CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761315Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Product Quality Assessment III

LABELS AND LABELING ASSESSMENT

Date of Assessment:	December 16, 2024
Assessor:	Liming Lu, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Scott Walsh, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XV
Application:	BLA 761315
Applicant:	Novo Nordisk Inc.
Submission Dates:	June 20, 2024 June 26, 2024 (medication guide in word version) August 23, 2024 (updated container labels per agency's request)
Product:	Alhemo (concizumab-mtci)
Dosage form(s):	injection
Strength and Container-Closure:	60 mg/1.5 mL (40 mg/mL) single-patient-use prefilled pen 150 mg/1.5 mL (100 mg/mL) single-patient-use prefilled pen 300 mg/3 mL (100 mg/mL) single-patient-use prefilled pen
Purpose of assessment:	The Applicant re-submitted a biologics license application seeking approval of concizumab-mtci for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors and hemophilia B (congenital factor IX deficiency) with factor IX inhibitors.
Recommendations:	The prescribing information, medication guide, instructions for use, container labels, and carton labeling are **acceptable** from an OPQA III 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

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

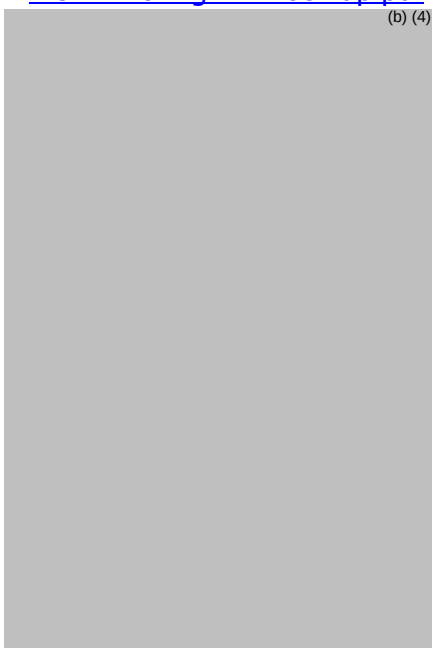
The prescribing information (December 16, 2024), medication guide (November 13, 2024), instructions for use (November 13, 2024), container labels and carton labeling (submitted on December 2, 2024) were assessed and found to be acceptable (see Appendix C) from an OPQA III labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on June 20, 2024)
  \\CDSESUB1\EVSPROD\bla761315\0056\m1\us\m1-14-1-2-annotated-draft-labeling-text.docx
- Medication Guide (submitted on June 26, 2024)
  \\CDSESUB1\EVSPROD\bla761315\0057\m1\us\m1-14-1-3-medication-guide.docx
- Instructions for Use (submitted on June 20, 2024)
  \\CDSESUB1\EVSPROD\bla761315\0056\m1\us\m1-14-1-3-ifu-1-5ml-60mg-40mg-per-ml.docx
  \\CDSESUB1\EVSPROD\bla761315\0056\m1\us\m1-14-1-3-ifu-1-5ml-150mg-100mg-per-ml.docx
  \\CDSESUB1\EVSPROD\bla761315\0056\m1\us\m1-14-1-3-ifu-3ml-300mg-100mg-per-ml.docx
- Container Labels (submitted on June 20, 2024 and August 23, 2024)
  60 mg/1.5 mL (40 mg/mL) single-patient-use prefilled pen
  \\CDSESUB1\EVSPROD\bla761315\0056\m1\us\m1-14-1-1-container-manuscript-60-mg-1-5-ml-40-mg-ml-mock-up.pdf

(b) (4)



\\CDSESUB1\EVSPROD\bla761315\0059\m1\us\m1-14-1-1-container-manu-60-mg-1-5-ml-40-mg-ml-mock-up.pdf

6 Page(s) 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(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(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: We noticed that the manufacturer was not listed using the appropriate qualifying phrase on the submitted carton labeling. We recommended revising the manufacturer statement using the qualifying phrase "Manufactured by:" to identify the licensed applicant. See 21 CFR 610.64 for examples of the qualifying phrase.

The applicant has revised as requested.

[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."

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(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, Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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

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

Comment/Recommendation: The prefilled pen provides sufficient area of the container to allow for visual inspection of the solution.

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

***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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	☐ 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)	✓ Yes ☐ No ☐ N/A

USP chapter <659> Packaging and Storage Requirements	

Comment/Recommendation:
We previously recommended the applicant to revise the package type term from "Single-patient use" to read "Single-patient-use" (note the use of 2 hyphens) during last review cycle.

The applicant has revised all instances of "single-patient use" to appear as "single-patient-use" on all the cartons and containers in the resubmission. The applicant's revisions are acceptable.

No 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) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ 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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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: The size of this label does not provide space for this information. This is acceptable as per 21 CFR 610.60(c).

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: The size of this label does not provide space for this information. This is acceptable as per 21 CFR 610.60(c).

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: We previously recommended the applicant, if space permits and the readability of other required information is acceptable, then consider revising the storage information to read: Before use: Store refrigerated at 36°F to 46°F (2°C to 8°C).

After first use: Store up to 86˚F (30˚C) for up to 28 days. Do not freeze or shake. Avoid direct light.

The applicant has revised the storage and handling statements to read: "Before first use: Store refrigerated at 36°F to 46°F (2°C to 8°C). After first use: Store up to 86˚F (30˚C) for up to 28 days. Do not freeze or shake. Avoid direct light." The applicant's revisions are acceptable.
The applicant has also revised the statement "Do not freeze or shake" to "Do not freeze" only CMC team has concluded that shaking has no impact to product quality, based on the submitted simulated shipping study in the CMC IR response.

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
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: 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,

[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.

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, the applicant's name as listed in field 2 of Form FDA 356h is the name of the person or legal entity to whom the license is issued. Ensure that the manufacturer name and address appear exactly as intended for the US license holder.
Confirm "Novo Nordisk Inc." is the manufacturer. Revise the licensed manufacturer statement to appear as:

Manufactured by: Novo Nordisk Inc.
Plainsboro, NJ 08536
US License No. 2161

Clarify the role of "Novo Nordisk A/S". The applicant may include the drug product facility on the carton labeling, prescribing information, patient labeling. However, ensure the applicant fulfilled comment 21 CFR 610.61(b) and there is adequate space on the labeling. The drug product facility should appear as:

At: Drug Product Facility Name
Address

The applicant has confirmed that "Novo Nordisk Inc." is the manufacturer and "Novo Nordisk A/S" is the drug product facility. The applicant has revised manufacturer information as requested to all submitted carton labeling.

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

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

Comment/Recommendation: The prefilled pen contains the preservative phenol.

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

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

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:
We previously recommended the applicant during last review cycle: Revise the storage information to read:
Before first use: Store refrigerated at 36°F to 46°F (2°C to 8°C).
After first use: Store refrigerated or at room temperature up to 86˚F (30˚C) for up to 28 days.
Store pen in the carton to protect from light. Do not Freeze or Shake.
Date of first opening __/__/__. Discard unused portion of the pen 28 days after first opening.
Do not store with needles attached.

The applicant has revised the storage information as requested except not include the centigrade symbol and Fahrenheit symbol following each numeric degree measure of temperature ranges. Thus, we requested the following recommendation to the applicant:
As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges. The presentation of the storage statement should be clearly stated to avoid storage errors. We recommend revising the storage statement to include the Centigrade symbol (℃) and Fahrenheit symbol (℉) following each numeric degree measurement of temperature ranges. For example: "36°F to 46°F (2°C to 8°C)".

The applicant has revised as requested.

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

Comment/Recommendation:
The applicant has revised the handling information as requested during last review cycle and the applicant's revisions are acceptable in the resubmitted labeling.

However, during resubmission cycle, the applicant has proposed to remove the statement "do not shake" as the simulated shipping study shows that shaking would have no impact on the product quality, which has been confirmed by the CMC team. Thus, the statement has been revised to "Do not freeze" only on the cartons.

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

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

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: We previously recommended the applicant the following during last review cycle:
Revise the names of the inactive ingredients "L-arginine" and "L-histidine" to read "arginine" and "histidine", which are their official USP monograph names.

To applicant: Consider deletion of the statement "[redacted]". Healthcare providers, caregivers and patients should recognize the total volume, xx mL, of the product can be delivered unless the labeling indicates otherwise.

Applicant's Response: The applicant revised the names of the inactive ingredients "L-arginine" and "L-histidine" to read "arginine" and "histidine" as recommended. In addition, the applicant deleted the statement [redacted] as suggested." Note the carton labeling still displays the statement "Dials in xx mg increments and contains xx mg total". The applicant's revisions are acceptable. Note: The applicant, Novo Nordisk, has other marketed products that include a reference to a deliverable volume.

According to 3.2.P.2.2 Drug Product Pharmaceutical Development in the re-submission, L-Arginine hydrochloride is added to the formulation [redacted] Revise the inactive ingredient "arginine" to "arginine hydrochloride" per USP monograph title in the inactive ingredients list for all three proposed cartons.

The applicant has 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: Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for **concizumab** products (i.e., there is no specific test method described in regulation for **concizumab** products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for **Alhemo** because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

We previously recommended the applicant to remove the statement "No U.S. standard of potency" from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable.

The applicant has removed the statement "No U.S. standard of potency" as recommended from the last review cycle and this statement is not in the resubmitted label/labeling.

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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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* Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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	☐ Yes ☐ No ☒ N/A

Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	

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

No 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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation:
We previously recommended the applicant to revise the carton labeling to include the statement "Dosage: See prescribing information" on the back panel during last review cycle.

The applicant has included the statement "Dosage: See prescribing information" on the back panel of all cartons as recommended in the resubmission. The applicant's revisions are acceptable.

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:
Recommend revising the dosage forms and strengths in the highlights of USPI in a customary and concise form so that the appropriate dosage form "injection" and package type term "single-patient-use" are included in this highlight section.

(b) (4)

The applicant has revised as requested.

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 or diluted drug; 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; confirm the appropriateness of infusion bags, infusion sets (e.g.,	☐ Yes ☐ No ☒ N/A

tubing, infusion aids, or filter membranes) incompatibilities with these components	

Comment/Recommendation:
Inserted the required verbatim statement per 21 CFR 201.57(c)(3)(iv). The required statement reads: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

We removed the reference to (b) (4) for the description of the drug product's identifying characteristics. We also removed "(b) (4) is part of the drug product's identifying characteristics, based on the evaluation of the submitted data. (b) (4)

The applicant has 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: Added dosage form "injection" in Section 3 as required per 21 CFR 201.57(c)(4) and removed (b) (4)" for clarity.

The applicant has 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 the proprietary name from the first paragraph which describes the drugs substance.

We deleted the chemical name and structural formula of the drug as it is not required to appear in Section 11 Description for biological products per 21 CFR 201.57(c)(12)(i)(F).

The information proposed in this paragraph is not required for this section. Thus, the information was deleted.
The paragraph read: "(b) (4))."

This statement is not necessary, because the first paragraph indicates the manufacturing process for the drug substance is by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.
The statement read: "(b) (4) ."

We added the established name with the conditionally acceptable 4 letter suffix in the paragraph discussing the drug product. We also added the dosage form.

Recommend removing the redundant information "(b) (4) ".

The applicant has revised as requested above.

The ingredient information was revised to clearly differentiate the 2 concentrations and 3 presentations of the drug product. In addition, the inactive ingredients were listed in alphabetical order (see *USP General Chapters <1091> Labeling of inactive ingredients*).

To ensure that all FDA approved labeling fulfils the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e), the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, arginine hydrochloride, histidine, phenol, polysorbate 80, sodium chloride, sucrose. Revise the ingredient information to the compendial names and definitions.

The ingredient information was revised to read:

(b) (4)

The applicant has accepted the recommendation of using compendial names. However, the applicant proposed to list excipients once in section 11, as the information on excipients is the same for all strengths. The inactive ingredients list proposed by the applicant as:

(b) (4)

Full Prescribing Information	
15 & 16 Hazardous 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 hazardous 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: Revised to the appropriate dosage form "injection".

Deleted (b) (4)

As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges. The presentation of the storage statement should be clearly stated to avoid storage errors. We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges.

Revised the reference weeks to days, which is more commonly used for a short period of time for drug usage and to be consistent with the wording used in the patient labeling including IFUs and carton and container.

Recommend adding the discard statement for clarity and to be consistent among the label/labeling.

(b) (4)

The applicant has revised as requested above.

Revised for clarity and to be consistent with the carton and container labeling. Additional text has been added, because your data indicates the product should be kept in the carton to protect the drug product from light and no data were submitted to support freezing or shaking.

The applicant responded that "the transport simulation (ISTA 3A) study support that shaking has no negative impact on the product quality and suggested to delete "do not shake", CMC team has confirmed this is acceptable. Thus, "Do not shake" statement has been deleted from all label/labeling.

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 (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:
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, the applicant's name as listed in field 2 of Form FDA 356h is the name of the

person or legal entity to whom the license is issued. Ensure that the manufacturer name and address appear exactly as intended for the US license holder. **Confirm** "Novo Nordisk Inc." is the manufacturer. Ensure that the manufacturer name and address appear exactly as intended for the US license holder. If necessary, please correct this on your Form FDA 356h.

Clarify the role of "Novo Nordisk A/S". The applicant may include the drug product facility on the carton labeling, prescribing information, patient labeling. However, ensure the applicant fulfilled comment 21 CFR 610.61(b) and there is adequate space on the labeling. The drug product facility should appear as:
At: Drug Product Facility Name
Address

The applicant has revised as requested.

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
STORAGE AND HANDLING	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges. The presentation of the storage statement should be clearly stated to avoid storage errors. We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges.

Revised the terminology from 4 weeks to 28 days.

The applicant has revised as requested.

MEDICATION GUIDE	
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: Revised the ingredient names to their compendial names. Included a separate statement for the pH adjusters. *The applicant has revised as requested.*

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ 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

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 Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022*). 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: Guidance for Industry *Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (*July 2022*). 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

Comment/Recommendation: Revised to be consistent with the prescribing information in all IFUs. (b) (4) [redacted] *The applicant has revised as requested.*

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

APPENDIX C. Acceptable Labels and Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

- Prescribing Information (submitted on December 16, 2024)
  \\CDSESUB1\EVSPROD\bla761315\0074\m1\us\m1-14-1-3-draft-uspi-clean.docx
- Medication Guide (submitted on November 13, 2024)
  \\CDSESUB1\EVSPROD\bla761315\0063\m1\us\m1-14-1-3-med-guide-clean.docx
- Instructions for Use (submitted on November 13, 2024)
  \\CDSESUB1\EVSPROD\bla761315\0063\m1\us\m1-14-1-3-ifu-60mg-clean.docx
  \\CDSESUB1\EVSPROD\bla761315\0063\m1\us\m1-14-1-3-ifu-150mg-clean.docx
  \\CDSESUB1\EVSPROD\bla761315\0063\m1\us\m1-14-1-3-ifu-300mg-clean.docx
- Container Labels (submitted on December 2, 2024)
  60 mg/1.5 mL (40 mg/mL) single-patient-use prefilled pen
  \\CDSESUB1\EVSPROD\bla761315\0066\m1\us\m1-14-1-1-container-mock-up-60-mg-1-5-ml-40-mg-ml.pdf

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Liming Lu

Digitally signed by Liming Lu
Date: 12/16/2024 03:16:22PM
GUID: 633d82d0001fb9cd8535e78c71271f3d

Scott Walsh

Digitally signed by Scott Walsh
Date: 12/16/2024 03:59:07PM
GUID: 60c8f29a00b4391894c7d9df3d4b6d1e

BLA Executive Summary
Assessment Date: 12/13/2024

1. Application/Product Information

BLA number	761315
Submission Type	Resubmission
Regulatory Pathway	351(a)
Associated IND/BLA	IND 111691
Review Designation	Standard Complete Response Resubmission
Applicant	Novo Nordisk Inc.
Indication	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with Hemophilia A with FVIII inhibitors and Hemophilia B with FIX inhibitors
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name Alhemo
	Non-proprietary Name/Code Name concizumab-mtci
	OBP Naming MAB HUMANIZED (IGG4) ANTI P10646 (TFPI1_HUMAN) [NN7415]
Drug Product Description	Concizumab drug product is a clear to slightly opalescent and colorless to slightly yellow solution that may contain translucent particles formulated in arginine (5.27 mg), histidine (5.12 mg), phenol (3.5 mg), polysorbate 80 (0.25 mg), sodium chloride (1.46 mg), sucrose (51.3 mg), and water for injection at pH of approximately 6.0. Concizumab is a recombinant humanized (b) (4) IgG4 monoclonal antibody targeting the K2 domain of the tissue factor pathway inhibitor (TFPI) isoforms, TFPIα and TFPIβ. Concizumab has a point mutation at serine-229 to proline (S229P) in the heavy chain (b) (4)
Dosage Form	Injection
Strength	60 mg/1.5 mL (40 mg/mL), 150 mg/1.5 mL and 300 mg/3 mL (100 mg/mL)
Route of Administration	Subcutaneous injection
Primary Container Closure System	• 1.5 mL or a 3.0 mL cartridge: (b) (4) glass cartridge closed with a (b) (4) rubber plunger-stopper and a (b) (4) rubber disc (cap).
Device Information	(b) (4) pen-injector

Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Zhong Zhao (1st review cycle)/ Scott Walsh	Hailin (Sheena) Wang
	Drug product		
	Immunogenicity Assay		
	Facility/ Microbiology	Richard Ledwidge	Virginia Carroll
	OPQAIII labeling	Liming Lu	
	RBPM	Melinda Bauerlien	
	ATL	Hailin (Sheena) Wang	
	Tertiary	Frances Namuswe	
OPQ Issued Consults	CDRH OPEQ/OHT3/DHT3C – Assessment of design controls, performance, stability, and suitability of the concizumab drug product pen-injector for its intended use		

2. Recommendation and Conclusion on Approvability
   Recommendation: Approval with PMCs/PMRs

   The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761315 for Alhemo manufactured by Novo Nordisk Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Alhemo 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.

3. CMC Information for Action Letter
   a. Manufacturing Location:
      - Drug Substance: (b) (4)
      - Drug Product:
        Cartridge manufacture site: Novo Nordisk A/S, Kalundborg, Denmark, FEI: 3002807751.
        Device assembly, labeling and secondary packaging: Novo Nordisk A/S, Værløse, Denmark, FEI: 3015545250.

   b. Fill size and dosage form:
      - 60 mg/1.5 mL (40 mg/mL) in a single-patient-use prefilled pen

- 150 mg/1.5 mL (100 mg/mL) in a single-patient-use prefilled pen
- 300 mg/3 mL (100 mg/mL) in a single-patient use-prefilled pen

c. Dating Period:
- Drug Substance: (b) (4) months at (b) (4) °C
- Drug Product: 24 months at 2-8 °C including an in-use period of 4 weeks below 30 °C
- For packaged products: Not packaged
- Stability Option: N/A

d. Exempt from lot release:
- Yes
- Rationale, if exempted: Alhemo is exempted from lot release per FR 95-29960. The overall control strategy, including manufacturing and release controls, is adequate to control lot-to-lot variability and product quality over the proposed shelf-life.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable:
CMC PMC#1 (4761-1): To implement the change (b) (4) in the concizumab drug product (DP). The final report including updates to the concizumab DP manufacturing process and all supporting studies for concizumab DP manufactured (b) (4) will be reported per 21 CFR 601.12.

Final report submission date: October 2027

CMC PMC#2 (4761-2): To commit to re-evaluate the shelf-life (b) (4) after sufficient release and stability data from commercial lots are collected no later than 3 years post-approval to support the concizumab-mtci drug product lifecycle. The revised shelf-life (b) (4) and adequate justifications will be reported per 21 CFR 601.12.

Final report submission date: April 2028

4. Basis for Recommendation
a. Summary:

The original BLA 761315 submission received a complete response recommendation due to a facility deficiency and multiple product quality and device constituent deficiencies related to inadequate control of drug substance, drug product and device constituents.

In the BLA resubmission on June 20, 2024, the Applicant adequately addressed the complete response comments and additional comments provided in the Complete Response Action Letter on April 24, 2023 and updated information in the Chemistry, Manufacturing, and Controls module of the BLA accordingly.

Concizumab binding to TFPI enhances FXa production during the initiation phase of coagulation which leads to improved thrombin generation and clot formation to achieve hemostasis in patients with Hemophilia A or B with or without inhibitors. Potency of concizumab is controlled using the coagulation assay. The coagulation time is measured by following the formation of fibrin polymers. The coagulation time is inversely dependent on the amount of concizumab in the sample. Dose-response curves are generated for samples and reference material. Potency of samples is determined relative to reference material, where potency of the reference material is (b) (4) U/mg. The results are reported as U/mg based on the content measured by SE-HPLC. Potency of each reference standard is adequately controlled at (b) (4) U/mg with acceptance criteria for mean and (b) (4) % CI within (b) (4) U/mg to prevent drift in potency of the product over time.

The concizumab drug substance (DS) manufacturing process consists of

The overall control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents,

microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for concizumab as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. (b) (4) The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. There are adequate controls in place to ensure the consistent functional performance of the (b) (4) pen-injector device.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for (b) (4) and Novo Nordisk A/S (FEI: 3015545250) proposed for concizumab DS and DP manufacture. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

The BLA is recommended for approval from a product quality, device functionality, immunogenicity, facility, microbiology and sterility assurance perspectives.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assay	-	Adequate
Facilities	-	Adequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
As an initial matter, we determined that no U.S. standard of potency has been prescribed for Alhemo (i.e., there is no specific test method described in regulation for Alhemo that establishes an official standard of potency). We next considered whether potency is a factor for Alhemo within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if “potency is a factor” and “no U.S. standard of

potency has been prescribed." We have determined that potency is not a factor for Alhemo for purposes of § 610.61(r) because lot variability is not a concern for Alhemo as Alhemo's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations
   a. Established Conditions based on ICH Q12 principles: No
      Comments: N/A

   b. Drug Substance:
      i. Protocols approved:
         1. 3.2.S.2.2 Column Lifetime and Conditions for Use and Re-use
         2. 3.2.S.2.3 Protocol for Establishment of the Working Cell Bank
         3. 3.2.S.2.4 Protocol for (b) (4) Steps
         4. 3.2.S.5 Protocol for Establishment of Novo Nordisk Primary and Secondary Reference Material
         5. 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment for On-going Stability Studies for Drug Substance
      ii. Residual risk: None
      iii. Future inspection points to consider: None

   c. Drug Product:
      i. Protocols approved:
         1. 3.2.P.3.5 Transportation Qualification Protocol
         2. 3.2.P.8.2 Stability Protocol and Commitment for On-going Stability Studies for Drug Product
         3. 3.2.P.8.2 Stability Commitment for Process Performance Qualification Batches
         4. 3.2.P.8.2 Stability Protocol and Stability Commitment for Primary Stability in Cartridge
         5. 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment for On-going Stability for Drug Product for (b) (4) Pen-injector
         6. 3.2.P.8.2 Stability Commitment for Comparability - (b) (4)
         7. 3.2.R Comparability Protocol – (b) (4)
      ii. Residual risk: None
      iii. Future inspection points to consider: None

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

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/

HAILIN WANG
12/13/2024 03:14:05 PM

FRANCES NAMUSWE
12/13/2024 03:15:38 PM

BLA Executive Summary
Assessment Date: April 10, 2023

1. Application/Product Information

BLA number	761315
Submission Type	Original Submission
Regulatory Pathway	NME 351 (a)
Associated IND/BLA	IND 111691
Review Designation	Priority Review
Applicant	Novo Nordisk Inc.
Indication	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with Hemophilia A with FVIII inhibitors and Hemophilia B with FIX inhibitors
Rx/OTC dispensed	Rx
Drug Product Name	Alhemo (proposed)
	concizumab-mtci
	MAB HUMANIZED (IGG4) ANTI P10646 (TFPI1_HUMAN) [NN7415]
Drug Product Description	Concizumab drug product is a clear to slightly opalescent and colorless to slightly yellow solution that may contain translucent particles formulated in arginine (5.27 mg), histidine (5.12 mg), phenol (3.5 mg), polysorbate 80 (0.25 mg), sodium chloride (1.46 mg), sucrose (51.3 mg), and water for injection at pH of approximately 6.0. Concizumab is a recombinant humanized (b) (4) IgG4 monoclonal antibody targeting the K2 domain of the tissue factor pathway inhibitor (TFPI) isoforms, TFPIα and TFPIβ. Concizumab has a point mutation at serine-229 to proline (S229P) in the heavy chain (b) (4)
Dosage Form	Liquid
Strength	(b) (4) 60 mg/1.5 mL (40 mg/mL), and 150 mg/1.5 mL and 300 mg/3 mL (100 mg/mL)
Route of Administration	Subcutaneous injection
Primary Container Closure System	Cartridge
Device Information	(b) (4) pen-injector

Co-packaged Product Information	None		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Zhong Zhao	Massod Rahimi
	Drug product		
	Immunogenicity Assays	Scott Walsh	Massod Rahimi
	Facility	Richard Ledwidge	Michael Shanks
	Microbiology		Virginia Carroll
	RBPM	Melinda Bauerlien	
	ATL	Massod Rahimi	
OPQ Issued Consults	CDRH OPEQ/OHT3/DHT3C – Assessment of design controls, performance, stability, and suitability of the concizumab drug product pen-injector for its intended use		

2. Recommendation and Conclusion on Approvability

Recommendation: Complete Response
The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761315 for Alhemo manufactured by Novo Nordisk Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Alhemo is well-controlled and will lead to a product that is pure and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Novo Nordisk Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

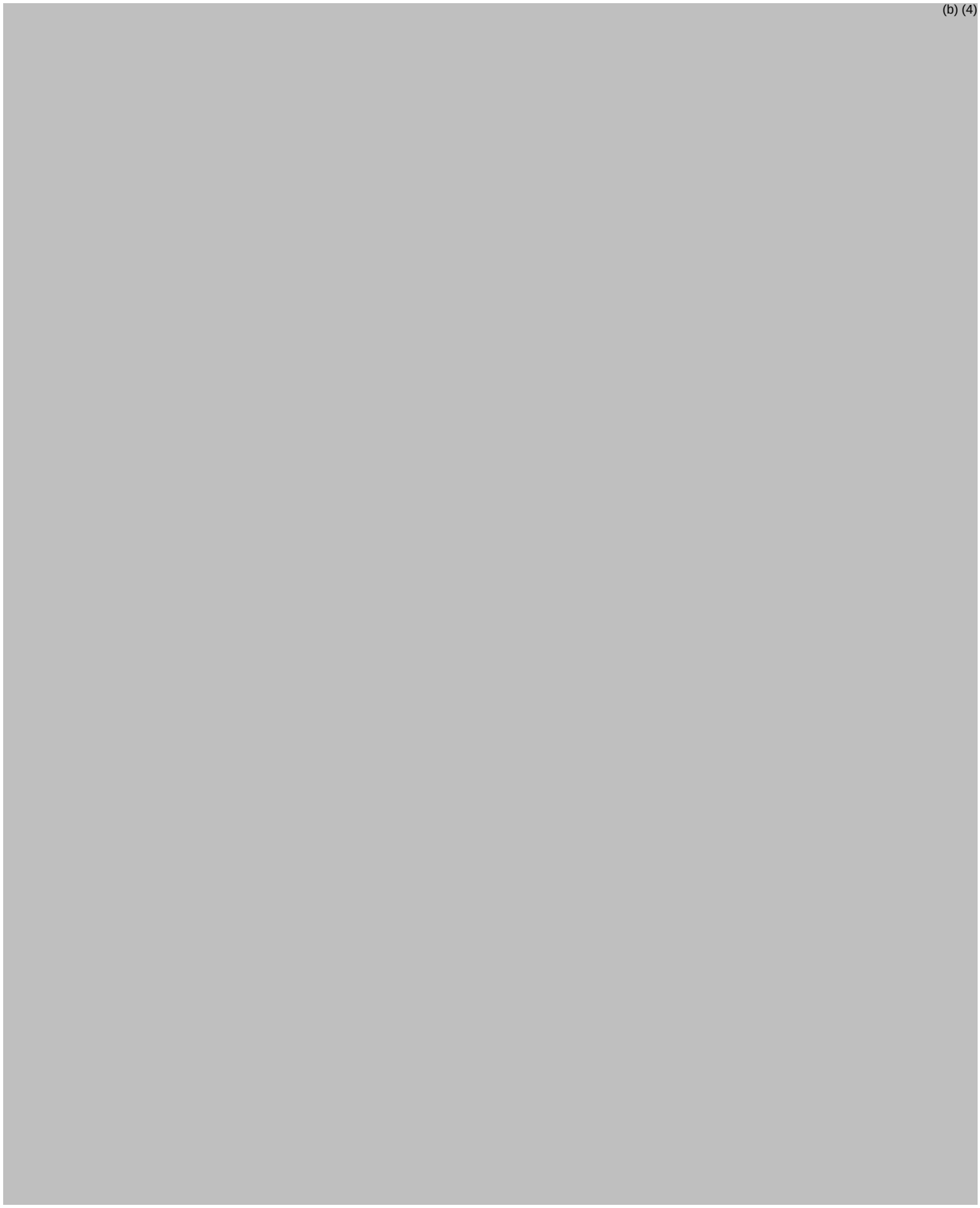
3. Draft Complete Response Comments and Additional Comments:

Complete Response Comments (provided by OBP, OPMA, and CDRH):

Product Quality

1. In the response received on 02/21/2023 to the Agency's information request (IR) comment 26 dated 02/08/2023, you described the control strategy for (b) (4) in the concizumab drug product (DP). In addition, in the response received on 02/28/2023 to the Agency's IR dated 02/16/2023, you provided an assessment for the risk of (b) (4) on safety and efficacy. The information and data provided are not sufficient to address the risk of the (b) (4) on safety and efficacy and the control strategy for the (b) (4) is inadequate to ensure product quality, safety, and efficacy. To ensure product quality, safety, and efficacy as it relates to (b) (4) address the following:

(b) (4)



2. The drug substance (DS) release and stability specifications and their justifications were provided in sections 3.2.S.4.1 and 3.2.S.4.5, respectively. Some of the proposed DS release and stability specifications acceptance

criteria are inadequate to ensure batch-to-batch consistency at release and on stability. To ensure batch-to-batch consistency at DS release and on stability, address the following:

(b) (4)

3. The DP release and stability specifications and their justifications were provided in sections 3.2.P.5.1 and 3.2.P.5.6, respectively. Some of the proposed DP release and stability (shelf-life) specifications acceptance criteria are inadequate to ensure batch-to-batch consistency at release and on stability. To ensure batch-to-batch consistency at DP release and on stability, address the following:

(b) (4)

(b) (4)

4. In the response received on 02/21/2023 to the Agency's IR comment 12 dated 02/08/2023, you revised the concizumab master cell bank (MCB) and working cell bank (WCB) stability protocols in section 3.2.S.2.3 to state that (b) (4) The revised MCB and WCB stability protocols are inadequate to ensure consistent cell bank performance and to determine if a new cell bank should be manufactured in a timely manner to prevent potential disruptions in manufacturing and drug shortage. To ensure consistent cell bank performance, revise the MCB and WCB stability protocols to include well-defined tests and acceptance criteria (b) (4)

5. In the response received on 02/21/2023 to the Agency's IR comment 18 dated 02/08/2023, you provided revised concizumab primary reference material (PRM) and secondary reference material (SRM) stability protocols in section 3.2.S.5. These protocols are inadequate to ensure consistent control over stability of the reference materials. To ensure consistent control over stability of the current reference materials, address the following:

(b) (4)

(b) (4)

6. In Table 4 in section 3.2.S.7.2, you provided the DS post-approval stability protocol to be conducted on at least one DS batch annually under the long-term storage condition (b) (4). The DS post-approval stability protocol is inadequate to ensure DS stability to the end of shelf-life post approval. To ensure DS stability to the end of shelf-life post approval, address the following:

(b) (4)

and the commercial container closure system (i.e., PET container with HDPE screw cap).

7. In Table 1 of the document Post-approval Stability Protocol and Stability Commitment for On-going Stability for Drug Product in section 3.2.P.8.2, you provided the post-approval stability protocol to be conducted on each "variant" of DP annually under the long-term storage condition (5°C). The DP post-approval stability protocol is inadequate to ensure DP stability to the end of shelf-life post approval. To ensure DP stability to the end of shelf-life post approval, address the following:

(b) (4)

8. In the response received on 02/21/2023 to the Agency's IR comment 22 dated 02/08/2023, you revised section 3.2.P.3.3 with a description of the sampling for identity testing and how tracking is assured. Although you described that the cartridge and pen-injector batches are tracked using LIMS, you did not provide sufficient information how this tracking links to the identity testing conducted as part of the release specifications. To comply with 21 CFR 610.14., revise section 3.2.P.3.3 to specify the physical characteristics that are used during tracking (e.g., cap color or markings) to ensure correct identity after all labeling operations.

Device Constituent

1. On 03/03/2023, we sent an IR requesting to include the essential performance requirements (EPRs) (i.e., dose accuracy, activation force, hold force, and injection time) of device constituents of the combination product in the DP post-approval stability protocol. (b) (4) Although you provided data to support that the device performed as expected up to the claimed shelf-life, the EPRs should also be included in the DP post-approval stability protocol in section 3.2.P.8.2 to ensure the EPRs are monitored post-approval to support batch-to-batch consistency. Therefore, as requested previously, add the EPRs (i.e., dose accuracy, activation force, hold force, and injection time) to the DP post-approval stability protocol.

2. On 03/07/2023, we sent an IR requesting to include the essential performance requirements (EPRs) (i.e., activation force, hold force, and injection time) of device constituents of the combination product in the DP release specifications. (b) (4) However, in order to align with the DP post-approval stability protocol, the requested EPRs (i.e., activation force, hold force, and injection time) should also be added to the DP release specifications.

Facilities

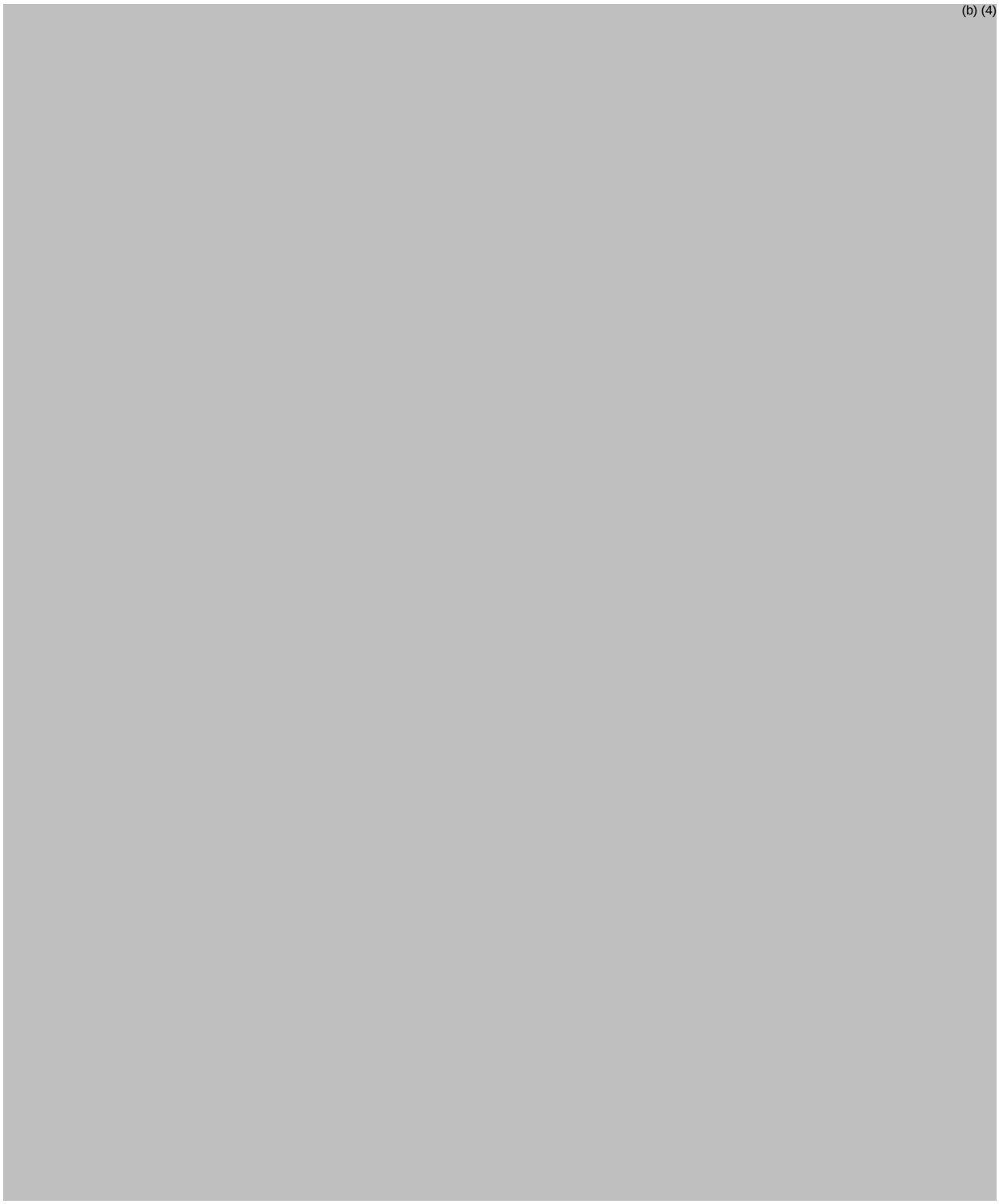
1. Following inspection of (b) (4) manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of the observations is required before this BLA may be approved.

Additional Comments (provided by OBP and OPMA):

Product Quality

(b) (4)

(b) (4)



4. In the response submitted on 02/21/2023 to the Agency's IR comment 13 dated 02/08/2023, you provided a revised protocol for the qualification of new WCBs in section 3.2.S.2.3. In the revised protocol, you propose that the

(b) (4)

(b) (4) The revised qualification protocol is inadequate to ensure product quality consistency. Address the following:

a. Meeting DS release acceptance criteria only is insufficient to support comparability. Per ICH Q5E, results within the established acceptance criteria, but outside historical manufacturing control trends, might suggest product differences that warrant additional study or analysis. Release data for the commercial scale DS batch manufactured using the new WCB should be compared to historical DS batch release data and the comparability assessment should include acceptance criteria that are based on historical DS batch release data. Revise the qualification protocol accordingly and include details of the comparability assessment such as the overall comparability approach and approach to setting and updating the comparability acceptance criteria for the release testing throughout the product lifecycle.

b. Revise the qualification protocol to include a commitment to place the first DS batch manufactured from a new WCB on stability.

c. The stability testing, acceptance criteria, and trending analysis for new WCBs in the qualification protocol (Table 2) should be revised based on the revisions made to the stability protocol for the current WCB.

If you choose to remove the qualification protocol from the BLA, requests to implement new cell banks (including MCBs) or protocol(s) to support qualification of new cell banks can be submitted as a prior approval supplement (PAS) if the BLA is approved.

5. The proposed DS release and stability acceptance criterion for content of ≥ (b) (4) mg/mL without an upper limit is not adequate because excessively high content could lead to product quality changes/differences. For example, differences in content may result in different stability profiles between pre- and post-change DS batches, thereby, impacting comparability assessments when manufacturing changes are made post-approval. Revise the acceptance criterion for DS content to include an upper and lower limit and to better align with manufacturing and clinical experience and provide adequate justification for the proposed acceptance criteria.

6. In Figures 7 and 8 in section 3.2.S.7.3, we note additional peaks in the RP-HPLC chromatograms under alkaline, light, and oxidation conditions in the

forced degradation studies performed on the DS and DP. You did not provide sufficient information for these additional peaks, such as the identity of the degradants in these peaks, their potential impact on safety and efficacy, and whether these degradants are present in DS and DP at release and under long-term and in-use storage conditions. Provide the identity of the degradants in the additional peaks observed in the RP-HPLC chromatograms, a risk assessment for their impact on safety and efficacy, and the control strategy for these potential degradants in DS and DP if applicable.

7. It appears that in addition to DS release testing (biological, chemical/physical) conducted at Novo Nordisk A/S Brennum Park Hillerød Hovedstaden 3400 Denmark (FEI number: 3003131673), the product quality of the DS is evaluated (b) (4) according to the tests and limits in Table 10 in section 3.2.S.2.4. You provided insufficient information on the purpose of conducting this additional product quality testing. Clarify the purpose for the product quality testing described in Table 10, including the actions taken if the test results are within or exceed the limits.

8. In Table 1 in section 3.2.P.3.1, you list Novo Nordisk A/S Brogårdsvej 66 Gentofte Hovedstaden 2820 Denmark (FEI number: 3002807748) and Novo Nordisk A/S Brennum Park Hillerød Hovedstaden 3400 Denmark (FEI number: 3003131673) as quality control testing sites for bulk DP and stability samples. However, according to the method validation reports, all the quality control tests were validated at Novo Nordisk A/S Brennum Park Hillerød Hovedstaden 3400 Denmark. Revise Table 1 in section 3.2.P.3.1 to provide clarity on which methods are performed at Novo Nordisk A/S Brogårdsvej 66 Gentofte Hovedstaden 2820 Denmark and Novo Nordisk A/S Brennum Park Hillerød Hovedstaden 3400 Denmark and provide the method validation results or method transfer results to support routine release and stability testing at each site if they have not already been provided in the BLA.

9. In the IR response received on 02/21/2023 to the Agency's IR comment 18 dated 02/08/2023, you stated that the specific activity acceptance criteria in the qualification protocols for new PRMs and SRMs are based on the (b) (4) The specific activity acceptance criteria are not sufficiently narrow to prevent reference material and product drift over time, and thus, the qualification protocols are inadequate. Address the following:

(b) (4)

If you choose to remove the qualification protocols for new PRMs and SRMs from the BLA, requests to implement new reference materials or new reference material qualification protocols can be submitted as a PAS if the BLA is approved.

10. The analytical methods that are used for critical in-process tests (b) (4) f the DS manufacturing process are described in section 3.2.S.2.4. In addition, this section contains validation or verification information and data for these analytical methods, where applicable. However, the description of the analytical methods for the various non-critical in-process tests (b) (4) and their respective validation or verification information and data were not provided. Revise section 3.2.S.2.4 to include the description of the analytical methods for the various non-critical in-process tests (b) (4) and their respective validation or verification information and data. Adequate information and data should be provided to demonstrate the analytical methods are suitable to evaluate the intended quality attributes in the in-process samples.

11. Your description of the approach for acceptance quality limit (AQL) following 100% visual inspection for the concizumab DP in section 3.2.P.3.3 is limited. Revise this section to include a description of AQL following 100% visual inspection, including the limits applied for each defined category of defect. In addition, revise section 3.2.P.3.5 to include the visual inspection results for the PPQ batches.

12. Section 3.2.P.3.3 does not include information for the filling speed in the filling step of the DP manufacturing process. Revise section 3.2.P.3.3 to include this information and provide data from PPQ runs supporting that the filling speed does not impact product quality.

13. In section 3.2.P.3.3, you describe that the DP cartridges (b) (4) You did not provide sufficient information for the controls that ensure consistency (b) (4) product quality and device functionality. Provide a description of the controls that ensure consistency (b) (4) of the DP cartridges and information and data to support that worst-case (b) (4) does not impact product quality and device functionality.

14. In the response received on 02/21/2023 to the Agency's IR comment 25 dated 02/08/2023, you stated that the shipper qualification and transport simulation studies support worse-case shipping conditions for the DP, and therefore, data from these studies support commercial shipping of DP from Denmark to the US. We do not agree with this assessment because while transport simulation studies provide supporting information, they do not replicate hazards that occur concurrently within a commercial supply chain and therefore, are generally not enough to address the potential risk of commercial shipping on product quality. To verify that product quality is not impacted by worst-case shipping conditions, provide product quality assessment of commercial product in the intended primary and secondary container (if applicable) prior to and after shipment. Stability-indicating CQAs should be assessed in the commercial shipping studies. In addition, temperature monitoring data recorded continuously throughout shipping from thermal couple probes placed inside and outside of the shipping container should be provided. In the absence of commercial shipping data, a shipping qualification protocol may be submitted to conduct concurrent shipping qualification.

15. You have on-going in-use stability studies to support the in-use period of 4 weeks for DP when stored below 30°C at the end of shelf-life. In Table 4 in

section 3.2.P.5.6, you propose (b) (4) We do not agree with this approach to setting the in-use testing criteria because the resulting acceptance criteria significantly exceed the clinical experience. Revise the in-use testing acceptance criteria for these purity attributes/tests based on the clinical experience to ensure the concizumab impurity/purity profile during the in-use period of 4 weeks when stored below 30°C at the end of shelf-life is consistent with the product profile shown to be safe in clinical studies. In addition, revise section 3.2.P.5.6 to include the in-use testing acceptance criteria for all quality attributes/tests (e.g., appearance, pH, specific activity, content, phenol content, and preservative efficacy test). Provide justification for the proposed in-use testing acceptance criteria.

16. In your Complete Response, provide updated data from the following studies that are ongoing:

    a. The commercial-scale (b) (4) and cation-exchange chromatography columns (in section 3.2.S.2.5).

    b. The on-going concizumab DS and DP stability studies (in sections 3.2.S.7 and 3.2.P.8).

    c. The on-going leachables studies for DS and DP (in sections S.6 and 3.2.P.2.4).

17. In your Complete Response, provide any updated batch analysis data for DS and DP as applicable for batches released since your original BLA submission.

Microbiology

1. (b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

Immunogenicity Assays

1. You provided information and data regarding the development and validation of various anti-drug antibody (ADA) assays used during clinical development of concizumab in sections 2.7.1, 5.3.1.4, and 5.3.5.3. The information and data are not sufficient to fully assess the adequacy of the validation of the ADA assays and the suitability of the ADA assays to evaluate clinical samples in the phase 3 (pivotal) clinical trial 4311. Address the following regarding the binding ADA (BADA) assay (anti-concizumab binding antibody assay, assay #3) and/or the neutralizing ADA (NADA) assay (anti-concizumab neutralizing antibody assay, assay #2) used to evaluate clinical samples in the phase 3 clinical trial 4311:

    a. The positive control used in the validation of the BADA and NADA assays and during the testing of clinical samples is described as an anti-concizumab monoclonal antibody. Additional information is needed to assess the adequacy of the positive control. Provide details (e.g., source, purification method, etc.) for the positive control anti-concizumab monoclonal antibody used in the validation of the BADA and NADA assays and during the testing of clinical samples.

b. The use of immunogenicity assays subject to hook (prozone) effects may result in false-negative results for clinical samples. For the BADA and NADA assays, the validation studies do not include assessment of hook effect on method performance. Provide assessment of hook effect on the BADA and NADA assays.

c. Lipids can interfere with immunogenicity assay results. The validation studies do not include assessment of lipemia on performance of the BADA and NADA assays. Provide assessment of lipemia on performance of the BADA and NADA assays to support testing of lipemic clinical samples. Alternatively, provide a justification why characterization of matrix interference by lipids is not needed for the BADA and NADA assays.

d. The sensitivity of the NADA assay decreases from 207 ng/mL in the absence and presence of 100 ng/mL concizumab to 1000 ng/mL in the presence of 800 ng/mL concizumab, even with the use of several sample pre-treatment steps (i.e., heat denaturation, acid, and BEAD immunoprecipitation) in the assay intended to overcome drug and target interference. Furthermore, the intra- and inter-assay precision for the medium and high positive controls were well above the FDA guidance recommended precision of 20% CV (intra-assay precision 29.5 – 42.2% CV; inter-assay precision: 33.8 – 42.2% CV) during validation of the NADA assay. Provide justification why this higher %CV is acceptable and describe how these results inform the suitability and reliability of the NADA assay in detecting NADAs in clinical samples. Alternatively, consider refining the assay parameters to optimize the assay precision.

4. Basis for Recommendation

a. Summary:

Concizumab binding to TFPI enhances FXa production during the initiation phase of coagulation which leads to improved thrombin generation and clot formation to achieve hemostasis in patients with Hemophilia A or B with or without inhibitors. Potency of concizumab is controlled using the coagulation assay. The coagulation time is measured by following the formation of fibrin polymers. The coagulation time is inversely dependent on the amount of concizumab in the sample. Dose-response curves are generated for samples and reference material. Potency of samples is determined relative to reference material. The results are reported as U/mg based on the content measured by SE-HPLC.

The concizumab drug substance (DS) manufacturing process consists of (b) (4)

The overall control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the DS and DP. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Although the BLA is recommended for approval from microbiology and sterility assurance perspectives, multiple product quality and device constituent deficiencies were identified that cannot be adequately addressed during the assessment period. These deficiencies include, but are not limited to:

- Inadequate characterization and control strategy (b) (4)
- Inadequate cell bank stability protocols,
- Inadequate reference material stability protocols,
- Inadequate DS and DP release and stability specifications,
- Inadequate DS and DP post-approval annual stability protocols.

In addition, during the inspection of the DS manufacturing site, (b) (4) investigators conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

b. Subdiscipline Recommendation:

Drug Substance	-	Inadequate
Drug Product	-	Inadequate
Immunogenicity Assay	-	Adequate
Facilities	-	Inadequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
Not applicable as OPQ does not recommend approval of this application.

5. Life-Cycle Considerations
Not applicable as OPQ does not recommend approval of this application.

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

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/

MASSOD RAHIMI
04/10/2023 06:28:13 PM

FRANCES NAMUSWE
04/10/2023 06:45:50 PM