

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761326Orig2s000

OTHER ACTION LETTERS

BLA 761326/ Original 1
BLA 761326/ Original 2

COMPLETE RESPONSE

Novo Nordisk Inc.
Attention: Helen Chen, MSc, RAC
Director, Regulatory Affairs
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Helen Chen:

Please refer to your biologics license application (BLA) dated and received April 10, 2023, and your amendments, under section 351(a) of the Public Health Service Act for NNC0148-0287 injection.

We acknowledge receipt of your submissions dated October 25, November 8, and December 4, 2023, which constituted a major amendment to this application and therefore extended the goal date by three months.

BLA 761326 provides for the use of NNC0148-0287 injection for the following indications which, for administrative purposes, we have designated as follows:

- (b) (4)
- BLA 761326/Original 2 – Type 2 diabetes mellitus in adults

The subject of this action letter is BLA 761326/Original 1 and BLA 761326/Original 2. No separate action letter will be issued for BLA 761326.

All future submissions to BLA 761326/Original 1 or BLA 761326/Original 2 should specify the BLA number and the Original number to which each submission pertains.

We have completed the review of BLA 761326/Original 1 and BLA 761326/Original 2, as amended, and have determined that we cannot approve these applications in their present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

Deficiencies for both BLA 761326/Original 1 AND BLA 761326/Original 2

FACILITY INSPECTIONS

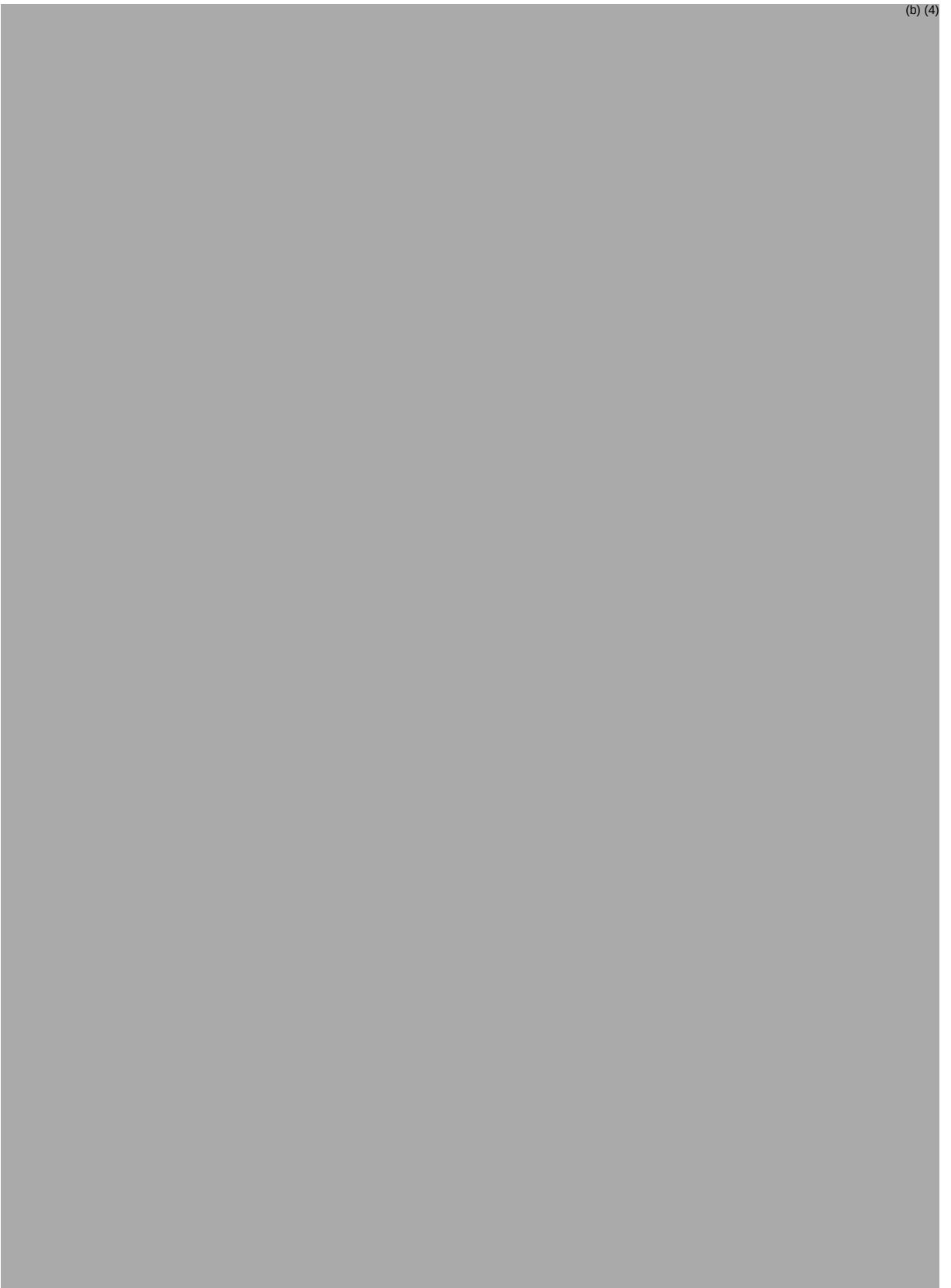
1. Following the pre-license inspection of Novo Nordisk A/S, Kalundborg, Denmark (FEI 3002807751), listed in this application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to submission of your complete response to your application. Your complete response should include the date(s) of the facility's response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies will be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)



¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

(b) (4)



Deficiency for BLA 761326/Original 1 ONLY

CLINICAL

Our assessment of the data submitted to support use for glycemic control in adults with type 1 diabetes is that the benefit-risk balance is unfavorable due to an unacceptably higher risk (vs. daily basal insulin comparator) of clinically meaningful hypoglycemia without evidence of any relative improvement in hemoglobin a1c reduction or other benefit (e.g., better adherence or patient satisfaction) versus available therapy. In ONWARDS 6, conducted in a type 1 diabetes population, there was a 50% higher incidence and 80% higher event rate of level 2 or level 3 hypoglycemia reported in the NNC0148-0287 arm compared to the insulin degludec arm using self-measured blood glucose (SMBG) data, and the risk of hypoglycemia was consistently higher regardless of method of data capture (SMBG or continuous glucose monitoring (CGM)). Our conclusion is that NNC0148-0287, when used in a type 1 diabetes population

following the ONWARDS 6 protocol, results in excess hypoglycemia that is likely a consequence of the dosing and titration algorithm used in ONWARDS 6 in the context of the time action profile of NNC0148-0287. Level 2 and 3 hypoglycemia are clinically significant events that have the potential to result in morbidity and mortality. Although NNC0148-0287 allows for fewer weekly injections for patients over daily basal insulin products, this feature on its face does not offset the observed difference in clinically meaningful hypoglycemia in ONWARDS 6.

As a path forward, provide new clinical data to demonstrate favorable benefit-risk for NNC0148-0287 in subjects with type 1 diabetes. We recommend that you request a post-action meeting to discuss a potential new glycemic control clinical study in participants with type 1 diabetes that would optimize the dosing and titration algorithm and assess other outcome(s) important to patients such as the patient experience with NNC0148-0287.

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 Resources² and Pregnancy and Lactation Labeling Final Rule³ 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.

If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.⁴

PROPRIETARY NAME

Please refer to correspondence dated, June 30, 2023, which addresses the proposed proprietary name, Awiqli FlexTouch. 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.

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

² <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

³ <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

⁴ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

and clinical studies/trials of the product 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 patient 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 product. Include an updated estimate of use for product marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

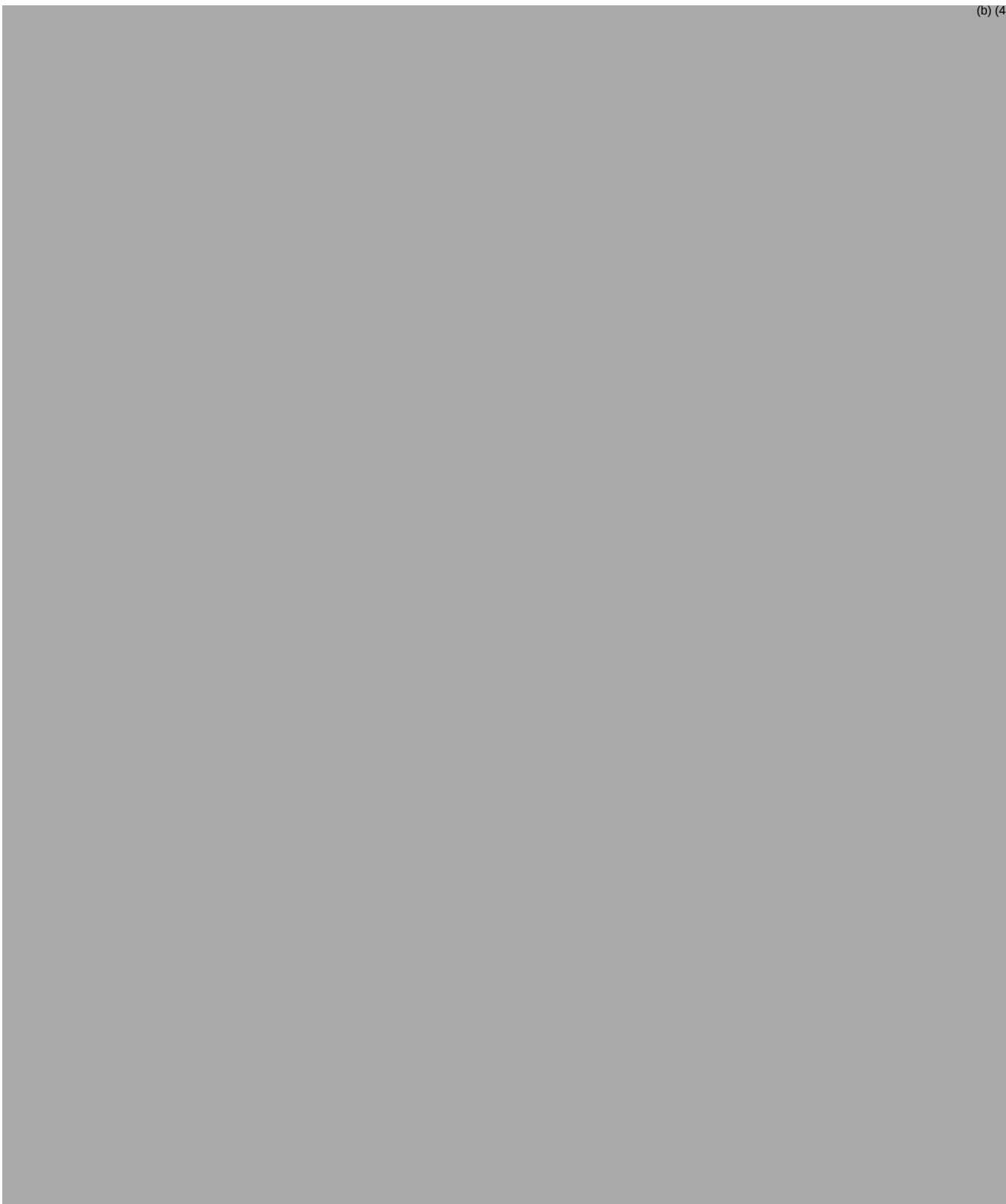
ADDITIONAL COMMENTS for ORIGINAL 1 and ORIGINAL 2

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

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

CMC

(b) (4)



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. 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 BLA 761326/Original 1 and BLA 761326/Original 2 may be approved. If you

U.S. Food and Drug Administration
Silver Spring, MD 20993
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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*.⁵

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

If you have any questions, call Ajmal Mohmand, Regulatory Project Manager, at 301-796-4951.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, M.D.
Deputy Director
Office of Cardiology, Hematology, Endocrinology,
and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

⁵ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.
U.S. Food and Drug Administration
Silver Spring, MD 20993
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
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