN ISO 11608-1:2015 and EN ISO 11608-5:2012.					
Length with cap	(b) (4)					
Diameter						
Anatomical sites for injection	As recommended in the Directions for Use					As recommended in the Instruction for use

Reviewer Comments

It is confirmed that the device used during the clinical study is identical to the final finished product except for the color change made to the body of the pen. This change would not affect device performance. This is acceptable.

Information Request #10

Biocompatibility of the cap, (b) (4) needle cover, body, and (b) (4) cap components of the pen-injector was assess by (b) (4). and provided in *Biological Evaluation Report – Single Dose Pen-Injector for Semaglutide*. In the summary of the report on page 14 section 8.2 and in the test reports provided by (b) (4) (Appendix H), it is indicated that two different devices were used for testing: Clinical (b) (4) and Commercial (b) (4) (cytotoxicity only), with the differences between the two being the white color of the body and (b) (4) cap. Commercial (b) (4) has "*two additional chemicals which only constitute small amounts (*(b) (4)*%)*". The justification provided that the difference (b) (4) in the white used in the body and (b) (4) cap components of the device being (b) (4)% and therefore insignificant is not acceptable. Even though it's a small

ratio, the new chemical may still be toxicologically potent. Additionally, even if the new chemical itself is not toxicologically potent, it in combination with the rest of the color/device may create new compounds which would be of biocompatibility concern. Please provide the compounds that are additional in the new device and a quantity for each compound added.

Sponsor Response

Novo Nordisk would like to clarify, which compounds have been added in the device constituent part of the single dose pen-injector for semaglutide (designated "Commercial (b) (4)" by the supplier).

For the (b) (4) cap component there are no added compounds.
For the body component two compounds are added:

(b) (4)

The compounds and the exact quantity (given in parentheses) used in the body and (b) (4) cap are presented in Table 22.

Table 22 Compounds in the body and (b) (4) cap

(b) (4)

With the exception of the specific quantities, this information can be found in the (b) (4). biocompatibility test report presented in appendix H of the 3.2.P.7 Biological Evaluation Report.

Reviewer Comments

Toxicologist Alan Hood was consulted regarding the response from the sponsor to determine acceptability of leveraging Clinical (b) (4) biocompatibility data for Commercial (b) (4) biocompatibility.

His response indicated that information provided by the sponsor is still insufficient to determine if the material change could raise irritation or sensitization concerns:

> *Sure thing. Just for clarification, are Clinical (b) (4) and Commercial (b) (4) the subject device of the NDA or just one of these?*
>
> *The percentage information in the table below is unclear because I cannot confirm that the percentages represent the (b) (4) material.*
>
> *In general, it is unlikely the chemicals below raise an irritancy or sensitization concern for the following reasons.*
>
> *The substances in the table (b) (4), which do not raise a toxicological concern (b) (4)*
>
> (b) (4)

[redacted] *the concentration* [redacted] *is too low to be a concern if the amount of it in the product is also small or if the subject device is Clinical* [redacted] *only that which does not contain this* [redacted].

Note: There is insufficient information below to calculate an amount of the chemicals in the table below.

A follow-up IR was sent to the sponsor based on Alan's recommendation. See below.

See Section 12.2.2 and Section 12.2.3 Interactive Review below.

Information Request #11

You provide your Corrective and preventive action (CAPA) summary in *21 CFR Part 820 Quality System Information for Devices*. In the summary, the following necessary elements you should have in your CAPA procedure are missing:

- Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications
- Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems
- Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems
- Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review
- Requires documentation of all CAPA activities

Please update your CAPA procedure summary to indicate how these elements are being addressed. Ensuring these elements are captured in CAPA procedures is necessary to ensure proper mitigation is in place to address all possible process and quality related issues.

Sponsor Response

The Novo Nordisk CAPA procedure captures all the elements of 21 CFR 820.100. The elements identified as part of this request will be captured in an updated version of the CAPA procedure summary section to include the information as shown below:

21 CFR 820.100	**Lines in the updated text below**
a. Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications	4- 9
b. Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems	26
c. Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems	18-22
d. Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review	18-22
e. Requires documentation of all CAPA activities	25

21 CFR 820.100 Corrective and preventive action (CAPA) (summary)

Novo Nordisk has established procedures in the Quality Management System to ensure Corrective and Preventive Action (CAPA) according to the requirements in 21 CFR 820.100.

Nonconforming products are handled according to the Deviations Standard Operating Procedure. The Standard Operating Procedure describes the segregation and evaluation of identified nonconforming products. The evaluation of nonconforming products includes a batch disposition decision and requires re-evaluation of the batch according to approved specifications. Batch disposition options (concession without rework, accept with reprocessing, reject or release with limitations) are described in the Deviations Standard Operating Procedure.

All relevant sources of quality data that may be of impact to continuous improvement principles, as well as the analysis of these data, are described in the CAPA Standard Operating Procedures. For each source of quality data, the following is described: data to be monitored, statistical methodology to be used, baseline, trigger points and frequency for the analysis.

At a minimum, the following data sources that may have information regarding quality are included: customer complaints, adverse events and returned products, outcome from audits, inspections, process performances, supplier evaluations, deviations, and concessions. It is mandatory to perform an investigation to identify the root cause of a deviating situation impacting (or potentially impacting) patient safety, product quality or compliance. The individual investigation is approved by QA and the CAPA Standard Operating Procedure describes that deviations (which include corrective and preventive actions) are a key element in the Quality Management Review ensuring dissemination to those directly responsible for assuring the quality of the product.

Relevant actions to correct and prevent recurrence of deviations need to be defined. The effectiveness of the defined and implemented actions is evaluated through an Effectiveness Check. All CAPAs and deviations are documented in the Novo Nordisk IT system. All the defined actions with potential impact on the device, processes and methods are implemented via the Change Control process. This ensures that the necessary verification and validation of the action will be done before implementation of the change.

Reviewer Comments

The CAPA summary was updated to include the requested information. This is acceptable.

Information Request #12

You provide a summary table of manufacturing control steps for the essential functions of the single dose pen-injector in Table 7 in the Manufacturing document. Please provide the process validation report for activation force and needle extension with an explanation of how/why these control steps are effective. Additionally, please provide testing on injection time on release. The current (b) (4) controls would not be effective in determining drug influence.

Sponsor Response

Novo Nordisk is providing the summary of the process validation, as well as the explanation for why/how the manufacturing control strategy for the performance of activation force (2.11.1.1), needle extension (2.11.1.2) and injection time (2.11.1.3) is effective. The information presented in this response is included as part of the following three documents:

- 3.2.P.7 Analysis of Functional Performance and Control Strategy: analysing the mechanical basis justifying why the proposed manufacturing control strategy is suitable, as well as addressing supplier controls.
- 3.2.P.3.4 Control of Critical Manufacturing Steps for the Drug-Device Combination

- Product: addressing how the manufacturing control strategy is implemented for the essential performance requirements
- 3.2.P.3.5 Process Validation for the Drug-Device Combination Product: providing the results of process validation for the essential performance requirements

In presenting the manufacturing control strategy for injection time in section 2.11.1.3, Novo Nordisk is also clarifying why an injection time release test is not included. The justification provided is based on the drug influence being negligible, due to low variability in viscosity.

(b) (4)

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Based on the data above supporting negligibility of drug influence on injection time, the submission of the summary of process validation and why/how the manufacturing control strategy for the performance of injection time is effective is acceptable.

12.2. Interactive Information Requests

12.2.1. Interactive Information Requests sent on 4/6/2021

Follow-On Deficiency – Information Request #13

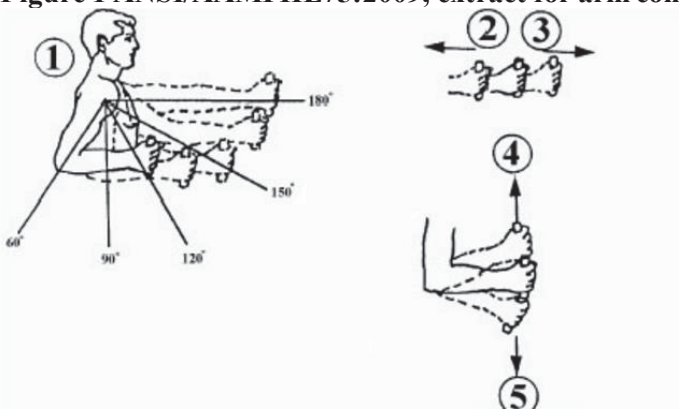
In Section 2.3.1 of *Response to FDA IR dated March 12, 2021*, the upper limit of (b) (4) for activation force is validated using pull movement towards the upper body. This is not acceptable as pull movement towards the upper body is not representation of activation force. Please provide anthropometric data using postures and motions representative of activation force. Analysis of appropriate postures and motions is necessary to

adequately validate this performance requirement. Please note that if your analysis results in a new specification, you should also provide updated design verification testing reports demonstrating your device meets this new specification.

Sponsor Response

Novo Nordisk would like to present an analysis of the appropriate postures and motions for the purpose of identifying the requirement limits for activation force for the single dose pen-injector. This analysis is done with reference to the postures presented in the human factors engineering standard ANSI/AAMI HE75:2009 [1] (Figure 1).

Figure 1 ANSI/AAMI HE75:2009, extract for arm control (section 7.3.5.3)



According to ANSI/AAMI HE75:2009, the upper extremity strength evaluation should account for differences in posture, especially of the elbow, shoulder and wrist. The interpretation for the motions shown in Figure 1 is as follows:

- The degree of elbow flexion (denoted by □ in Figure 1) sets the basis for the different levels of strength. Where the angle adopted for injection is between two angles in the standard, the weakest angle of the two is selected as the baseline.
- The motions pull-push (denoted by □ and □ in Figure 1) are pictured as a movement along an imaginary horizontal axis.
- The motions up-down (denoted by □ and □ in Figure 1) are pictured as a movement along an imaginary vertical axis.

For the use of the single dose pen-injector, the wrist remains in a locked position.

Analysis of the appropriate postures and motions

To aid in the analysis of the appropriate postures and motions, the photographs in Figure 2 and Figure 3 show a person injecting with a single dose pen-injector in the stomach and upper legs. These are the two injection sites indicated in the instructions for use (IFU) that are primarily used during self-injection.

Injection into the upper arm is expected to be an injection site used by healthcare providers. Healthcare providers will use a range of positions and motions that can optimize their strength compared to self-injection. Therefore, the analysis of self-injection into the stomach and upper legs represents a more challenging use scenario.

Injection into the stomach

Figure 2 Analysis of postures and motions for using the single dose pen-injector into the stomach

Note: the single dose pen-injector is not intended to be used to inject through clothing.
The photograph on the left depicts the degree of elbow flexion of 60° (in Figure 1). The middle and right photographs provide an example of self-injection when the pen-injector is placed at the stomach. The single dose pen-injector is activated by pulling the single dose pen-injector towards the stomach, a movement resulting from the combined rotation of the shoulder and bending of the elbow. This is therefore the primary motion denoted as a "pull" motion (in Figure 1).

Calculations with a " pull" motion for injection into the stomach

The calculations according to the "pull" motion (in Figure 1) presented in the document 3.2.P.7 Analysis of Functional Performance and Control Strategy and referenced in the Novo Nordisk response submitted on March 25, 2021 to the March 12, 2021 FDA Information Request (question 3 - Device) used the lowest value for the "pull" movement at a 60° elbow flexion in HE75 as the arm strength baseline ((b) (4) marked with a light blue box in the ANSI/AAMI HE75:2009 extract shown in Table 1 below).

(b) (4)

Injection into the upper leg

Figure 3 Analysis of postures and motions for using the single dose pen-injector into the upper leg

Note: the single dose pen-injector is not intended to be used to inject through clothing.
The photograph on the left depicts the degree of elbow flexion of 90° (in Figure 1). The middle and right photographs provide an example of self-injection when the pen-injector is placed on the upper leg. The single dose pen-injector is activated by pushing the single dose pen injector down towards the upper legs, a movement resulting from the slight increase of the elbow flexion. This is therefore the primary motion denoted as a "down" motion (in Figure 1).

Calculations with a " down" motion for injection into the upper leg

In addition to the information presented in the document 3.2.P.7 Analysis of Functional Performance and Control Strategy and referenced in the Novo Nordisk response submitted on March 25, 2021 to the March 12, 2021 FDA Information Request (question 3 - Device), Novo Nordisk would like to present calculations for the "down" motion.

These calculations are also based on the strength data according to ANSI/AAMI HE75:2009 (see Table 1). The arm strength within the degree of elbow flexion for the upper leg injection site derived from the analysis in Figure 3 is marked with a green box.

Table 1 Arm strength for "□ pull" (stomach injection) and "□ down" (upper leg injection) motions according to ANSI/AAMI HE75:2009

Degree of elbow flexion	(2) Pull		(5) Down	
	Left	Right	Left	Right
180°	(b) (4)			
150°				
120°				
90°				
60°				

NOTE 1—Force is given in N (pounds).

The maximum strength that can be exerted using the weakest arm when the elbow flexion is 90º (see Figure 1) when performing an "down" motion is (b) (4) (for the worst-case 5th percentile strength to males, see Table 1). Therefore:

(b) (4)

• in accordance to the ANSI/AAMI HE75:2009, the male values should be reduced to (b) (4) of the male strength to account for female strength values of the upper extremities (5th percentile females)
• the additional factor (b) (4) is chosen as a safety margin to ensure even people with reduced strength may operate the pen-injector.

Conclusion

According to the calculations provided in this response, Novo Nordisk confirms that the upper limit of activation force for the single dose pen-injector of (b) (4) is acceptable.

In the event that a user would not be able to activate the single dose pen-injector, the risk of being unable to activate the single dose pen-injector is further minimized by the user being able to optimize their strength by either choosing their dominant arm or assisting themselves with the second arm. In a real-life scenario, it is expected that users will choose the dominant arm, as well as optimize their position for strength and control.

Reviewer Comments

The response to the follow up deficiency elaborated on the representation of the pull motion for activation force – it is representative of injection into the stomach. Since there are two injection sites (stomach and thigh) for this AI, an additional analysis was provided on the injection force for the thigh. The analysis includes using down force for males at 90 degrees. According to ANSI/AAMI HE75:2009, to adjust the strengths to account for females the force should be reduced by 50%-60% for medical devices intended for use solely by females.

The sponsor reduced the force by 43.5% (b) (4) however they also went a step further to reduce the force by an additional factor (b) (4) to ensure even people with reduced strength would be able to operate the device. With

the additional reduction factor (b) (4) the down motion force equates to (b) (4). Since the sponsor performed a further reduction that was not required, this estimation to (b) (4) is acceptable; without the further reduction (b) (4). If this value were to be the maximum limit for the specification, it would exceed benchmark values therefore the (b) (4) is more appropriate.

This is acceptable.

12.2.2. Interactive Information Requests sent on 4/15/2021

Follow-On Deficiency - Information Request #14

Based on the information provided to FDA Device Request 9 regarding biocompatibility of Commercial (b) (4) additional information is needed on the chemicals presented in Table 22. Please report the quantity in nanograms or micrograms per device for each chemical in the table. This information is necessary to confirm worst-case exposure will be small to support the decision to leverage Clinical (b) (4) biocompatibility for Commercial (b) (4).

Sponsor Response

Novo Nordisk would like to report the quantity in micrograms per device for each chemical presented in Table 22 in the response to Device Request 9 dated March 25, 2021. The requested information is provided in Table 1 and Table 2 below.

Table 1 Components in Clinical (b) (4)

(b) (4)

Table 2 Components in Commercial [redacted]

Reviewer Comm

Alan Hood was consulted again and raised concerns regarding weight and the lack of a toxicological risk assessment. He also pointed me to the CDRH [redacted] webinar. See his comments regarding the response:

Strange. The [redacted] ug indicates the quantity is in the hundreds of milligram quantity, which is not small. Of course, small is relative; however, most [redacted] are present in a medical device [redacted] at much lower quantities due to (a) low percentage, (b) low [redacted] density, and (3) small surface area. The information below indicates that the body and cap are relatively large ([redacted] Is this true? Does the entire [redacted] contact the body?

Of these [redacted], the [redacted] that raises the greatest toxicity concern are [redacted]; however, the quantities of these [redacted] appear to be small if the quantity represents the total amount present. Although the other [redacted] are relatively lower toxicity, the quantities of these [redacted] appear quite high. To verify the reported total quantities [redacted] in Commercial [redacted] represent the total present, the Sponsor could provide documentation of the percentages [redacted]

Because the Sponsor appears to be stating that the total quantity [redacted] are known, it is unclear why the Sponsor has not conducted a toxicological risk assessment (i.e., reported a margin of safety) of these color additives. Are we not requesting a toxicological risk assessment [redacted]

With Alan's response, watched the webinar and decided to contact Rong Guo, biocompatibility focal point, for recommendation on if full biocom data would be needed based on this change. See her comments:

It would be ideal to test the final finished device component. Ask sponsor to provide a risk analysis.

What is the device to be used for? If per injector, or syringes, we evaluate the non-fluid pathway, which is the intact skin contact part. Based on the low risk of intact skin contact and the ratio of these [redacted] in the final device, I think it's reasonable to accept sponsor's risk analysis or justification for not performing CSI on the final finished device component. These [redacted] are commonly used in food or cosmetics:

(b) (4)

Based on her recommendation, the follow up deficiency below was sent.

12.2.3. Interactive Information Requests sent on 4/19/2021

Follow-On Deficiency - Information Request #15

We refer to your submission dated April 16, 2021, and your response to FDA Request 1. Based on the quantities of the chemical additives to the Commercial (b) (4) presentation of the device, please provide a Risk Assessment for the change to justify the (b) (4) is biocompatible and will not interact with the rest of the raw materials causing new irritants. Please note that this risk assessment will be sufficient justification for now; however, biocompatibility testing for the Final Finished Product is still necessary. Since Cytotoxicity testing has already been conducted, Irritation and Sensitization testing is still needed. Once completed, please file the updated biocompatibility report in the Design History File.

Sponsor Response

As requested, Novo Nordisk is hereby providing a Risk Assessment for the change of the chemical additives in the Commercial (b) (4) presentation of the device that is used for the single dose pen-injector for semaglutide. This Risk Assessment is based on the results from cytotoxicity, irritation and sensitization test data from related autoinjectors.

A summary of the biological evaluation report for the related autoinjector "(b) (4) Autoinjector" is presented in Appendix A. The (b) (4) Autoinjector is commercialized by Novo Nordisk in Japan with a semaglutide drug product for the treatment of Type 2 Diabetes Mellitus. Appendix A also shows a comparison between the (b) (4) Autoinjector and the Commercial (b) (4) The biological evaluation report summary for the (b) (4) Autoinjector presents the tests and results relevant to support the risk assessment for irritation and sensitization for the Commercial (b) (4).

(b) (4)

Finally, Novo Nordisk would like to confirm that irritation and sensitization testing will be performed on the Final Finished Product and that the updated biocompatibility report will be filed in the Design History File.

Risk assessment for the change of the chemical additives in the Commercial (b) (4) presentation of the single dose pen-injector

The Risk Assessment presented here is based on the results from cytotoxicity, irritation and sensitization test data from related autoinjectors.

The same materials, [redacted] are used in the related autoinjectors to which reference is being made (see Table 1 for comparisons to the Commercial [redacted]). It is for these related autoinjectors ([redacted] Autoinjector and "Similar Autoinjector", an [redacted] device approved in the US under the responsibility of another manufacturer) that cytotoxicity, sensitization and irritation testing was performed.

All three autoinjectors are fixed-dose autoinjectors for single use, with a prefilled syringe, for once-weekly use, with a comparable maximal injection time.

Table 1 Material comparison between related autoinjectors

Device	Commercial [redacted] (for the single dose pen-injector for semaglutide)	[redacted] Autoinjector (clinical and marketed versions, commercialized by Novo Nordisk)		Similar Autoinjector (designed and manufactured by [redacted] for another manufacturer)
Biological evaluation tests performed	• Cytotoxicity	• Cytotoxicity • Sensitization • Irritation		• Cytotoxicity • Sensitization • Irritation
Component	Body	Needle Cover	Cap	Front Shell, Rear Cover and Housing Connector
[redacted]				

The Body of the Commercial [redacted], the Needle Cover and Cap of the [redacted] Autoinjector and [redacted], [redacted] of a Similar Autoinjector shown in Table 1 are supplied by the same [redacted] supplier.

A higher quantity (w/w%) of [redacted] is presented in the [redacted] Autoinjector and the Similar Autoinjector compared to Commercial [redacted].

The Similar Autoinjector contains a higher quantity (w/w%) of [redacted] compared to Commercial [redacted]

The autoinjectors are manufactured with the same manufacturing process, [redacted].

The Commercial [redacted], the [redacted] Autoinjector and the Similar Autoinjector are classified as a surface device (contact to intact-skin). All three devices share the same [redacted] material. In addition, both the [redacted] Autoinjector and the Similar Autoinjector also contain the other compounds found in Commercial [redacted]

A summary of test results for the (b) (4) Autoinjector and the Similar Autoinjector for the endpoints of cytotoxicity, sensitization and irritation are shown in Table 2 and Table 3. All results were negative for cytotoxicity, sensitization and irritation.

Table 2 Summary of Biocompatibility Testing Conducted on (b) (4) Autoinjector

ISO Standard	Test	Results
10993-5	Cytotoxicity- MEM Elution Test in L-929 Mouse Fibroblast Cells	No reactivity at 24 and 48 hours
10993-10	Maximization Test for Delayed-Type Hypersensitivity in Hartley Guinea Pigs	Non-sensitizer
10993-10	Intracutaneous (Intradermal) Reactivity Test in New Zealand White Rabbits	Non-irritant

Table 3 Summary of Biocompatibility Testing Conducted on Similar Autoinjector

ISO Standard	Test	Results
10993-5	Cytotoxicity- MEM Elution Test in L-929 Mouse Fibroblast Cells	No reactivity at 24 and 48 hours
10993-10	Maximization Test for Delayed-Type Hypersensitivity in Hartley Guinea Pigs	Non-sensitizer
10993-10	Intracutaneous (Intradermal) Reactivity Test in New Zealand White Rabbits	Non-irritant

Previous biocompatibility test results from autoinjectors comparable to the Commercial (b) (4) passed the endpoints of cytotoxicity, sensitization and irritation. The comparable autoinjectors and the Commercial (b) (4) use the same suppliers (b) (4). The comparable autoinjectors and the Commercial (b) (4) have the same manufacturing process at (b) ( ).
The following points are considered crucial to provide a basis for the risk assessment for irritation and sensitization for the Commercial (b) (4):

- The material composition of the (b) (4) Commercial, (b) (4) Autoinjector and the Similar Autoinjector show (b) (4) the same.
- The (b) (4) Autoinjector and the Similar Autoinjector both contain (b) (4) at a higher quantity (w/w %) than Commercial (b) (4).
- The (b) (4) Autoinjector and the similar autoinjector both contain (b) (4) where the (b) (4) Autoinjector contains a slightly lower quantity (w/w %) and the Similar Autoinjector contains a higher quantity (w/w %) than Commercial (b) (4).
- In addition, both the (b) (4) Autoinjector and the Similar Autoinjector also contain the other compounds found in Commercial (b) (4)

The test results for irritation and sensitization for the two comparable autoinjectors are considered to represent equal or worst-case scenarios for evaluating the biocompatibility of the Commercial (b) (4) The passed endpoints for the comparable autoinjectors for irritation and sensitization are therefore seen as evidence for the biocompatibility (b) (4) as well as of the biocompatibility in the event of their potential interaction (b) (4) present in the Final Finished Product of the Commercial (b) (4).

In conclusion, exposure to any or all of the constituents in the Commercial (b) (4) via intact dermal contact during use of the autoinjectors is considered to be of no safety concern/negligible risk for the user from a toxicological perspective. Therefore, this risk assessment, based on the comparable autoinjectors justify the (b) (4) is biocompatible and will not interact with the rest of the raw materials causing new irritants.

Furthermore, Novo Nordisk will ensure that irritation and sensitization testing is conducted for the Final Finished Product of Commercial [(b) (4)]. The updated biocompatibility report will be filed in the Design History File.

Table 4 Comparison of Commercial [(b) (4)] with [(b) (4)] Autoinjector for biocompatibility purposes

	Commercial [(b) (4)] (for the single dose pen-injector for semaglutide)	[(b) (4)] Autoinjector (clinical and marketed versions, commercialized by Novo Nordisk)	Comparability for biocompatibility
Intended use / Indication for use	A single dose single patient pre-filled pen-injector to be used for subcutaneous injection of the glucagon-like-peptide-1 (GLP-1) analogue semaglutide as an adjunct to a reduced-calorie diet and increased physical activity for weight management.	A single dose, single patient, pre-filled pen-injector intended for once weekly subcutaneous injection of GLP-1 analogue semaglutide for the treatment of T2DM in patients.	The frequency of use is identical (once weekly). The duration of therapy is assumed to be life-long treatment in both indications, as this is the worst-case scenario. From the comparison of the intended user groups in both indications, there are no expected differences with regard to handling of the device (see handling steps).
Handling steps (Human factors)	Key steps include removing cap, injecting dose by pressing the pen-injector against the injection site, 5-10 seconds injection time while a yellow bar progressively blocks the window, removal and disposal of pen-injector	Key steps include removing cap, injecting dose by pressing the pen-injector against the injection site, 5-10 seconds injection time while a yellow bar progressively blocks the window, removal and disposal of pen-injector	No difference in handling steps
Length with the Cap (approximately)	[(b) (4)]		No difference in dimension and form
Diameter (approximately)			No difference in dimension and form

Reviewer Comments

The risk assessment compared the to be marketed device (Commercial [(b) (4)]) to two related autoinjectors with the similar intended uses, handling steps and dimensions. The chemical make-up of all three devices were provided. [(b) (4)] Clinical [(b) (4)] and Commercial [(b) (4)] [(b) (4)] The results in the analysis show that the [(b) (4)] Autoinjector and the Similar Autoinjector both have higher concentrations [(b) (4)] in their devices compared to the subject Commercial [(b) (4)] device. It is also confirmed that the autoinjectors are manufactured with the same manufacturing process. Biocompatibility summaries for the [(b) (4)] Autoinjector and Similar Autoinjector show that all results were negative for cytotoxicity, sensitization and irritation.

This risk assessment along with the sponsors agreement to providing irritation and sensitization testing for the final finished combination product (Commercial [(b) (4)]) in the Design History File, this response is acceptable. (please note that cytotoxicity testing for Commercial [(b) (4)] was already provided which is why only irritation and sensitization are being indicated in the response).

12.2.4. Interactive Information Requests sent on 4/23/2021

In section 2.4.1 of your response to our March 12, 2021, information request, you justify the [(b) (4)] needle cover override force by noting that ISO 11608-5:2012 states that the needle cover "shall withstand a minimum load as determined by the risk assessment (at least two times its actuation force)". Your response is inadequate for the following reasons:

a. Please note that the standard says "at least" two times the activation force. The purpose of this specification is to mitigate the risk of accidental needle sticks. As such, the specification for this performance requirement should not only be set to be a minimum 2x the activation force, but should also be informed by a risk assessment that considers an adult user's strength capabilities. The current (b) (4) force specification is well within the adult populations capabilities as demonstrated by the anthropometric study used to evaluate the activation force specification.
b. Additionally, you provide scenarios that consider the distinguishability of the two forces. However, you did not provide any user capability evidence that validated this distinguishability or the set specifications.

Therefore, please increase the needle cover override force specification and evaluate the provided data to the new specification at a confidence and reliability of 95%/99%. Otherwise, provide additional justification, with evidence of validation that considers user capabilities, to support the current specification and distinguishability mitigation.

Sponsor Response

Novo Nordisk will increase the needle cover deflection specification by defining the applied force for data analysis to (b) (4). The needle cover deflection specification represents the performance of the needle cover override force, when measuring deflection at a specified applied force.
This new specification limit is supported by a risk assessment, presented in section 2.2.1, which considers the user strength and pain-perception capabilities, as well as the two scenarios presented as part of a previous answer to the Agency (Response to FDA Request dated April 23, 2021, Request 4).
Finally, Novo Nordisk will present the re-analysis of the provided design verification data based on the new specification limit at a confidence interval of 95% and a probability content of 99% after preconditioning according to ISO 11608-1 conditions and after accelerated aging (section 2.2.2).

Risk assessment for the choice of applied force of (b) (4)

Novo Nordisk will present different arguments supporting the acceptability of the updated applied force of (b) (4) in the needle cover deflection specification.

- Section 2.2.1.1 presents the considerations that are generally applicable (user group considerations)
- Section 2.2.1.2 presents the considerations that are scenario-specific. The two scenarios presented in this answer correspond to the scenarios presented as part of a previous answer to the Agency (Response to FDA Request dated April 23, 2021, Request 4).

General arguments

The following general arguments support the acceptability of the updated applied force of (b) (4) in terms of the user group's strength capabilities:

- The user will not apply their maximum force
  As per AAMI/ANSI HE75:2009, Section 7.3.5.1 'Factors affecting strength' [1], '*It is seldom appropriate to expect people to exert their maximum strength*' in their interaction with medical devices. Additionally, a stronger user of the single dose pen-injector is expected to apply a smaller proportion of their maximum strength when operating the device than a weaker one, resulting in a similar absolute force being applied.
- Obesity patients are not expected to be stronger on upper extremities used for overriding a locked device
  Although there are studies proposing that the obese population is stronger than the population of healthy weight, such studies are contested and are generally associated to lower extremities [2]. The general strength of the obese user-group is therefore not expected to exceed that of the general population for the muscles needed to override the needle cover lock in the two scenarios described in section 2.2.1.2.

Scenario-specific argumentations

The following arguments support the acceptability of the updated applied force of (b) (4) in terms of specific scenarios:

3. Scenario 1: Pushing a locked device against the skin
4. Scenario 2: Handling a used single dose pen-injector and accidentally interacting with the needle cover

Scenario 1: Pushing a locked device against the skin

Table 1 shows an evaluation of the applied force limit and the resulting static pressure on the skin, when a user intends to inject with a used single dose pen-injector. The table also estimates pain perception, by calculating how a force equal to the limit specified in the needle cover deflection specification is related to pain onset for the patient.

The pressure-pain threshold is defined as the point at which a sensation of pressure changes into a sensation of pain [3]. The pressure pain threshold is typically given in kg/cm2 and in some publications, Pascals (conversion factor equivalent to the gravitational acceleration of 9.81 m/s2). Depending on the place on the body, the pressure pain threshold ranges from 2 kg/cm2 to 4.5 kg/cm2 [3][4]. The pressure pain threshold range is also dependent on the presence of other diseases, on gender [3] and, potentially, body mass index. A further assumption for pain considerations is that the user will avoid injecting into nerves/bone, associated with lower pain thresholds [5].

The assessment presented in Table 1 uses the pressure pain threshold values on healthy female subjects of Montenegro *et al.*, 2012 [6] as a reference for injections into the abdomen. The abdomen as the place for measurement is considered relevant for the intended use of the single dose pen-injector. The highest reported pressure pain threshold level for the abdomen is 2.93 kg/cm2. The value of 2.93 kg/cm2 is therefore taken as a baseline to determine the expected pain onset experienced by the patient.

For the single dose pen-injector the contact area between the skin and the device is that of the front of the needle cover. The needle cover is ring-shaped, with an outer diameter of (b) (4) and inner diameter of (b) (4) Therefore, the resulting contact area for the front of the needle cover is (b) (4) Using the contact area and the specified needle cover deflection force (both the original and the value updated as part of this response) the calculation of pressure on the skin is given in Table 1 in kg/cm2.

An example of the calculation of the pressure on the skin for an increased specification of (b) (4) is presented below:

$$Pressure\ on\ the\ skin = \frac{Increased\ specification\ in\ \mathrm{N}}{Needle\ cover\ surface\ area} \times conversion\ \mathrm{N}\ to\ \mathrm{kg}$$

(b) (4)

Table 1 Evaluation of the excess force confirmed for two proposed applied forces for the needle cover deflection test and the associated pressure on the skin and expected pain/discomfort

Condition	Comparison to the specified upper activation force limit (b) (4)	Comparison to the nominal activation force (b) (4)	Calculated pressure** on the skin from applying the specified force limit	Ratio of pressure pain threshold (baseline is 2.93 kg/cm²)***
Initial limit (b) (4)	(b) (4)			
Updated limit (b) (4)				

* In line with the minimum requirement in ISO 11608-5 ("*at least two time the actuation force*")

** Conversion factor between kg/cm² and SI pressure units (Pascal) uses the gravitational acceleration as

***Reported as the Pressure-Pain Threshold, based on pain perception algometry measurements on women with a healthy weight

Table 1 shows that:

- The proposed updated limit of (b) (4) will guarantee a needle cover override function that is at least (b) (4) times higher than the activation force upper limit (around (b) (4) times higher than the nominal value of (b) (4) The updated limit of (b) (4) will therefore guarantee an additional increase in the distinguishability between the activation force and the needle cover override force, compared to the original proposed limit.

- The calculated pressure is used to determine a ratio against a described pressure-pain onset value of 2.93 kg/cm2 [6]. According to these calculations, the updated limit of (b) (4) would result in a sensation of pain that is approximately (b) (4) times higher than the reported threshold level of pressure-pain onset on the abdomen of healthy women. The conclusion from this ability to cause pain with a locked device is that the user would stop pressing in order to observe the state of the device, as a response to the unexpected pain.

Scenario 2: Handling a used single dose pen-injector and accidentally interacting with the needle cover
When analysing a scenario where a user handles a used single dose pen-injector in a way that could accidentally leads to interaction with the needle cover, these movements would be understood as clumsy/uncoordinated motions. These motions would result in lower force compared to the deliberate force that is expected when intending to activate the device.

Evaluation of the provided data to the increased specification for the needle cover override force measured as deflection
The results from measurement of the needle cover deflection have been re-analyzed for an applied force of (b) (4) The data are reported in Table 2 and Table 3. The data are reported including a full statistical summary (mean, standard deviation, min, max, *p*-value, *k*-value) and the corresponding upper tolerance value.
Therefore, the needle cover override force intended to prevent the re-use of a used single dose pen-injector (see Scenario 1) will be sufficient to mitigate the risk posed by accidental contact with the needle cover during handling.

Table 2 Needle cover override, deflection, according to ISO 11608-1 conditions for semaglutide C 3.2 mg/ml (0.75 ml single dose pen-injector variant)

Test item	Sample size	Test condition[2]	Acceptance criteria[3]	Results (mm)	Conclusion
Single dose pen-injector with semaglutide C[1,4]	60	Standard atmosphere, 23°C ± 5°C, 50% RH ± 25% RH	(b) (4)	(b) (4)	Pass
	60	Cool atmosphere, 5°C ± 3°C			
	60	Warm atmosphere, 40°C ± 2°C, 50% RH ± 10% RH			
	60	Cold storage final device			
	30	After free fall from 1.0 m			
	20	After vibration			

[1] Tests performed at (b) (4) on batches as reported in 3.2.P.7 Test Report According to EN ISO 11608-1, EN ISO 11608-5 and JIS T 3226-1 Needle Based Injection System for Medical Use and Test Report for Injection Time, Table 15
[2] Preconditions based on ISO 11608-1, Table 3. Cold storage reflects the intended storage of the product. Warm storage is excluded, as the maximum storage temperature is 5°C ± 3°C.
[3] One-sided tolerance limits are described by confidence: 95%, probability content, p: 99%
[4] The data generated on the 0.75 ml single dose pen-injector using the semaglutide C formulation covers both the 0.5 ml and 0.75 ml variant, as this feature is independent of the drug product formulation and fill-volume.

Table 3 **Needle cover override, deflection, after accelerated shelf-life equivalent to (b) (4) months for semaglutide C 3.2 mg/ml (0.75 ml single dose pen-injector variant)**

Test item	Sample size	Test conditions	Acceptance criteria[3]	Results (mm)	Conclusion
Single dose pen-injector with semaglutide C[1,3]	60	Standard atmosphere, 23°C ± 5°C, 50% RH ± 25% RH after accelerated shelf-life conditions corresponding to storage at (b) (4) at 5°C ± 3°C and (b) (4) at 23°C ± 5°C, 50% RH ± 25% RH	(b) (4)	(b) (4)	Pass

[1] Tests performed at (b) (4) on drug product batch no. HW52W68

[2]One-sided tolerance limits are described by confidence: 95%, probability content, p: 99% (k-factor: 2.807)

[3]The data generated on the 0.75 ml single dose pen-injector using the semaglutide C formulation covers both the 0.5 ml and 0.75 ml variant, as this feature is independent of the drug product formulation and fill-volume.

Conclusion

Novo Nordisk will increase the needle cover deflection specification by defining the applied force for data analysis to (b) (4) The needle cover deflection specification represents the performance of the needle cover override force, when measuring needle cover deflection at a specified applied force.

The proposed updated limit of (b) (4) will guarantee a needle cover override force that is at least (b) (4) -times higher than the activation force upper limit and around (b) (4) times higher than the nominal value of (b) (4) The updated limit of (b) (4) will therefore guarantee an additional increase in the distinguishability between the activation force and the needle cover override force, compared to the original proposed limit.

In addition, calculations based on a limit of performance documented at an applied force of (b) (4) indicate that pushing a locked device into the skin would likely result in pain above a pressure pain threshold. The expectation under such a scenario is that the user would stop pressing in order to observe the state of the device, as a response to the unexpected pain.

The conclusion from a risk assessment regarding the use of a force of (b) (4) in the needle cover deflection test is supported by the expected intended use and users of the single dose pen-injector, including potential re-use of a locked device (Scenario 1 in 2.2.1.2) or accidental contact with the needle cover during handling (Scenario 2 in 2.2.1.2).

Additionally, Novo Nordisk has re-analyzed the design verification test data based on the new specification limit of (b) (4) at a confidence interval of 95% and a probability content of 99% after preconditioning according ISO 11608-1 conditions and after accelerated aging. From the data presented, it is concluded that the single dose pen-injector complies to the new specification limit.

Based on the risk assessment in 2.2.1 and the device performance during design verification shown in 2.2.2, the proposed updated specification for the needle cover deflection is adequate to additionally mitigate the risk of accidental needle sticks. Thus, Novo Nordisk confirms that the needle cover deflection specification will be implemented by change controls as part of the quality management system.

Reviewer Comment

The Needle Cover Override force was updated to (b) (4) instead of (b) (4). A risk assessment for the choice of (b) (4) was provided:

General Argument Comments:

The needle cover is a safety device intended to prevent patients from accidentally exposing the needle after a completed injection. The general arguments presented that the user will not apply their maximum force or the assumption that obese user-group is not expected to exceed that of the general population is not validated. Anthropometric data provided in the injection force validation indicates that adult users can exert strengths up to (b) (4).

Scenario-specific Arguments Comments:
Scenario 1: Pushing a locked device against the skin – pain threshold levels for the abdomen on healthy females are presented. From the data, the highest reported pressure pain threshold level of the abdomen (2.93 kg/cm^2) is taken as the baseline to determine the expected pain onset experienced by the patient. The pressure of the needle cover on the skin is calculated using the new (b) (4) specification, needle cover surface area and the conversion factor of N to kg. This is also done for the old (b) (4) specification. The conclusion is drawn that the updated limit will result in a sensation of pain approximately (b) (4) times higher than the reported threshold of pressure-pain onset on the abdomen of healthy women. A final note is made that the (b) (4) force is (b) (4) times greater than the upper limit activation force of (b) (4) and therefore there is an increased distinguishability between the activation force and the needle cover override force.
These analyses are not appropriate validation methods of this new specification. The specification is not evaluate likelihood of a user overriding the needle cover based on the discomfort it may cause them or the notable increased force it takes compared to a normal injection; the force should be evaluated on the users ability, are users able to override the force or is it out of their strength capabilities.

Scenario 2: Handling a used single dose pen-injector and accidentally interacting with the needle cover – it is noted that the scenario where a user would handle a used device in a way that could interact the needle cover is one which a user is acting clumsy/uncoordinated and that these movements would result in lower force strengths compared to deliberate forces. This is again an assumption based rational. No validating data is provided to support this claim.

Despite the lack of acceptable validation for this new specification, together with reinforcements that the device is has been used by visual feedback and the acceptability of HF reports, the raised Needle Cover Override force specification to (b) (4) is acceptable.

Though the sponsor did not provide Kact values themselves, based on my calculations the values are well within the acceptance criteria.

This is acceptable.

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/

HAMET M TOURE
04/30/2021 12:12:22 PM
Documentation of review on behalf of CDRH

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	03/15/2021
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 215256
Product Type:	Combination Product
Drug Constituent Name and Strength	semaglutide injection 0.25 mg/0.5 mL , 0.5 mg/0.5 mL, 1 mg/0.5 mL, 1.7 mg/0.75 mL, 2.4 mg/0.75 mL
Device Constituent:	prefilled pen injector
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novo Nordisk, Inc (Novo Nordisk)
Submission Date:	12/4/2020
OSE RCM #:	2020-2568, 2020-2567
DMEPA Safety Evaluator:	Jason Flint, MBA, PMP
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 215256 for semaglutide injection.

The device user interface consists of a pen-injector (Figure 1) with label, carton and a patient leaflet consisting of an Instructions for Use (IFU) and a Patient Packaging Insert (PPI). The proposed prefilled pen injector device constituent part is intended as an adjunct to a reduced calorie diet and increased physical activity for weight management in adult patients.

1.1 PRODUCT DESCRIPTION

See appendix F for images of the carton and container labeling and IFU.

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

We reviewed the human factors validation study protocol on March 10, 2020[1]. Novo Nordisk indicates that they incorporated our recommendations with one exception. Novo Nordisk excluded adolescents from the human factors validation study because adolescents are not included in the indication supported by the NDA.

We note that the applicant uses the name (b) (4) ***" throughout their HF Validation Study Report; however we are currently reviewing the proposed proprietary name "Wegovy***" for this product.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B

[1] Schlick, James. Human Factors Validation Study Protocol Review for semaglutide injection IND 126360. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20200310. RCM No.: 2020-208.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F
Analysis of Differentiation Study Results	G
Differentiation Study Comparators	H

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed (Table 2), and our analysis to determine if the results support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

The HF validation study included untrained participants as follows:

User Group	Number of Pen-injector Experienced Participants	Number of Pen-injector Naïve Participants
Adult Patients	15	15
Healthcare Providers (HCP)	15	NA
Pharmacists	15 (differentiation only)	NA
Caregivers	15	15

The HF validation study included simulated use of the product, and assessment of participants' ability to differentiate between the proposed product and a selection of comparator products. We note that for HCP participants, the applicant included a broader range of comparator products. See Appendix G for a table of comparators used in the differentiation study.

3.2 RESULTS AND ANALYSES

Table 2 describes the study results, Novo Nordisk, Inc's analyses of the results, and DMEPA's analyses and recommendations.

Identified Issues and DMEPA's Findings – Simulated Use		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	There were 11 failures that led to underdose because participants lifted the pen-injector from the injection pad prematurely. The subjective data and the Applicant's root cause analysis stated: • Test artefact. Simulated environment. Three participants attributed their use error to aspects of the simulated test environment such as nervousness, rushing, or use of an injection pad. (One participant noticed pooling on the injection pad after the first simulated injection and thought the pooling was a byproduct of injecting into an injection pad rather than into skin and consequently, she did not adjust her actions during her second simulated injection.) • Negative transfer. Prior device experience. Four participants applied their prior knowledge and experience with other devices that deliver medication more quickly to the pen-injector. • Multistep injection process. The IFU presents step 4 (Inject (b) (4) ®) across two columns of information with multiple directions and visual cues. Although the step title directs the participant to inject the medication, the step is relatively complex and relies on the user to read the full two columns of information thoroughly to understand how to administer a complete injection. As such, one participant who did not read all of step 4 ultimately removed the pen-injector prematurely, resulting in an underdose. • Pen-injector mechanics require constant firm grip. The pen-injector mechanics require users to hold the pen-injector down fully with a firm grip for the entire duration of the	Based on the URRA, if this task is omitted or not performed correctly, there is risk of lack of clinical efficacy. We agree with the Applicant's root cause analyses for these use errors. Our review of the study results identified subjective feedback that indicated that while some use errors were due to test artefact or negative transfer, some appear to be related to the pen injector design and the layout of the IFU. Our review of the labels and labeling (user interface, etc.) finds that the IFU does include instructions for step 4 (Inject (b) (4)) which spans across two columns; however, this arrangement is not unique to this product, and additional labeling changes may not reduce the occurrence of this use error. We discussed the errors associated with the device design as it relates to the requirement of a firm grip for the duration of the injection to deliver a full dose with our colleagues at CDRH, who noted that the specifications for the device did not indicate any issue that should result in engaging the needle cover prematurely. Based on our overall assessment, we have no recommendations for this use error.

	injection. Loosening grip on the pen-injector can cause the needle cover to engage. • Ambiguous auditory feedback. The pen-injector produces an audible click sound at the start of the injection and near the end of the injection. The pen-injector relies on users to read the IFU to know this information or observe the yellow bar to understand that the injection is complete rather than only relying on the clicks to determine injection completeness. • High IFU visual density. The IFU cover has relatively high information and visual density (e.g., text, colours, font sizes, graphics). As such, one participant mistook the IFU for promotional material and put it aside, thereby relying fully on his own knowledge how to administer an injection and resulting in an underdose. The applicant has not proposed additional mitigations to address these use errors.	
2.	There were 3 failures due to inadvertent activation of the needle cover. For example, participants did not press hard enough to activate the injection, and when they adjusted their grip, the needle guard activated. The subjective data and the Applicant's root cause analysis stated: • Pen-injector mechanics require constant firm grip. The pen-injector mechanics require users to hold the pen-injector down fully with a firm grip for the entire duration of the injection. Loosening grip on the pen-injector can cause the needle cover to engage. As such, two participants inadvertently engaged the needle cover prematurely, resulting in an underdose. • Increased force required to administer an injection when holding pen-injector at angle. The IFU depicts an illustration of the pen-injector being injected at a 90-degree angle and does not explicitly state that	Based on the URRA, if this task is omitted or not performed correctly there is risk of lack of clinical efficacy. We agree with the Applicant's root cause analyses for this use error. Our review of the study results identified subjective feedback that indicated that these use errors were attributed to the device design as it relates to the force required to activate and hold the pen injector, and the location of the viewing window. Our review of the user interface finds that the location of the viewing window is not unique to this pen-injector, and therefore we do not have recommendations for this aspect of the device design. We discussed the errors associated with the device design with our colleagues at CDRH, who note that the requirement to inject at 90 degrees is common among other prefilled pen injectors. Based on our overall assessment, we have no recommendations for this use error.

	users cannot administer an injection if the pen-injector is held at an angle other than 90 degrees. One participant who referenced the IFU when administering a simulated injection, held the pen-injector at a slightly less than 90-degree angle, which therefore required her to use more force to activate the injection than needed when the pen injector is held at a 90-degree angle. The additional force led her to adjust her grip, which provided a change in pressure on the pen-injector. This change in pressure resulted in an unexpected needle deployment, which caused the participant to lift the pen-injector from the injection cushion slightly and consequently engage the needle cover, thereby resulting in an incomplete simulated injection. • Viewing angle of yellow bar. The pen window enables users to see the yellow bar move to indicate the injection status (i.e., not started, in progress, complete) This window is visible on two sides of the pen-injector. Depending on the injection orientation, users can or cannot observe the yellow bar in the pen window. The applicant has not proposed additional mitigations to address these use errors.	
3.	One participant experienced difficulty understanding how to activate pen-injector drug delivery. We note that the Applicant indicates that this was a "Use difficulty", however, the participant applied pressure to the needle cover with her hand to trigger needle activation and drug delivery, which should be considered a use error. The subjective data and the Applicant's root cause analysis stated: • Inconspicuous built-in needle. The pen-injector's built-in needle is obscured within the needle cover, thereby relying on users to know independently or reference the IFU to	Based on the URRA, if this task is omitted or not performed correctly there is risk of lack of clinical efficacy. We agree with the Applicant's root cause analysis for this use error. Our review of the study results identified subjective feedback that indicated that the participant activated the needle guard while trying to locate the injection end. Our review of the user interface finds that this design feature is not unique to this pen-injector. However, we note that adding a "Needle End" label to help users identify which end of the pen-injector contains the needle could mitigate this use error.

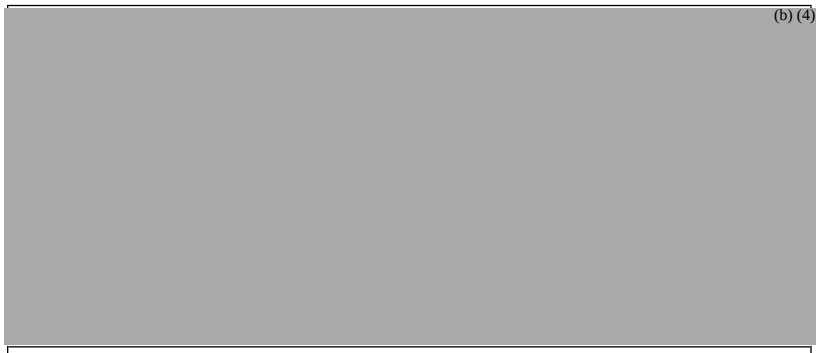
	understand the single-use pen-injector's needle location. The applicant has not proposed additional mitigations to address these use errors.	Based on our overall assessment, we find the user interface can be improved. We provide recommendation in Table 4 to address this concern. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.
4.	One participant experienced difficulty determining if each simulated injection was complete. The subjective data and the Applicant's root cause analysis stated: • Test artefact – Unclear instructions. At the end of the test material presentation period, one participant misunderstood the test administrator's verbal instructions to return the test materials to the drawer after the exploration period. She believed that this instruction meant she was no longer permitted access to those materials during the subsequent tasks. As such, she did not reference the IFU during the simulated injection tasks and consequently experienced difficulty determining if she had administered complete simulated injections. The applicant did not propose any additional mitigations to address this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of lack of efficacy. We agree with the Applicant's root cause analysis that this use error was related to test artifact, and we have no recommendations.

We note that the applicant did not assess the task of identifying that the drug was not expired, or that it was clear and colorless in the URRA or within the HF validation study. With respect to the task of checking whether the medication was clear and colorless, the applicant gave the following rationale:

> "pen injectors with unclear/colored drug will not be included in the study. Furthermore, it is anticipated that several participants will skip the step of checking if the drug is clear and colorless, as they would not expect a faulty pen-injector in a usability evaluation setting. Moreover, the step of checking if the drug is clear and colorless might be done simultaneously in a real life setting during e.g. unpacking or removal of the cap, making it unfit for testing in UT228. Based on these rationales Novo Nordisk will not include the step concerning checking the drug is clear and colorless in UT228."

We disagree with the applicant's rationale about checking that the drug is clear and colorless. By not assessing this task, we do not have an assessment of the clinical impact of failure to complete this task or data on whether participants who did fail to complete this task or completed the task incorrectly, attributed the failure to the user interface.

We conducted a heuristic evaluation of the proposed IFU with respect to the critical tasks "Check the expiration date" and "Check that the medication is clear and colorless," and identified that there is information about these tasks in the Important Information Section and in Step 1 Prepare for your injection. The important information section contains the statements "Check that TRADENAME has not expired" and "Check that TRADENAME is clear and colorless." In contrast, the instructions in step 1 includes bulleted statements indicating when a user should not use their medication. (Figure 2) We are concerned that the negative "Do not" statement may be overlooked, and the statement (b) (4) (b) (4) may be misinterpreted (b) (4) (b) (4). We provide a recommendation in table 4 to address this concern.



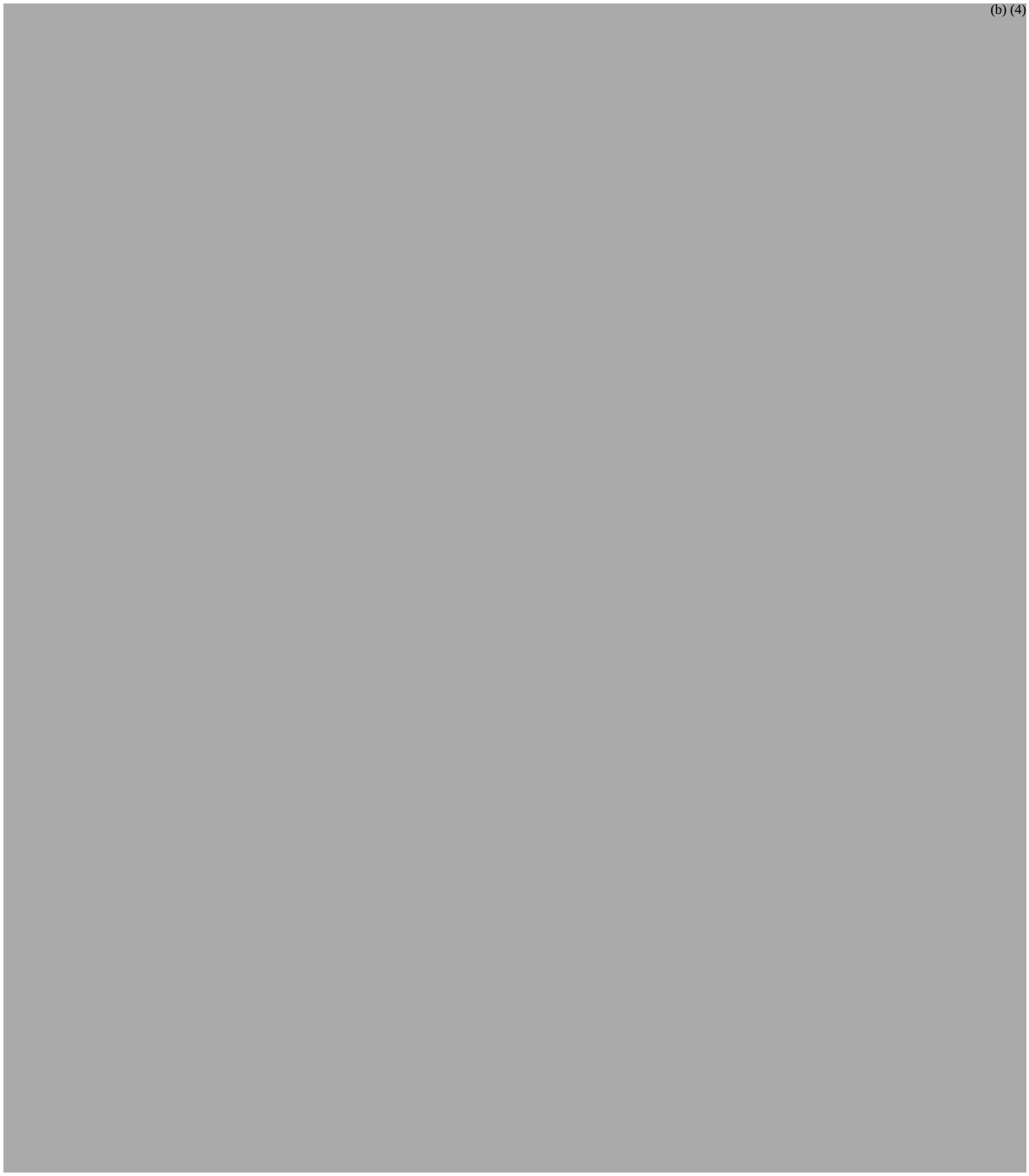
Instructions in Step 1.

SIMULATED USE - ANALYSIS OF NON-CRITICAL TASKS

There were no errors with non-critical tasks.

DIFFERENTIATION STUDY

All of the differentiation errors in the study were between the different strengths of the proposed product. Based on our heuristic review, and the results of the differentiation study, we determined that the different strengths are adequately differentiated. See Appendix G for a detailed analysis.



Tables 3 and 4 below include the identified medication error issues with the submitted packaging, label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 3: Identified Issues and Recommendations for Division of Diabetes, Lipid Disorders, and Obesity (DDLO)			
	Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information			
1.	Use of trailing zero for dosing statements in Section 2, Dosage and Administration	Trailing zeros have led to ten-fold overdoses.[2]	Remove the trailing zeros throughout this section (e.g. change 1.0 mg to 1 mg).
2.	Section 16: How supplied/Storage and Handling includes the term (b) (4) (b) (4) however, the container labels and carton labeling use the package type term, "single dose."	Inconsistent package type terms may result in confusion.	We recommend that the Office of Pharmaceutical Quality convey the correct package type term to the applicant and that the correct package type term is used consistently across all labels and labeling.

[2] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2021 FEB 25]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Table 4: Identified Issues and Recommendations for Novo Nordisk, Inc. Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.(entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Product Design			
1.	We note that one participant in the HF validation study had difficulty understanding where the needle end of the pen-injector was located.	This use difficulty could lead to accidental activation of the pen-injector, or inadvertent needle stick injury.	Consider adding a label to the pen-injector to indicate to the user which end is the “needle-end”. We have determined that this change would not require additional human factors data.
Instructions For Use			
1.	We note that Step 1 in the Instructions for Use contains the statement (b) (4) (b) (4)	We are concerned that a user may overlook the preceding “Do not” statement and misinterpret the statement (b) (4) (b) (4)	We recommend rewriting this step to eliminate the potential for misinterpretation. For example: The TRADENAME medicine is not clear and colorless through the pen window.

Carton Labeling			
1.	The recommended dosage statement can be improved.	To ensure consistent language with the prescribing information.	To ensure consistency with the Prescribing Information, revise the statement, (b) (4) (b) (4) to read "Recommended Dosage: See prescribing information."
Carton and Container Labeling			
1.	As currently presented, the format for the expiration date is not defined.	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

4. CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrate that representative users can use the product safely and effectively. Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 3 for the Division and Table 4 for Novo Nordisk, Inc. We ask that the Division convey Table 4 in its entirety to Novo Nordisk, Inc so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR NOVO NORDISK, INC

We found the results of your human factors (HF) validation study acceptable. Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4 and we recommend that you implement these recommendations prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for semaglutide injection that Novo Nordisk, Inc submitted on 12/4/2020.

Table 5. Relevant Product Information	
Initial Approval Date	12/05/2017
Therapeutic Drug Class or New Drug Class	Glucagon-like-peptide (GLP-1) receptor agonist
Active Ingredient (Drug or Biologic)	semaglutide
Indication	Adjunct to a reduced-calorie diet and increased physical activity for weight management in subjects with an initial Body Mass Index (BMI) of ≥ 30 kg/m^2 (obese) or 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity. (b) (4)
Route of Administration	subcutaneous
Dosage Form	Injection
Strength	0.25 mg/0.5 mL; 0.5 mg/0.5 mL; 1 mg/0.5 mL; 1.7 mg/0.75 mL; 2.4 mg/0.75 mL
Dose and Frequency	0.25 mg to 2.4 mg once weekly
How Supplied	Carton containing 4 pens
Storage	Refrigerated
Container Closure/Device Constituent	(b) (4) Autoinjector with prefilled injection liquid.
Intended Users	Patients, Caregivers, Healthcare Providers
Intended Use Environment	Home environment and medical facility

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On 1/22/2021, we searched the L:drive and AIMS using the terms, 'semaglutide' to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified one previous reviews[3], and we confirmed that our previous recommendations were implemented or considered.

[3] Schlick, J. Human Factors Validation Study Protocol Review for semaglutide injection IND 126360. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20200310. RCM No.: 2020-208.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in EDR via:
N/A

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
Human Factors Summary Report
Human Factors Study
APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

We sent an information request on 02/18/2021 requesting the full use-related risk analysis. The applicant's response is here: \\CDSESUB1\evsprod\nda215256\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud\weight-management\5354-other-stud-rep\dv3396-ut228\user-related-risk-analysis.pdf

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[4] along with postmarket medication error data, we reviewed the following labels and labeling submitted by Novo Nordisk on 12/4/2020.

- Container label (0.25 mg)
- Carton labeling (0.25 mg)
- Professional Sample Container Label (0.25 mg)
- Professional Sample Carton Labeling (0.25 mg)
- Instructions for Use
- Medication Guide
- Prescribing Information

5 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[4] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Appendix G: Analysis of differentiation study results

Identified Issues and DMEPA's Findings – Product Differentiation		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the task "Select correct carton" there were 5 use errors. For example, two participants selected a higher dose than they were prescribed, and 3 selected lower doses than they were prescribed. The subjective data and the Applicant's root cause analysis stated: • Test artefact. Inability to store own medication. To simulate a worst-case scenario, before the start of each session the test team placed the cartons, including the participant's prescribed carton, inside the refrigerator. Participants were unable to store their own or their loved one's medication and consequently could not rely on their own memory of where they stored the medication or other visual cues such as a handwritten patient name to identify their medication. • Similar carton appearance. The (b) (4) cartons are visually identical except for their respective dose sizes and dose size indicator colours (e.g., aqua for 0.25 mg, brown for 1 mg, and blue for 1.7 mg). The cartons include the same (b) (4) product name, graphics, and text layout. Furthermore, the (b) (4) 0.25 mg and (b) (4) 1.7 mg cartons' dose size indicators use a blue hue (i.e., aqua, blue; AN1). As such, these similarities led two participants to select the incorrect (b) (4) carton. • Identical 0.75 ml volume. The (b) (4) 1.7 mg and 2.4 mg pen-injectors contain 0.75 ml of medication, whereas the (b) (4) 0.25 mg, 0.5 mg, and 1 mg pen-injectors contain 0.5 ml of medication. Consequently, one participant who recalled the 0.75 ml	We agree with the Applicant's root cause analyses for these differentiation errors. Our review of the study results identified subjective feedback that indicated that test artefact may have played a role in these use errors. For example, some participants indicated that they would use different strategies to keep their medication separate from another person's medication, particularly if the medications looked similar. Our review of the carton labeling did not find additional mitigations to improve differentiation between different strengths.

	volume rather than dose size did not know which of the (b) (4) 1.7 mg/0.75 ml and (b) (4) 2.4 mg/0.75 ml cartons to select. The applicant did not propose any additional mitigations to address this use error.	
2.	For the task "Select pen-injector" there were 4 use errors. For example, one participant selected a pen-injector with a higher dose than was prescribed, and three selected pen-injectors with lower doses. The subjective data and the Applicant's root cause analysis stated: • Similar pen-injector appearance. The (b) (4) pen-injectors are visually identical except for their respective dose sizes and dose size indicator colours (e.g., blue for 1.7 mg and dark grey for 2.4 mg). The pen-injectors include the same (b) (4) product name, grey cap, graphics, and text layout. As such, these similarities led two participant to select the incorrect (b) (4) pen-injector. • Multiple coding of blue and grey elements. The (b) (4) pen-injectors contain blue and grey elements (i.e., blue expiration date box on pen-injector labelling, grey pen-injector cap) that are identical for all dose sizes. Additionally, there are also (b) (4) pen-injectors with blue (i.e., 1.7 mg) and grey (i.e., 2.4 mg) accent colours. One participant recalled that his prescribed pen-injector contained blue and grey elements but could not recall which elements were blue and grey. As a result, he incorrectly selected the pen-injector with a blue expiration date box on grey labelling rather than the blue labelling with a grey pen-injector cap. • Inattention. One participant did not pay close attention to the instructions provided in the task prompt and the test administrator's further task explanation. He knew his target dose	We agree with the Applicant's root cause analyses for these differentiation errors. Our review of the study results identified subjective feedback that indicated the similar appearance between the pen injectors, particularly with the use of grey and blue elements across different presentations contributed to these differentiation errors. Our review of the labels and labeling (user interface, etc.) confirms the findings from the root cause analysis. However, based on subjective feedback from participants, some participants indicated that they would use different strategies to keep their medication separate from another person's medication, particularly if the medications looked similar. Our review of the container labeling did not find additional mitigations to improve differentiation between different strengths.

	size (0.5 mg) and correctly selected his prescribed pen-injector during the post-test interview, suggesting he did not pay full attention to the task instructions, despite reading the task card aloud, summarising the task's instructions, and listening to the test administrator's verbal instructions. The applicant did not propose any additional mitigations to address this use error.	

Appendix H: Table of comparator products used in the differentiation study

Healthcare Provider Differentiation Comparators										
Comparator category	(b) (4) 0.25 mg		(b) (4) 0.5 mg		(b) (4) 1 mg		(b) (4) 1.7 mg		(b) (4) 2.4 mg	
	Carton	Pen-injector	Carton	Pen-injector	Carton	Pen-injector	Carton	Pen-injector	Carton	Pen-injector
(b) (4) dose strength	(b) (4) 0.5 mg	(b) (4) 0.5 mg	0.25 mg	0.25 mg	0.25 mg	0.25 mg	0.25 mg	0.25 mg	0.25 mg	(b) (4) 0.25 mg
	(b) (4) 1 mg	(b) (4) 1 mg	(b) (4) 1 mg	1 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg	0.5 mg	(b) (4) 0.5 mg
	(b) (4) 1.7 mg	(b) (4) 1.7 mg	1.7 mg	1.7 mg	1.7 mg	1.7 mg	1 mg	1 mg	1 mg	(b) (4) 1 mg
	(b) (4) 2.4 mg	(b) (4) 2.4 mg	2.4 mg	2.4 mg	2.4 mg	2.4 mg	2.4 mg	2.4 mg	1.7 mg	(b) (4) 1.7 mg
Basal/Mix insulin	Levemir® FlexTouch®	Levemir® FlexTouch®			Novolin® 70/30 FlexPen®	Humulin® 70/30 KwikPen®	Ryzodeg® 70/30		Ryzodeg® 70/30	
	Tresiba® 100U	Tresiba® 200U								

	FlexTouch®	FlexTouch®								
	Novolin® N FlexPen®	Toujeo® SoloStar® 300IU								
	Toujeo® SoloStar® 300IU									
Bolus insulin			Admelog® SoloStar®							
GLP-1			Xultophy®	Xultophy®	Adlyxin™ 10mcg and 20 mcg		Ozempic® 1 mg	Victoza® 6mg/ml	Ozempic® 1 mg	Victoza®
			Adlyxin™ 20 mcg							
Weight management			Saxenda®				Saxenda®			
[(b) (4)] auto injector pen	PraluentTM 75 mg/ml	PraluentTM 75 mg/ml					PraluentTM 150 mg/ml	PraluentTM 150 mg/ml		

Patients and Caregiver Differentiation Comparators										
Comparator category	[(b) (4)] 0.25 mg		[(b) (4)] 0.5 mg		[(b) (4)] 1 mg		[(b) (4)] 1.7 mg		[(b) (4)] 2.4 mg	
	Carton	Pen-injector	Carton	Pen-injector	Carton	Pen-injector	Carton	Pen-injector	Carton	Pen-injector
[(b) (4)] dose strength	[(b) (4)] 0.5 mg	[(b) (4)] 0.5 mg	0.25 mg	0.25 mg	[(b) (4)] 0.25 mg	[(b) (4)] 0.25 mg	0.25 mg	0.25 mg	0.25 mg	0.25 mg
	[(b) (4)] 1 mg	[(b) (4)] 1 mg	[(b) (4)] 1 mg	1 mg	[(b) (4)] 0.5 mg	[(b) (4)] 0.5 mg	[(b) (4)] 0.5 mg	0.5 mg	0.5 mg	0.5 mg

	(b) (4) 1.7 mg	(b) (4) 1.7 mg	(b) (4) 1.7 mg	(b) (4) 1.7 mg	(b) (4) 1.7 mg	(b) (4) 1.7 mg	(b) (4) 1 mg	(b) (4) 1 mg	1 mg	1 mg
	(b) (4) 2.4 mg	(b) (4) 2.4 mg	(b) (4) 2.4 mg	2.4 mg	(b) (4) 2.4 mg	(b) (4) 2.4 mg	(b) (4) 2.4 mg	2.4 mg	1.7 mg	1.7 mg
Basal/Mix insulin	Levemir® FlexTouch®	Toujeo® SoloStar® 300IU			Novolin® 70/30 FlexPen®	Humulin® 70/30 Kwik Pen®	Ryzodeg® 70/30		Ryzodeg® 70/30	
	Toujeo® SoloStar® 300IU									
Bolus insulin			Admelog® SoloStar®							
GLP-1				Xultophy®	AdlyxinTM 10mcg and 20 mcg		Ozempic® 1 mg	Victoza® 6mg/ml		Victoza®
			Xultophy®						Ozempic® 1 mg	
Weight management			Saxenda®				Saxenda®			
	PraluentTM 75 mg/ml	PraluentTM 75 mg/ml					PraluentTM 150 mg/ml	PraluentTM 150 mg/ml		
(b) (4) auto injector pen		PraluentTM 150 mg/ml								

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/

JASON A FLINT
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LOLITA G WHITE on behalf of MILLIE B SHAH
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