# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761315Orig1s000

# OTHER ACTION LETTERS

BLA 761315

**COMPLETE RESPONSE**

Novo Nordisk
Attention: Ge (Larry) Bai
Director, Regulatory Affairs
P. O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Mr. Bai:

Please refer to your biologics license application (BLA) dated and received August 24, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for NNC0172-2021 injection.

We also acknowledge receipt of your amendment dated April 19, 2023, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

## CLINICAL AND CLINICAL PHARMACOLOGY

(1) Despite fixed maintenance doses of NNC0172-2021 significant fluctuations in concentrations were noted in patients over the treatment period. At the target exposure range of 200 - 4000 ng/mL, target-mediated drug disposition (TMDD) plays a dominant role in NNC0172-2021 clearance, leading to rapid drug elimination and a relatively shorter half-life at the proposed doses of 0.15 - 0.25 mg/kg. As a result, NNC0172-2021 concentrations can decline steeply to subtherapeutic levels with missed doses. When concentrations decline to levels much lower than 200 ng/mL, in the absence of a loading dose, it may take several days of consecutive dosing to gradually return to target concentrations of >200 ng/mL. Given that a NNC0172-2021 concentration above 200 ng/mL is key to the therapeutic effect, you will need to provide a plan for dosing after one or more missed doses. This may include a plan for additional NNC0172-2021 pharmacokinetics (PK) monitoring and/or a repeat loading dose. In addition, the importance of adherence to daily dosing and maintenance of therapeutic NNC0172-2021 levels should be stressed in a Medication Guide, labeling and educational materials. Furthermore, we have concerns that your plan to require

only a single occurrence of PK monitoring after four weeks of dosing may not be sufficient to ensure consistent therapeutic drug levels, and you may need to propose more frequent routine PK monitoring or provide further clarification on why the single PK measurement is sufficient.

**DEVICE**

(2) As stated in the Late-Cycle Meeting on March 9, 2023, the validation of the (b) (4) NNC0172-2021 ELISA is inadequate to support the use of the assay in testing clinical specimens. Specifically, for the correlation/cross-validation study, you should include an evaluation of a sufficient number of native patient samples and include samples that cover a range of NNC0172-2021 levels that are pertinent to dose adjustment decisions (e.g., NNC0172-2021 levels <200ng/mL, 200-4000ng/mL and >4000ng/mL), in order to demonstrate safe use of the (b) (4) NNC0172-2021 ELISA for patients.

(3) In the precision study, include an assessment of instrument-to-instrument and lot-to-lot precision, as multiple instruments and reagent lots will be used clinically and an estimate of device imprecision including these components of precision should be understood prior to device use.

(4) For the assay specificity/interference study, we identified substances (hemoglobin, cholesterol, triglyceride, Factor VII (NOVOSeven), biotin, ledipasvir and acetaminophen) in which interference may be observed at the levels tested. Conduct a dose-response study to determine at which concentrations these substances no longer interfere with the (b) (4) NNC0172-2021 ELISA.

(5) Provide the sample stability data using (b) (4) NNC0172-2021 ELISA (b) (4)

(6) Finally, provide a root-cause analysis to address the underestimation of NNC0172-2021 concentrations for contrived samples by the (b) (4) NNC0172-2021 ELISA as was seen for specific validation studies (i.e., interference, carryover, dilution scheme and sample stability studies).

The Center for Devices and Radiological Health (CDRH) strongly recommends that each of the above issues are further discussed in a post-action meeting.

**PRODUCT QUALITY**

(9) In the response received on February 21, 2023 to the Agency's information request (IR) comment 26 dated February 8, 2023, you described the control strategy for (b) (4) in the NNC0172-2021 drug product (DP). In addition, in the response received on February 28, 2023 to the Agency's IR dated

February 16, 2023, you provided an assessment for the risk (b) (4) on safety and efficacy. The information and data provided are not sufficient to address the risk of (b) (4) on safety and efficacy and the control strategy for (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)

(10) 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:


(11) 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)

(12) In the response received on February 21, 2023 to the Agency's IR comment 12 dated February 8, 2023, you revised the NNC0172-2021 master cell bank (MCB) and working cell bank (WCB) stability protocols in section 3.2.S.2.3 to state tha (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) for the MCB and WCB.

(13) In the response received on February 21, 2023 to the Agency's IR comment 18 dated February 8, 2023, you provided revised NNC0172-2021 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)


(14) 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:


(15) 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)

(16) In the response received on February 21, 2023 to the Agency's IR comment 22 dated February 8, 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

(17) On March 3, 2023, we sent an IR requesting to include the 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.

(18) On March 7, 2023, we sent an IR requesting to include the 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.

## FACILITY INSPECTION

(19) 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.

## PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

## CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

## PROPRIETARY NAME

Please refer to correspondence dated, November 21, 2022 which addresses the proposed proprietary name, Alhemo. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

**SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

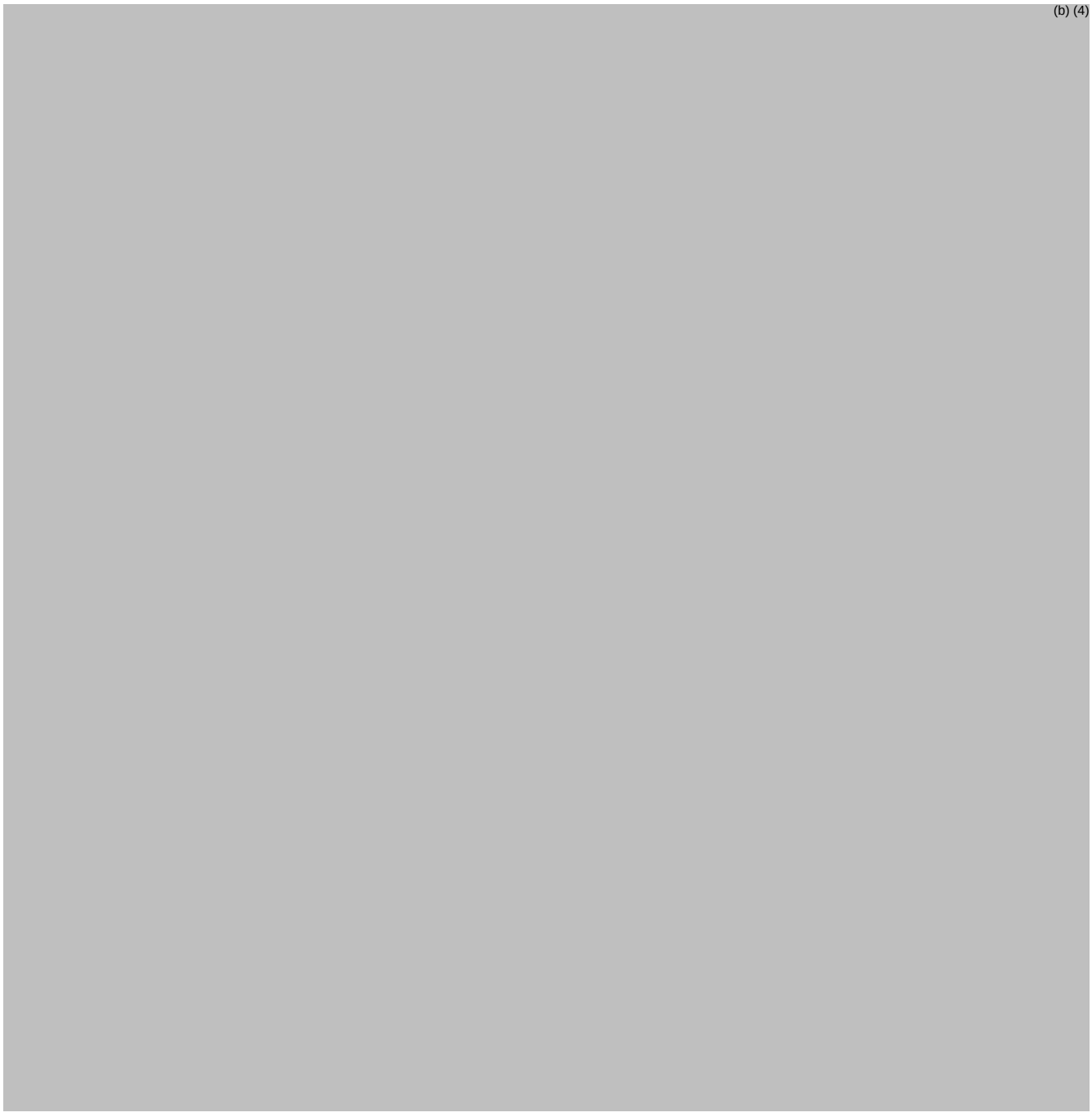
(8) Provide English translations of current approved foreign labeling not previously submitted.

## ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

## PRODUCT QUALITY

(b) (4)



(b) (4)

(4) In the response submitted on February 21, 2023, to the Agency's IR comment 13 dated February 8, 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) 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 February 21, 2023, to the Agency's IR comment 18 dated February 8, 2023, you stated that the specific activity acceptance criteria in the qualification protocols for new PRMs and SRMs are based on the (b) (4)

(b) (4) he 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) of 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 NNC0172-2021 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) s. 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 February 21, 2023, to the Agency's IR comment 25 dated February 8, 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 NNC0172-2021 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 resubmission, provide updated data from the following studies that are ongoing:

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

b. The on-going NNC0172-2021 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 resubmission, provide any updated batch analysis data for DS and DP as applicable for batches released since your original BLA submission.

Microbiology

(b) (4)



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(b) (4)

Immunogenicity Assays

(27) You provided information and data regarding the development and validation of various anti-drug antibody (ADA) assays used during clinical development of NNC0172-2021 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-NNC0172-2021 binding antibody assay, assay #3) and/or the neutralizing ADA (NADA) assay (anti-NNC0172-2021 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-NNC0172-2021 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-NNC0172-2021 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 NNC0172-2021 to 1000 ng/mL in the presence of 800 ng/mL NNC0172-2021, 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.

**HUMAN FACTORS**

The comments in this section are not intended to convey human factors (HF) approvability issues with your proposed product; however, it will be necessary for you to consider how any revisions to your proposed product to address the deficiencies outlined above will impact your user interface.

If your user interface is revised in response to the complete response, you should update your use-related risk analysis (URRA) to determine whether any new risks, including new critical tasks or failure modes are introduced by the changes. You will need to provide this information to the Agency to determine whether the changes to your user interface will require submission of additional HF data to validate the revised user interface.

If you determine that an additional HF study does not need to be submitted, submit your justification, updated URRA, comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your revised user interface and the user interface that is the subject of the complete response. We strongly recommend you submit this information to the Agency for review prior to resubmitting BLA 761315 to ensure the Agency agrees with your determination regarding the HF data need to support your revised user interface.

If you determine that you do need to submit the results of an additional HF validation study for your revised user interface, we recommend you submit your study protocol for feedback from the Agency before commencing your study to the IND, and prior to resubmitting BLA 761315. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

The results from the HF validation study indicate that there are additional labeling mitigations that can be implemented to address use errors that occurred with critical tasks. In addition to the consideration of the deficiencies above, we recommend you also implement the recommendations below. We have determined that in this instance,

you may implement these revisions in the Identified Issues and Recommendations table below without submitting additional HF validation data for Agency review.

| Identified Issues and Recommendations for Novo Nordisk Inc. | | | |
|---|---|---|---|
| | **Identified Issue** | **Rationale for Concern** | **Recommendation** |
| **Instructions for Use (IFU) – all strengths – PDF versions** | | | |
| 1. | The location of the graphics in Step 2 can be improved to increase the visibility and prominence of the key sub-steps (i.e., attaching the needle and removing the needle caps). | In the HF validation study, there were use-related events (i.e., use errors, close calls, and a use difficulty) with the attach the needle and remove the needle caps tasks.<br><br>Based on the URRA, if the remove the needle caps tasks are omitted or not performed correctly, there is risk of reduced protection against bleeds. | Relocate Step 2 graphic A to appear directly below the first bullet (i.e., "…See A.").<br><br>Additionally, relocate Step 2 graphic B to appear directly below the third bullet ("…See B.").<br><br>For example, we refer you to the formatting used in your Tresiba FlexTouch Pen IFU and your Norditropin FlexPro Pen IFU. |
| 2. | The title of Step 3 can be improved to clarify that users should test the flow of the prefilled pen (i.e., prime the prefilled pen) prior to each injection. | In the HF validation study, the subjective feedback and root cause analysis information indicated some participants overlooked the instruction to the test the flow before each injection or did not know the task was necessary for each subsequent injection after the 1st injection.<br><br>Lack of prominence of a use task might result in the task being omitted due to being overlooked. | Revise the title of Step 3 from "(b) (4)" to now read "Prime before each dose. Dial to '1' and test the flow before each dose." |
| 3. | Users may confuse the Step 4 graphic depicting an example dose with their prescribed dose. | In the HF validation study, there were use-related events (i.e., use errors) in which participants incorrectly dialed the dose depicted in the IFU | Revise the Step 4 graphic to include two dose examples. We find this revision might prompt users to identify the graphics as examples and not as the intended dose. For example, we note the Tresiba FlexTouch Pen |

| Identified Issues and Recommendations for Novo Nordisk Inc. | | | |
|---|---|---|---|
| | **Identified Issue** | **Rationale for Concern** | **Recommendation** |
| | | instead of the prescribed dose.<br><br>Based on the URRA, if the set the intended dose task is not performed correctly, there is risk of thromboembolism or reduced protection against bleeds. | IFU and the Norditropin FlexPro Pen IFU include graphics containing two dose examples.<br><br>Also, consider zooming in on the dose counter and dose pointer part of the prefilled pen for the two dose examples to improve readability. |
| 4. | The injection angle depicted in the Step 5 graphic is unclear. (b) (4) Additionally, the placement of the hand in the graphic can be improved. | In the HF validation study, there were use-related events (i.e., use errors) with the insert needle in subcutis task. We specifically note subjective feedback which indicate the IFU graphic appears to show the pen being injected from the side.<br><br>Based on the URRA, if the insert the needle task is omitted or not performed correctly, there is risk of pain or injection site reaction. | Revise the Step 5 graphic to more clearly depict the prefilled pen being injected into the injection site at a 90-degree. |
| 5. | Step 5 can be improved to increase the visibility and prominence of the key sub-steps (i.e., press and hold the button, count slowly to 6 after the dose counter has returned to <0>). | In the HF validation study, there were use-related events (i.e., use errors) with the inject the dose task. We specifically note subjective feedback which indicated participants overlooked part of IFU Step 5 sub-step (e) and found the wording of IFU Step 5 sub-step (e) unclear.<br><br>Based on the URRA, if the inject the dose task is | Increase the prominence of Step 5 sub step (b) (4) by dividing Step 5 into separate steps:<br>• revise Step 5 sub step (b) (4) to Step 6 [and renumber subsequent steps accordingly])<br>Or into separate groups of steps:<br>• revise Step 5 sub steps (b) (4) to Step 5 and revise Step 5 sub steps (b) (4) to Step 6 [and renumber subsequent steps accordingly]). |

| Identified Issues and Recommendations for Novo Nordisk Inc. | | | |
|---|---|---|---|
| | **Identified Issue** | **Rationale for Concern** | **Recommendation** |
| | | omitted or not performed correctly, there is risk of reduced protection against bleeding events due to underdose. | Include a graphic directly below Step 5 sub step (e) that depicts the step of counting slowly to 6 after the dose counter has returned to <0> (similar to Figure P in the Tresiba FlexTouch Pen IFU).<br><br>Additionally, consider revising Step 5 sub step (b) (4) "(b) (4) [redacted]" to now read "Once the needle has returned to <0>, count slowly to 6 while the needle is still in your skin". |
| 6. | Step 6 can be improved to more prominently convey the risk associated with touching inside of the bottom of the pen needle (e.g., needle stick injury).<br><br>Additionally, the term "(b) (4)" in the IFU may not clearly convey the location of the exposed needle on the inside of the bottom of the pen needle. (b) (4) [redacted] | In the HF validation study, 1 participant experienced a needle stick injury due to being poked with the back of the needle.<br><br>Based on the URRA, if a user experiences a needle stick injury (via the needle front or back-end or a contaminated needle), there is risk of a puncture wound or skin abrasion/infection. | Revise the statement (b) (4) [redacted]" to now read "Do not touch the pen needle on either side to avoid sticking yourself with the needle".<br><br>Additionally, label the location of the ends of the needle on the Step 6 graphic and consider adding an additional graphic to depict the needle from the back end. |

| Identified Issues and Recommendations for Novo Nordisk Inc. | | | |
|---|---|---|---|
| | **Identified Issue** | **Rationale for Concern** | **Recommendation** |
| | (b) (4) | | |
| 7. | The title of Step 7 can be improved to mitigate the risk of users not recapping the pen. | In the HF validation study, there were use-related events (i.e., use errors and a use difficulty) with the put on the pen cap task.<br><br>Based on the URRA, if the put on the pen cap task is omitted or not performed correctly, there is risk of discomfort or loss of nonsignificant functionality or quality. | Revise the title of Step 7 from "(b) (4)" to now read "Recap the pen". |
| 8. | The post-opening expiration date information in the Important information about your pen section is unclear. | In the HF validation study, there were use-related events (i.e., use errors, a use difficulty, and a close call) with the knowledge check/comprehension question "How many days can a pen be used for?" in which participants misinterpreted the post-opening expiration date information or had difficulty interpreting the post-opening expiration date information.<br><br>Based on the URRA, if users do not correctly interpret the post-opening expiration date, there is risk of reduced protection against bleeding events due to exceeding in-use time. | Revise the statement (b) (4) to "After 28 days, you must throw away (discard) your pen in an FDA-cleared sharps disposal container". |

| Identified Issues and Recommendations for Novo Nordisk Inc. | | | |
|---|---|---|---|
| | **Identified Issue** | **Rationale for Concern** | **Recommendation** |
| 9. | The storage information in the Storing section of the IFU can be improved to increase the prominence of the storage conditions. | Lack of prominence of the product storage information might pose of risk of deteriorated drug medication errors. | Revise the headers “Before first use” and “After first use” to appear in bold font. |
| 10. | The storage information includes an unfamiliar term, “cooling element”, that might not be readily understood by lay users. | Lack of unclarity regarding product storage might pose of risk of deteriorated drug medication errors. | Define and clarify the term “cooling element” in the Storing section of the IFU to improve lay user understanding. Please note you may consider including examples of a cooling element, if appropriate. |
| 11. | The presentation of Step 6 in the PDF version of the draft IFUs submitted in the October 31, 2022 Response to Information Request is different from the Word versions submitted on August 24, 2022. Specifically, the PDF version of the IFUs includes information related to “Do you need a larger dose than you can dial”. However, the Word version of the IFUs includes this information below a blank box to the right of the graphic depicting a sharps container. | We need to understand the proposed Word IFU format to provide a comprehensive review of the IFUs. | Clarify whether “Do you need a larger dose than you can dial” will appear in the box in Step 6 in the commercial IFUs. |

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Courtney Hamilton, Regulatory Project Manager at 301-796-6849 or at Courtney.Hamilton@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Lisa Yanoff, MD
Deputy Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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LISA B YANOFF
04/24/2023 12:22:01 PM