CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761156Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	August 27, 2020
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Patrick Lynch, PhD, Product Quality Assessor Lead OBP/Division of Biotechnology Review and Research 2
Application:	BLA 761156
Applicant:	Novo Nordisk Inc.
Submission Date:	August 28, 2019
Product:	Somapacitan-beco
Dosage form(s):	injection
Strength and Container-Closure:	10 mg/1.5 mL (6.7 mg/mL) single-patient use prefilled pen
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information, patient labeling, and instructions for use (submitted on August 26, 2020), and container labels and carton labeling (submitted on July 23, 2020) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

CONCLUSION

The prescribing information, patient labeling, and instructions for use (submitted on August 26, 2020), and container labels and carton labeling (submitted on July 23, 2020) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling
Prescribing Information (submitted on August 28, 2019
\\cdsesub1\evsprod\bla761156\0001\m1\us\draft-pi.pdf)

Patient Information Labeling (submitted on August 28, 2019
\\cdsesub1\evsprod\bla761156\0001\m1\us\draft-ppi.pdf)

Instructions for Use (submitted on August 28, 2019
\\cdsesub1\evsprod\bla761156\0001\m1\us\draft-ifu.pdf)

3 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	☐ Yes ☐ No ☒ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to the manufacturer's name listed on FDA form 356h per 21 CFR 610.61(a) and preferably include the US license number as follows:
Manufactured by: Novo Nordisk Inc
U.S. License No. xxxx
The Applicant revised (b) (4) *according to 21 CFR 610.64. For BLAs, the manufacturer is considered to be the Applicant on Form FDA 356h (Novo Nordisk Inc) and the qualifying phrase used to indicate the manufacturer is "Manufactured by". Your labeling was revised* (b) (4)

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

(b) (4) according to 21 CFR 610.64. Revise the manufacturer's statement to the qualifying phrase "Manufactured by".

Applicant's response: According to 21 CFR 600.3(t), a Manufacturer means any legal person or entity engaged in the manufacture of a product subject to license under the act; " Manufacturer" also includes any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards (b) (4) (b) (4)

To clearly communicate this information in the label in a manner consistent with 21 CFR 610.64, Novo Nordisk believes it is correct to state (b) (4) (b) (4) or "Manufactured by (b) (4) Novo Nordisk Inc."

OBP Labeling response: It is not correct to provide the manufacturer's information using the phrase (b) (4) OBP's historical practice is to display the applicant from the Form FDA 356h as "Manufactured by". FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards". A manufacturer thus includes a license applicant, who may or may not own the facilities engaged in significant manufacturing steps, when such an applicant assumes responsibility for compliance with the applicable product and establishment standards, including, but not limited to, 21 CFR Parts 210, 211, 600 through 680, and 820. Therefore, we find the applicant written on Form FDA 356h is considered the following terms: license applicant, license manufacturer, or manufacturer. Additionally, you are proposing to use the U.S. license number 1261 which was issued to Novo Nordisk Inc. For many of the products regulated by OBP, applicants engage in contract manufacturing arrangements in which a license manufacturer establishes a contract with another entity(ies) to perform some or all of the manufacture of a product as a service to the license manufacturer. The labeling for final products prepared under a contractual agreement must comply with the applicable provisions of 21 CFR 610.60 through 610.65, and 21 CFR Parts 201, where applicable. Specifically, the labeling must display the applicant's name, address, and license number to comply with 21 CFR 610.60(a)(2), and 21 CFR 610.61(b). All of the manufacturer information should appear consistently throughout all separate pieces of labeling including the container label(s), carton labeling, PI, and Patient Labeling (PPI, MG, or IFU).
The Applicant revised t (b) (4) have Novo Nordisk Inc and US license number appear on container label. OBP labeling finds this acceptable.

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No

	☐ N/A

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	✓ Yes ☐ No ☐ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the strength statement from "10 mg/1.5 mL Prefilled Pen" to "6.7 mg/mL" since the entire contents of the pen are not delivered for every recommended dosage. The total volume of the pen will be expressed as the net quantity.
Applicant's response: As the somapacitan pen only contains 1.5 mL and that the entire contents of the pen would not be delivered for every recommended dosage, Novo Nordisk proposes to present the strength per total volume as: "10 mg/1.5 mL (6.7 mg/mL)" per the April 2013 draft guidance.
The Applicant's response is acceptable at this time since FDA guidance and USP General Chapter <7> Labeling do not provide recommendations or standards for expression of strength for single-patient-use containers.

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: partial label see carton

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

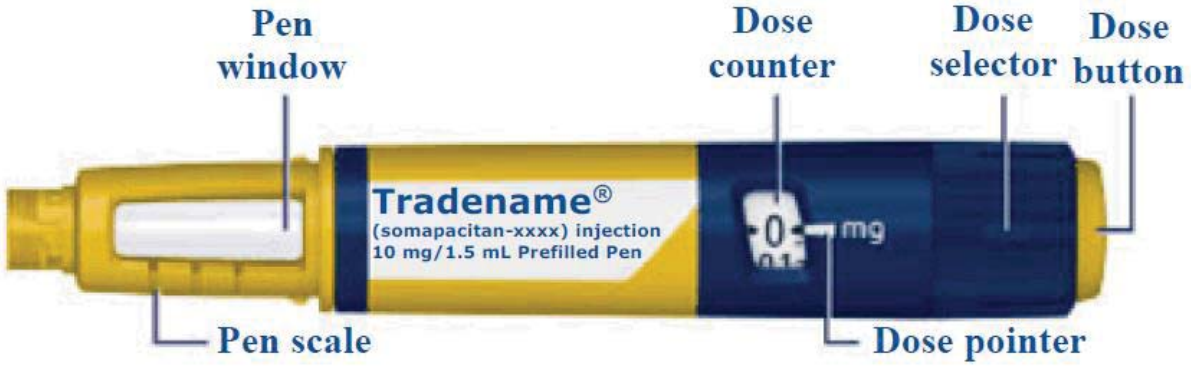
No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	☐ Yes ☐ No ☒ N/A

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Acceptable visual inspection window



Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the route of administration statement to appear after the strength statement on the principal display panel as follows:
Tradename
(somapacitan-xxxx) injection
6.7 mg/mL
For Subcutaneous Use
The Applicant revised the route of administration as requested

***NDC numbers* (container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the package type term to describe the container closure from (b) (4) to "Single-patient use prefilled pen"
The Applicant revised as requested

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011	✓ Yes ☐ No

Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic	☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the net quantity, 1.5 mL, and ensure that it appears away from the strength statement, 6.7 mg/mL.
Applicant's response: To be consistent with the proposal to present the strength per total volume, Novo Nordisk proposes keep the text as "10 mg/1.5 mL".
Applicant's response is acceptable

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: partial see carton

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A

Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: partial see carton

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise storage requirements for readability as follows: "**Storage:** Before first use, refrigerate [36°F to 46°F (2°C to 8°C)] in carton to protect from light. Do Not Freeze or Shake. After first use, refrigerate up to 6 weeks OR keep at room temperature (up to 77°F (25°C)) for up to 72 hours (3 days). Avoid direct heat. Must discard if kept above 86°F (30°C)." *Applicant's response: Due to the limited amount of space available on the container labeling, the additional text requested by the Agency and to align the information that would appear on the container label for the trade and sample presentations, Novo Nordisk proposes to* (b) (4) *Storage information is still included on the trade and sample cartons and PI.* *OBP labeling response: Consider adding the word "refrigerate" as the primary storage condition for patients who may throw away the carton.* *The Applicant's response revised as requested*

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to the manufacturer's name and address listed on FDA form 356h and include the US license number as follows per 21 CFR 610.61(b):
Manufactured by: Novo Nordisk Inc
Plainsboro NJ 08536
U.S. License No. xxxx

We note that the manufacturer's information was revised to (b) (4) (b) (4) (b) (4). Revise to the qualifying phrase used to indicate the manufacturer as "Manufactured by: Novo Nordisk Inc". For BLAs, the manufacturer is considered to be the Applicant on Form FDA 356h. If Novo Nordisk A/S is considered the distributor then consider adding "Distributed by: Novo Nordisk A/S" and the address.

Applicant's response: According to 21 CFR 600.3(t), a Manufacturer means any legal person or entity engaged in the manufacture of a product subject to license under the act; " Manufacturer" also includes any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards. (b) (4) (b) (4)

To clearly communicate this information in the label in a manner consistent with 21 CFR 610.64, Novo Nordisk believes it is correct to state (b) (4) (b) (4) *or "Manufactured by* (b) (4) *Novo Nordisk Inc."*

OBP Labeling response: It is not correct to provide the manufacturer's information using the phrase (b) (4) *OBP's historical practice is to display the applicant from the Form FDA 356h as "Manufactured by". FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an*

applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards". A manufacturer thus includes a license applicant, who may or may not own the facilities engaged in significant manufacturing steps, when such an applicant assumes responsibility for compliance with the applicable product and establishment standards, including, but not limited to, 21 CFR Parts 210, 211, 600 through 680, and 820. Therefore, we find the applicant written on Form FDA 356h is considered the following terms: license applicant, license manufacturer, or manufacturer. Additionally, you are proposing to use the U.S. license number 1261 which was issued to Novo Nordisk Inc. For many of the products regulated by OBP, applicants engage in contract manufacturing arrangements in which a license manufacturer establishes a contract with another entity(ies) to perform some or all of the manufacture of a product as a service to the license manufacturer. The labeling for final products prepared under a contractual agreement must comply with the applicable provisions of 21 CFR 610.60 through 610.65, and 21 CFR Parts 201, where applicable. Specifically, the labeling must display the applicant's name, address, and license number to comply with 21 CFR 610.60(a)(2), and 21 CFR 610.61(b). All of the manufacturer information should appear consistently throughout all separate pieces of labeling including the container label(s), carton labeling, PI, and Patient Labeling (PPI, MG, or IFU). The Applicant revised as requested

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: see storage statement recommendation

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: contains phenol see ingredient list

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Delete [redacted] (b) (4) for consistent presentation of strength in labeling.
The Applicant revised as requested
Consider revising the number of containers statement from [redacted] (b) (4) to read "1 x 1.5 mL single-patient use prefilled pen" on the principal display panel to include the package type term.
The Applicant revised as requested

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the strength statement appearing on all panels after the proper name and dosage form from "10 mg/1.5 mL Prefilled Pen" to "6.7 mg/mL" since the entire contents of the pen are not delivered for every recommended dosage. The total volume of the pen will be expressed as the net quantity.

Applicant's response: Novo Nordisk is proposing to present the complete strength information as "10 mg/1.5 mL (6.7 mg/mL)" to be consistent with the April 2013 draft guidance.
OBP Labeling response: The Applicant's response is acceptable at this time since FDA guidance and USP General Chapter <7> Labeling do not provide recommendations or standards for expression of strength for single-patient-use containers.

Remove the boxed strength statement "10 mg" from all panels.
Applicant's response: Novo Nordisk proposes to retain the boxed strength statement as "10 mg" as this follows the April 2013 Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. One of the concerns described in the guidance about presentation of product strength is if the strength is expressed in units of

measure incongruent with those used in the dosing instructions, the wrong dose can be administered. As the doses are given in milligrams in the proposed PI and IFU, it would be more consistent with the dosing instructions to highlight "10 mg" in the strength box instead of "6.7 mg/mL" or the complete strength statement. Highlighting that the pen contains a total of 10 mg of somapacitan would also assist the pharmacist when they are calculating the number of pens to provide to the patient based on the total prescribed dose.

OBP Labeling response: OBP labeling defers to DMEPA regarding medication error related concerns of having both boxed "10 mg" and "Once weekly" which may imply that the dose is 10 mg once weekly. Since the pen is designed to dial to up to a 4 mg dose, including the boxed 10 mg statement on labeling may lead one to believe that it will deliver a dialed dose of 10 mg. Additionally, the boxed "10 mg" does not describe what 10 mg represents. We recommend to delete the boxed "10 mg" statement and include the dose dial increment information "Prefilled pen dials in 0.05 mg increments, delivers doses from 0.05 mg to 4 mg, and contains 10 mg total".

Applicant's response: Novo Nordisk still proposes to present "10 mg" boxed as this (b) (4) (b) (4) *information is also repeated as part of the new dose increment text. To address a potential confusion that the dose may be 10 mg once weekly, on the primary panel "once weekly" has been moved below the text on the panel and "10 mg" has been moved to the middle of the top part of the panel in order to sufficiently separate the two from each other and further minimize confusion. The dose increment statement proposed by the Agency has been abbreviated to "Dials in 0.05 mg increments and contains 10 mg total".* (b) (4) (b) (4) *The appropriate dose for any patient would be determined by the physician based on the additional dosage and administration information presented in section 2 of the PI. To fit the additional text described above, the colored bar on the principle display panel is shortened.*

The Applicant revised the boxed strength statement to "10 mg pen" and added the statement "Dials in 0.05 mg increments and contains 10 mg total".
The Applicant's response is acceptable

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise storage requirements for readability and to add a space for the user to write the date first used as follows: "**Storage:** Before first use, refrigerate pen at 36°F to 46°F (2°C to 8°C) in original carton to protect from light. Do Not Freeze. Do Not Shake. After first use, refrigerate pen for up to 6 weeks OR keep at room temperature (up to 77°F (25°C)) for up to 72 hours (3 days). Avoid direct heat. Must discard if kept above 86°F (30°C).
Date of first use: __/__/__. Discard unused portion."

Applicant's response: Edits have been made to the proposed text (b) (4) (b) (4) *and to better align the after-first-use text with the in-use stability study designs used to support the room temperature storage conditions. The applicant referred to in-use stability study submissions to support removal* (b) (4) *Applicant revised language to "**Storage:** Before first use, refrigerate pen at 36°F to 46°F in original carton to protect from light. Do Not Freeze. After first use, refrigerate pen for up to 6 weeks,* (b) (4) *Avoid direct heat. Must discard if kept above 86°F."*

OBP Labeling's response: We note that edits have been made to the proposed text to remove the temperature in Celsius. It is standard labeling practice for FDA approved products to provide the temperature in both Fahrenheit and Celsius. Additionally, since the 72 hour RT storage is not intended to be an alternate storage requirement but to allow for portability of the pen, revise as follows for clarity:

> "**Storage:** Before first use, refrigerate pen at 36°F to 46°F (2°C to 8°C) in original carton to protect from light. Do Not Freeze. Do Not Shake. After first use, refrigerate pen for up to 6 weeks and write the date of first use below. If kept at room temperature (up to 77°F (25°C)) for more than 72 hours then discard pen. Avoid direct heat. Must discard if kept above 86°F (30°C).
> Date of first use: __/__/__. Discard unused portion."

Applicant's response: Novo Nordisk accepts the Agency's changes to the storage text, with some additional edits, except for the inclusion of the statement (b) (4)
The storage text has been proposed revised to the following: "Before first use, refrigerate pen at 36°F to 46°F (2°C to 8°C) in original carton to protect from light. Do Not Freeze. After first use, refrigerate pen for up to 6 weeks and write the date of first use below. Can be kept temporarily at room temperature (up to 77°F (25°C)) for up to 72 hours. Avoid direct heat. Must discard if kept above 77°F (25°C) for more than 72 hours or above 86°F (30°C). Date of first use: __/__/__. Discard unused portion."
The Applicant's revision is acceptable

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: See usual dosage statement recommendation below

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Relocate the route of administration statement, "For subcutaneous use only", from the back panel to appear after the strength statement on the principal display panel of the carton labeling as follows:
Tradename
(somapacitan-xxxx) injection
6.7 mg/mL
For Subcutaneous Use
The Applicant relocated the route of administration statement as requested

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: On the side panel, revise from (b) (4) (b) (4) to read "Each single-patient use prefilled pen

has a deliverable volume of 1.5 mL. Each mL of solution contains 6.7 mg of somapacitan-xxxx, histidine (0.68 mg), mannitol (44 mg), phenol (4 mg), poloxamer 188 (1 mg), and Water for Injection, USP. Hydrochloric acid and sodium hydroxide may be added to adjust the pH." Delete the redundant statement [redacted] (b) (4) from the principal display panel. *The Applicant revised as requested*

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the appropriate information to carton labeling per 21 CFR 610.61(r), the following items shall appear on the label affixed to each package containing a product: Minimum potency of the drug product expressed in terms of official standard of potency, or if potency is a factor and no US standard of potency has been prescribed, the words "No U.S. standard of potency" preferably placed on a side panel after the ingredient list. *The Applicant added "No U.S. standard of potency"*

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No

	☒ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Delete [redacted] (b) (4) since the package type term is intended to describe the container closure system and the package type term will be included in the contents statement. *The Applicant revised as requested*

Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A

Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the net quantity statement "1.5 mL" to appear preferably in the upper right corner of the principal display panel.
Applicant's response: To be consistent with the proposal to present the strength per total volume, the net quantity statement is kept as part of the complete strength statement.
OBP Labeling's response: Applicant's response is acceptable and that the net quantity is included in the content's statement "1 x 1.5 mL single-patient use prefilled pen.

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the usual dosage statement "Dosage: See Prescribing Information". Delete the redundant statement (b) (4)
The Applicant revised as requested

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised to the customary appearance of the dosage form, injection, for FDA approved labelling.
Additionally, we revised added the package type term "single-patient use" and revised the strength presentation from "10 mg/1.5 mL" to "6.7 mg/mL" since the entire contents of the pen are not delivered for every recommended dosage. The total volume of the pen will be expressed as the net quantity.
Applicant's response: for consistency with the proposal for the carton and container labeling, Novo Nordisk proposes to present the strength statement as: "10 mg/1.5 mL (6.7 mg/mL)". Applicant's response is acceptable

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted drug; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes); confirm product's incompatibilities, and ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised to the color and clarity of the solution per your submission to the BLA as "clear to slightly opalescent and colorless to slightly yellow solution"
Applicant revised as requested
We recommend that the dose dial increments be included as important information for the health care professional "The TRADENAME prefilled pen dials in 0.05 mg increments and delivers doses from 0.05 mg to 4 mg"
Applicant revised as requested

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised the strength presentation from "10 mg/1.5 mL" to 6.7 mg/mL since the entire contents of the pen are not delivered for every recommended dosage. The total volume of the pen will be expressed as the net quantity.
Applicant's response: for consistency with the proposal for the carton and container labeling, Novo Nordisk proposes to present the strength statement as: "10 mg/1.5 mL (6.7 mg/mL)".
Applicant's response is acceptable
We revised to the customary appearance of the dosage form, injection, for FDA approved labelling. *Applicant revised as requested*

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: We deleted (b) (4) from this first paragraph since it discusses the drug substance. *Applicant revised as requested.*
Added the cell line as this is considered important information for the healthcare provider. *Applicant revised as requested.*
Information (b) (4) statements were removed from this section since this is not required information for this section of the PI and has been stated in section 12. *Applicant revised as requested.*
We added the dosage form per 21 CFR 201.57(c)(12). *Applicant revised as requested.*
Consider revising this sentence to include the package type term to describe the container closure (b) (4). *Applicant revised as requested.*
We revised the ingredient information from the table format to the paragraph format and provided the ingredients per mL of solution in alphabetical order. *Applicant revised as requested.*
We added the pH per 21 CFR 201.57(c)(12). *Applicant revised as requested.*

Full Prescribing Information	
15 & 16 Cytotoxic Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: xxxx is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised to the color and clarity of the solution per your submission to the BLA as "clear to slightly opalescent and colorless to slightly yellow solution". *Applicant revised as requested.*
We revised to clarify that there is one pen per carton. *Applicant revised as requested.*
We deleted the redundant sentence (b) (4) (b) (4) since this is conveyed in the sentence "A tradename prefilled pen must never be shared..". *Applicant revised as requested*
We removed this sentence (b) (4) to reduce redundancy and clutter since the information provided below separates out before and after first use. *Applicant revised as requested.*
We combined the intent of this sentence (to store pen in carton to protect from light) to the first sentence of this paragraph for clarity. *Applicant revised as requested*
We added the instruction (b) (4).
Applicant's response: Novo Nordisk proposes to remove the text (b) (4) from the storage information based on the available data in the BLA demonstrating that the somapacitan drug product was shown to be stable after exposure to mechanical stress *Applicant's response is acceptable*
Revised the RT storage conditions as follows: (b) (4) (b) (4) (b) (4) Avoid direct or excessive heat. Avoid sunlight. (b) (4) discard if kept above 86°F (30°C)." *Applicant revised as requested*
This statement (b) (4) was deleted to reduce confusion. *Applicant revised as requested*
We added (b) (4) (b) (4) (b) (4). *Applicant revised as requested*

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64	✓ Yes ☐ No ☐ N/A

(Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	

Comment/Recommendation: Revise to the manufacturer's name and address listed on FDA form 356h and include the US license number as follows:
Manufactured by: Novo Nordisk Inc
Plainsboro NJ 08536
U.S. License No. xxxx
Applicant's response: Novo Nordisk has revised the text to be consistent with the proposed carton submitted as part of the response to FDA's Carton and Container Labeling Comments dated May 18, 2020.
OBP labeling' s response to carton and container submitted June 1, 2020: For BLAs, the manufacturer is considered to be the Applicant on Form FDA 356h (Novo Nordisk Inc) and the qualifying phrase used to indicate the manufacturer is "Manufactured by". Your labeling was revised (b) (4) which is the qualifying phrase for a distributor according to 21 CFR 610.64. Revise the manufacturer's statement to the qualifying phrase "Manufactured by".
The Applicant revised as requested

Medication Guide Evaluation (N/A)

Patient Information Labeling Evaluation

PATIENT INFORMATION LABELING	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: revised the dosage form to appear in lower case letters and on the line after the proper name
The Applicant revised as requested

PATIENT INFORMATION LABELING	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for Patient Labeling: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and	✓ Yes ☐ No ☐ N/A

Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	

PATIENT INFORMATION LABELING	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised the inactive ingredient list to appear in alphabetical order for consistency with the prescribing information
The Applicant revised as requested

PATIENT INFORMATION LABELING	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Revise to the manufacturer's name and address listed on FDA form 356h and include the US license number as follows:
Manufactured by: Novo Nordisk Inc
Plainsboro NJ 08536
U.S. License No. xxxx
The Applicant revised the manufacturer name and address as requested

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for IFU: Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	☐ Yes ☐ No ☒ N/A

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). *21 CFR 610.61 (add the US license number for consistency with the carton labeling),* *21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise to the manufacturer's name and address listed on FDA form 356h and include the US license number as follows:
Manufactured by: Novo Nordisk Inc
Plainsboro NJ 08536
U.S. License No. xxxx

The Applicant revised as requested

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on August 26, 2020 \\CDSESUB1\evsprod\bla761156\0056\m1\us\draft-pi.pdf)

Instructions for Use (submitted on August 26, 2020 \\CDSESUB1\evsprod\bla761156\0056\m1\us\draft-ifu.pdf)

Patient Information (submitted on August 26, 2020 \\CDSESUB1\evsprod\bla761156\0056\m1\us\draft-ppi.pdf)

Container Labels (submitted on July 23, 2020)

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following This Page

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 8/27/2020 02:35:31PM
GUID: 50814c7000007a3d59329f660d8ddf02

Patrick Lynch

Digitally signed by Patrick Lynch
Date: 8/27/2020 02:41:11PM
GUID: 54bfb193000693c35f4278034f85d77a

Recommendation: Approval

BLA Number: 761156
Office of Product Quality Application Team Lead Review

Review Date: April 27, 2020

Drug Name/Dosage Form	Sogroya, Injection
Strength/Potency	10 mg/1.5 mL prefilled pen
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indications	Replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency
Applicant/Sponsor	Novo Nordisk Inc.

Product Overview

Sogroya is long-acting recombinant human growth hormone (hGH) derivative with a single substitution in the amino acid backbone (leucine at position 101 substituted with cysteine) to which an albumin binding moiety (side-chain) is attached. Binding of endogenous albumin to the side-chain delays elimination of the drug, thereby prolonging the duration of action compared to hGH. The mechanism of action is mediated through binding to growth hormone receptors (GHR) to induce (b) (4) signaling, which stimulates somatic growth and a broad range of metabolic activities. A proposed indirect mechanism of action is mediated through activation of insulin-like growth factor I (IGF-I) expression, which in turn stimulates growth in multiple tissues. The drug substance is produced by (b) (4) (b) (4) The final drug product is a clear and colorless or almost colorless solution for injection, provided in a prefilled pen injector. Sogroya drug product is formulated in (b) (4) L-histidine, (b) (4) poloxamer 188, (b) (4) phenol, (b) (4) mannitol, and water for injection (WFI) up to 1.5 mL at pH 6.8.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Arulvathani Arudchandran	OPQ/OBP/DBRRII
Drug Product	Arulvathani Arudchandran	OPQ/OBP/DBRRII
Immunogenicity Assays	Arulvathani Arudchandran	OPQ/OBP/DBRRII
Labeling	Vicky Borders-Hemphill	OPQ/OBP
Microbiology/Facilities Drug Product	Wayne Seifert	OPQ/OPMA/DBM
Microbiology/Facilities Drug Substance	Ziyang Su	OPQ/OPMA/DBM

Microbiology/Facilities Team Lead	Candace Gomez-Broughton	OPQ/OPMA/DBM
Small Molecule	Sharon Kelly	OPQ/ONDP/DNDAPI
Small Molecule Team Lead	Su (Suong) Tran	OPQ/OPF/DMA
Application Technical Lead	Patrick Lynch	OPQ/OBP/DBRRII
Tertiary Reviewer for OBP	Xianghong (Emily) Jing	OPQ/OBP/DBRRII
RBPM	Kelly Ballard	OPQ/OPRO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Linda Galgay	OND/ORO/DRO-CHEN
Cross-disciplinary Team Lead	Marina Zemskova	OND/OCHEN/DGE
Medical Officer	Geanina Roman-Popoveniuc	OND/OCHEN/DGE
Pharm/Tox	Huiqing Hao/Federica Basso (TL)	OND/OCHEN/DPT-CHEN
Clinical Pharmacology	Abir Absar/Jaya Vaidyanathan (TL)	OTS/OCP/DCEP
Statistics	Alexander Cambon/Feng Li (TL)	OTS/OB/DBII

1. Names:
   a. Proprietary Name: Sogroya
   b. Trade Name: Sogroya
   c. Non-Proprietary/USAN: Somapacitan[1]
   d. Company Code: Somapacitan
   e. CAS Name:

      Somatotropin [101-cysteine] (human), (101→4')-thioether with *N*-[14,14-dioxido-1,10,16-trioxo-31-(1*H*-tetrazol-5-yl)-3,6-dioxa-14-thia-9,15-diazahentriacont-1-yl]-L-γ-glutamyl-L-γ-glutamyl-2-[2-(2-aminoethoxy)ethoxy]acetyl-N^6-(2-mercaptoacetyl)-L-lysine
      (CAS registry number: 1338578-34-9)

   f. Common Name: TBD[1]
   g. INN Name: Somapacitan
   h. Compendial Name: Not established
   i. OBP Systemic Name: CONJ: RPROT P01241 (SOMA_HUMAN) PC4008 [NNC01950092]

Submissions Reviewed:

Submission(s) Reviewed (OPQ office)	Document Date
STN 761156/1, Original Submission	August 28, 2019
STN 761156/4 (OPMA)	September 13, 2019
STN 761156/6 (OPMA)	September 26, 2019

[1] The non-proprietary (i.e., proper) name with distinguishing suffix of four lowercase letters is pending. For ease of review, the drug substance/API is referred to as somapacitan.

STN 761156/9 (OBP)	November 1, 2019
STN 761156/10 (OPMA)	November 6, 2019
STN 761156/12 (OBP)	November 14, 2019
STN 761156/13 (OBP)	December 2, 2019
STN 761156/16 (OPMA)	December 26, 2019
STN 761156/17 (OBP)	January 8, 2020
STN 761156/18 (OBP, OPMA)	January 10, 2020
STN 761156/22 (OBP, OPMA)	February 4, 2020
STN 761156/26 (OBP)	March 6, 2020
STN 761156/27 (OBP, OPMA)	March 12, 2020
STN 761156/28 (OPMA)	March 13, 2020
STN 761156/32 (OBP)	April 3, 3030
STN 761156/34 (OPMA)	April 6, 2020
STN 761156/35 (OPMA)	April 9, 2020
STN 761156/37 (OBP)	April 17, 2020
STN 761156/38 (OBP)	April 21, 2020
STN 761156/39 (OBP, OPMA)	April 22, 2020
STN 761156/43 (OPMA)	May 4, 2020
STN 761156/46 (OPMA)	May 28, 2020

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]
(b) (4)[2]	III		(b) (4)	3	N/A
[2]	III			3	N/A
	III			3	N/A
	III			3	N/A
	III			3	N/A

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

[2] DMF submitted to the Center for Biologics Evaluation and Research.

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application; therefore, the DMF did not need to be reviewed.

B. Other documents:

Document	Application Number	Description
IND Application	116327	IND for development of somapacitan
BLA[3]	021148	License for Norditropin (somatropin), which is a hGH product held by Novo Nordisk. Prior knowledge from Norditropin is referenced in support of this application.

3. Consults:

A consult to CDRH for assessment of the (b) (4) pen-injector was requested by OND.

Center	Office	Topic	Recommendation	Assessor
CDRH	OPEQ/OHTIII/DHTIIIC	Pre-filled Pen Device	Pending	Matthew Ondeck/Rumi Young (TL)

4. Environmental Assessment:

A categorical exclusion from submitting an Environmental Assessment of somapacitan is requested per 21 CFR 25, section 25.31. The protein molecule is a biodegradable product derived from a biological system. The small molecule side-chain has no known adverse effects on humans or the environment. The expected concentration at the point of entry into the aquatic environment is well below 1 part per billion. No extraordinary conditions exist.

The request for categorical exclusion is granted.

[3] NDA 021148 referenced in the application was converted to BLA during the review cycle.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761156 for Sogroya manufactured by Novo Nordisk. The data submitted in this application are adequate to support the conclusion that the manufacture of Sogroya is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

The original OPQ Application Team Lead (ATL) review that recommended approval of the application pending final assessment of a late cycle amendment pertaining to microbiology methods information was completed and signed on May 5, 2020. The original ATL review was updated with this memo to update the outcome of the final microbiology assessment and to incorporate the conclusion of the immunogenicity assays assessment. This review reflects the final OPQ ATL review and recommendation.

B. Approval Action Letter Language:

- Manufacturing location:
    - Drug Substance: (b) (4)
    - Drug Product:
      Novo Nordisk A/S
      Hagedornsvej 1
      Gentofte
      Hovedstaden 2820
      Denmark

- Fill size and dosage form: 10 mg in 1.5 mL solution in a pre-filled pen
- Dating period:
    - Drug Product: 24 months: 2-8 °C
    - Drug Substance: (b) (4)
    - For packaged products: Not packaged
    - Stability Option:
      We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance under 21 CFR 601.12.
- Exempt from lot release
    - Sogroya is exempted from lot release because it is a specified product per 601.2(a).

C. Benefit/Risk Considerations:

Sogroya is indicated for replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency, which is a chronic illness associated with abnormalities in body composition. Addition of the albumin binding moiety to the GH protein prolongs the *in vivo* half-life to allow for once weekly administration.

The manufacturing processes for Sogroya are well controlled and consistently produce product that is pure and potent. The drug substance process is qualified for removal of impurities. The overall control strategy for drug substance and drug product is comprehensive for control of raw materials, process performance, and product quality attributes. Sogroya is sensitive to temperature. (b) (4) (b) (4) (b) (4). Agreement was reached with Novo Nordisk to further mitigate this risk by tightening temperature control limits during transportation and adjusting recommended storage and handling instructions on the label for the drug product. OPQ recommends the label include clear instructions to not freeze the product, and to discard the product if exposed to temperatures above 30°C.

The commercial manufacture of Sogroya drug substance at (b) (4) (b) (4), and drug product at Novo Nordisk A/S in Gentofte, Denmark is recommended for approval by OPQ. The immunogenicity assays used to evaluate anti-drug antibodies in clinical studies provided in support of this BLA are adequately validated and suitable for their intended purpose. Additional data and information to support the overall quality assessment are in the OPQ primary technical reviews for product quality, small molecule side-chain intermediate, microbiology, facilities, and labeling. Additional data and information to support the immunogenicity assay assessment are in the primary technical review for product quality. OPQ primary technical reviews are located in Panorama.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to drug substance and drug product.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Specific bioactivity (potency)	Efficacy	Intrinsic to the molecule. No change through expiry when stored under	(b) (4)	N/A

		recommended storage conditions.		
Growth hormone receptor binding (potency)	Efficacy	Intrinsic to the molecule. No change through expiry when stored under recommended storage conditions.	(b) (4)	N/A
Albumin binding (potency)	Efficacy and Pharmacokinetics. (b) (4) (b) (4) could impact *in vivo* half-life and duration of activity	Intrinsic to the molecule. Minimal change is expected when stored under recommended storage conditions.		N/A
Identity (identity)	Safety and Efficacy	Intrinsic to the molecule		N/A
High Molecular Weight Protein (HMWP) Species/Aggregates (b) (4)	Efficacy and Immunogenicity HMWP are biologically inactive. High levels could impact efficacy	(b) (4) (b) (4) on stability Increase upon exposure to heat, low pH, and light Increase upon exposure to freeze/thaw of the DP		SE-HPLC method is stability-indicating HMWP are stability-indicating attributes
(b) (4)	Efficacy and Pharmacokinetics (b) (4) (b) (4) could impact biological activity (b) (4) and albumin binding (b) (4)	On stability Increases upon exposure to heat		AIE-HPLC method is stability-indicating (b) (4)

Hydrophilic forms (b) (4)	Immunogenicity	(b) (4) (b) (4), on stability Increases upon exposure to heat and high pH Increase during storage under recommended storage conditions	(b) (4)
(b) (4)	Efficacy and Immunogenicity (b) (4) (b) (4) High levels could impact efficacy.	(b) (4) Increases upon exposure to light	
Related substances (b) (4)	Immunogenicity	(b) (4) (b) (4) on stability Increases upon exposure to heat and high pH Increases during storage under recommended storage conditions	
Related impurities (b) (4)	Immunogenicity	(b) (4) (b) (4) on stability Increases upon exposure to heat and light Increases during storage under recommended storage conditions	

Others (b) (4)	Immunogenicity	(b) (4) (b) (4) on stability Increases upon exposure to heat, low pH, and light. Increases during storage under recommended storage conditions	(b) (4)	N/A
	Efficacy, Pharmacokinetics, Immunogenicity (b) (4)	(b) (4)		N/A
	Efficacy, Pharmacokinetics, Immunogenicity (b) (4)			N/A
Content (General)	Efficacy	Decreases upon exposure to freeze/thaw of the DP		N/A
pH (General)	Product stability, patient comfort	(b) (4) (b) (4) DS and DP formulation		N/A

B. Drug Substance Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy	Other

Appearance (general)	Safety	(b) (4)	N/A
Host Cell Proteins (b) (4)	Safety and Immunogenicity		N/A
Host Cell DNA (b) (4)	Low hypothetical safety or immunogenicity risk		N/A
(b) (4)	(b) (4)		N/A
	Safety, Immunogenicity		N/A
	Safety Potentially genotoxic		N/A
	Safety		N/A
(b) (4) chemicals	Safety		N/A

(b) (4)		(b) (4)	
Leachable components (b) (4)	Safety and Efficacy Leached components may impact product stability		N/A
Bacterial endotoxins (Contaminant)	Safety and purity		N/A
Bioburden (Contaminant)	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)		N/A

- **Description:**
  Somapacitan is a covalent conjugate of recombinant human growth hormone (hGH) derivative produced in *Escherichia coli* cells, with an albumin binding moiety (side chain) attached to the Cysteine 101 amino acid by chemical conjugation. The sequence of the recombinant protein differs from endogenous hGH by a single amino acid substitution (L101C). After injection, endogenous albumin binds non-covalently to the side chain, which is comprised of (b) (4) and hydrophilic spacer. Binding of albumin functions to increase the *in vivo* half-life of the molecule by decreasing renal clearance and metabolic degradation. Somapacitan is a 191 amino acid protein with an average molecular weight of 23290.56 Da, and an approximate isoelectric point of 4.9. The molar extinction coefficient at A_{280} nm is approximately 16360 $M^{-1}cm^{-1}$.

- **Mechanism of Action (MoA):**
  The growth hormone (GH) portion of somapacitan binds to GH receptor on target cells, which induces a conformational change that results in activation of (b) (4) signaling. GH signaling stimulates somatic growth, including skeletal and muscle growth,

and a broad range of metabolic activities. A proposed indirect mechanism of action is mediated through stimulation of insulin-like growth factor I (IGF-I) expression, which in turn stimulates growth in multiple tissues, including bone.

- **Potency Assay:**
  Induction of cell growth is tested by a quantitative cell-based assay using BA/F3 murine pro-B cell line that depends on growth hormone for growth and survival. Cell proliferation is measured using a redox indicator reagent that detects metabolic activity. The measured fluorescent signal is proportional to the number of cells undergoing respiration. Somapacitan stimulates BA/F3 cell proliferation resulting in a dose-dependent increase in fluorescent signal. Mean bioactivity values are calculated using model curve fits from four-parameter logistic curves of dose response data. Bioactivity values are determined relative to the reference standard. Specific bioactivity (U/mg) is reported as the mean bioactivity relative to protein content obtained by the SE-HPLC method (monomer peak). The cell-based bioassay is appropriately validated.

- **Reference Materials:**
  (b) (4)

- **Critical starting materials or intermediates:**
  A two-tiered cell banking system consisting of a master cell bank (MCB) and working cell bank (WCB) is in place to ensure continued source of product. (b) (4)
  (b) (4)
  (b) (4)
  . WCBs are prepared by expansion of vials of the MCB. The cell lines are appropriately tested to ensure product safety. Viability of both the MCB and WCB is monitored as part of a stability program. A protocol for establishment of

future WCBs is provided in the BLA with qualification parameters and acceptance criteria suitable to prevent drift in product quality.

(b) (4)

- **Manufacturing process summary:**

(b) (4)

The BLA contains sufficient information and validation results that indicate the raw material program, facilities and equipment, manufacturing process, release, and stability programs are adequately controlled resulting in the production of a consistent product. Additional information is in the Product Quality and DS Microbiology primary technical reviews.

- **Container closure:**
The DS container closure system is (b) (4) 1 L bottles with high-density polyethylene (HDPE) screw closures. Compatibility of the container closure system is supported by DS stability studies carried out in containers of

the same material. Extractables and leachables studies support the use of the container closure system.

- **Dating period and storage conditions:**
  The data provided in the BLA support the establishment of a shelf life of (b) (4) months for somapacitan drug substance when stored at (b) (4).

C. Drug Product Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (Contaminant)	Safety and Efficacy (degradation or modification of the product by contaminating microorganisms)	(b) (4)	(b) (4)	N/A
Endotoxin (Contaminant)	Safety			N/A
Container Closure Integrity (Sterility assurance)	Safety			N/A
Appearance (general)	Safety			N/A
Particles	Safety and Immunogenicity			N/A

(product and process-related impurities)		(b) (4)	
Dose accuracy	Safety, Efficacy		N/A
Extractable volume	Efficacy		N/A
(b) (4)	Safety, stability, patient comfort		N/A
(b) (4)	Stability		N/A
Osmolality	Stability, patient comfort		
Leachable components (b) (4)	Safety		N/A

- **Potency and Strength:**
  Sogroya is suppled at 6.7 mg/mL strength. The prefilled pen contains 10 mg in 1.5 mL volume. Potency is defined as specific bioactivity relative to protein content. The cell-based assay used to determine bioactivity is the same as described in the DS section of this memo. The DP specification for specific bioactivity is (b) (4) U/mg for release and stability.

- **Summary of Product Design:**
  Sogroya is supplied as a sterile solution for subcutaneous injection, which is provided in 1.5 mL glass cartridges assembled into prefilled pen-injectors. Each 10 mg prefilled pen of Sogroya is formulated in (b) (4) Histidine, (b) (4) Poloxamer 188, (b) (4) Phenol, (b) (4) (b) (4) and Mannitol at pH 6.8. The deliverable dose ranges are (b) (4) mg per dose for treatment naïve patients, or (b) (4) for patients switching from daily growth hormone. The product is designed to allow for administration of multiple once-weekly doses from the prefilled pen. Once opened, Sogroya is stored for up to 6 weeks at 2-8°C, which is referred to as the in-use period.

- **List of Excipients:**
  Excipients include Histidine (USP, Ph.Eur., JP), Hydrochloric acid (USP, Ph.Eur., JP), Mannitol (USP, Ph.Eur., JP), Poloxamer 188 (USP, Ph.Eur., JPE), Phenol (USP, Ph.Eur., JP), Sodium hydroxide (USP, Ph.Eur., JP), and Water for injections (USP, Ph.Eur., JP).

- **Reference Materials:**
  The same reference material is used for testing DS and DP.

- **Manufacturing process summary:**
  The DP manufacturing process includes (b) (4) (b) (4) (b) (4) Container closure integrity testing using a validated method is included in the stability program.

- **Container closure:**
  The primary container closure system for Sogroya consists of a 1.5 mL Type I colorless glass cartridge, rubber plunger (b) (4), and (b) (4) rubber disk (b) (4) (b) (4) The cartridges are assembled into pen-injectors, which shield the product from light.

- **Dating period and storage conditions:**
  The stability data in the BLA support a shelf life for Sogroya of 24 months when stored at the recommended storage condition of 2-8°C and protected from light. Stability data in the BLA also support an in-use period of 6 weeks at 2-8°C, including unrefrigerated storage period for no more than 72 hours at or below 30°C.

D. Novel Approaches/Precedents:
None

E. Any Special Product Quality Labeling Recommendations:
Store Sogroya refrigerated at 2-8°C and protected from light. Do not shake. Do not freeze the product. Avoid direct or excessive heat. Avoid sunlight. The prefilled pen can be kept at room temperature (up to 77°F (25°C) in the original carton for up to 72 hours (3 days). Must discard if kept above 86°F (30°C).

F. Establishment:

Overall Recommendation: Approval			
Drug Substance			
Site Information	**Responsibility**	**Inspectional Observations**	**Final Recommendation**
Novo Nordisk US Bio Production Inc. 9 Technology Dr.,	Manufacture of DS	A PLI was conducted from February 6 to 14, 2020. A six item Form 483 was issued at	Approval—based on PAI/PLI

West Lebanon, New Hampshire 03784 FEI Number: 3012593913	(b) (4)	(b) (4) (b) (4) The inspection was classified VAI. Refer to the Form 483 for additional details.	
	(b) (4)	A PAI was conducted from January 15 to 17, 2020 by ORA. A one item Form 483 was issued. The inspection was classified VAI. Refer to the Form 483 for additional details.	Approval—Based on PAI/PLI
		Not inspected for this application	Approval—No evaluation necessary
		Not inspected for this application	Approval—Based on previous history
		Not inspected for this application	Approval—Based on previous history
		Not inspected for this application	Approval—No evaluation necessary

(b) (4)		
	Not inspected for this application	Approval—Based on previous history

Drug Product			
Site Information	**Responsibility**	**Inspectional Observations**	**Final Recommendation**
Novo Nordisk A/S Hagedornsvej 1 DK-2820, Gentofte, Denmark FEI Number: 3002807748	Manufacture of DP Quality control testing of (b) (4) DP (microbiological tests) Storage of primary packaging materials for (b) (4) DP	Not inspected for this application. Refer to the Pre-license/Pre-approval Inspection Waiver Memo for additional details.	Approval—Based on previous history
Novo Nordisk A/S Brogardsvej 66, DK-2820, Gentofte, Denmark FEI Number: 3002807748	Quality control testing of (b) (4) DP (chemical/physical and biological tests), and excipients	Not inspected for this application. Refer to the Pre-license/Pre-approval Inspection Waiver Memo for additional details.	Approval—Based on previous history
Novo Nordisk A/S Brennum Park DK-3400, Hillerød, Denmark FEI Number: 3003131673	Quality control testing of (b) (4) DP (chemical/physical tests) Storage of excipients Develop (b) (4) pen-injector design specifications Maintain design history file for (b) (4) pen-injector	A PAI was conducted from January 15 to 17, 2020 by ORA. A one item Form 483 was issued. The inspection was classified VAI. Refer to the Form 483 for additional details.	Approval—Based on PAI/PLI
Novo Nordisk A/S Kirk Værløsevej 30 DK-3500, Værløse, Denmark	Assembly, labeling, secondary packaging of finished DP Quality control of (b) (4) pen-injectors (dose accuracy)	A PAI was conducted from January 13 to 14, 2020 by ORA. No Form 483 was issued. The inspection was classified NAI.	Approval—Based on PAI/PLI

FEI Number: 3015545250	Storage of printed packaging materials, (b) (4) finished DP		
(b) (4)		Not inspected for this application	Approval—No evaluation necessary
		Not inspected for this application	Approval—No evaluation necessary
Novo Nordisk A/S Novo Alle 1 Bagvaerd Hovedstaden 2880 Denmark FEI Number: 3000151819	Overall batch release	Not inspected for this application	Approval—No evaluation necessary

G. Facilities:

There are no outstanding facilities issues.

H. Lifecycle Knowledge Management:

a. Drug Substance:
   i. Protocols approved:
      1. Annual stability protocol for drug substance
      2. Stability protocol for extension of drug substance shelf life
      3. Qualification of future working cell banks
      4. Qualification of future primary and secondary reference materials
      5. Concurrent qualification of column lifetimes
   ii. Outstanding issues/residual risk: None
   iii. Future inspection points to consider: None

b. Drug Product
   i. Protocols approved:
      1. Annual stability protocol for drug product
      2. Stability protocol for process performance qualification batches
      3. Transportation qualification protocol for drug product
   ii. Outstanding issues/residual risk: None

iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
	Product Type				
1.	Recombinant Product		X		
2.	Naturally Derived Product			X	
3.	Botanical			X	
4.	Human Cell Substrate/source material			X	
5.	Non-Human Primate Cell Substrate/Source Material			X	
6.	Non-Primate Mammalian Cell Substrate/source material			X	
7.	Non-Mammalian Cell Substrate/Source Material		X		
8.	Transgenic Animal source			X	
9.	Transgenic Plant source			X	
10.	New Molecular Entity		X		
11.	PEPFAR drug			X	
12.	PET drug			X	
13.	Sterile Drug Product		X		
14.	Other: [fill in information]			X	
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			X	
16.	Comparability Protocol(s)			X	
17.	End of Phase II/Pre-NDA Agreements			X	
18.	SPOTS (special products on-line tracking system)			X	
19.	USAN assigned name		X		
20.	Other [fill in]			X	
	Quality Considerations				
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements			X	
27.	Real Time release testing (RTRT)			X	
28.	Parametric release in lieu of Sterility testing			X	
29.	Alternative Microbiological test methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial analytical procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other {fill-in}			X	

Patrick Lynch

Digitally signed by Patrick Lynch
Date: 6/16/2020 11:54:12AM
GUID: 54bfb193000693c35f4278034f85d77a

Xianghong Jing

Digitally signed by Xianghong Jing
Date: 6/16/2020 11:56:39AM
GUID: 54983cd700435181eca33ebeed0ccdd1

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/

KELLY R BALLARD
07/06/2020 10:21:30 AM