CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208751Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208751 SUPPL # N/A HFD #

Trade Name Fiasp

Generic Name insulin aspart

Applicant Name Novo Nordisk

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the

NDA #(s).

NDA# 20986 Novolog

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets

"clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

NN1218-3852 Efficacy and Safety of FIAsp compared to insulin aspart both in Combination with insulin detemir in Adults with Type 1 Diabetes

NN1218-3853 Efficacy and Safety of FIAsp Compared to Insulin Aspart in Combination with Insulin Glargine and Metformin in Adults with Type 2 Diabetes

NN1218-4049 Efficacy and safety of FIAsp in a basal-bolus regimen versus basal insulin therapy, both in combination with metformin in adult Subjects with type 2 diabetes

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

Note: Two clinical trials (NN1218-3852 and NN1218-3853) listed above compared Fiasp to Novolog. These clinical trials are not considered to be bioavailability studies because these trials assessed the primary efficacy endpoint of change in HbA1c from baseline to end of treatment period.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a

previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒
Investigation #3	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒
Investigation #3	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

NN1218-3852 Efficacy and Safety of FIAsp compared to insulin aspart both in Combination with insulin determir in Adults with Type 1 Diabetes

NN1218-3853 Efficacy and Safety of FIAsp Compared to Insulin Aspart in Combination with Insulin Glargine and Metformin in Adults with Type 2 Diabetes

NN1218-4049 Efficacy and safety of FIAsp in a basal-bolus regimen versus basal insulin therapy, both in combination with metformin in adult Subjects with type 2 diabetes

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1, 2, and 3		!
		!
IND # 106878	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that

the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Callie Cappel-Lynch
Title: Regulatory Project Manager
Date: September 19, 2017

Name of Division Director signing form: Lisa Yanoff on behalf of Jean-Marc Guettier
Title: Clinical Team Leader

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
09/20/2017

LISA B YANOFF
09/20/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208751	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Fiasp Established/Proper Name: insulin aspart Dosage Form: injection		Applicant: Novo Nordisk Inc. Agent for Applicant (if applicable): N/A
RPM: Callie Cappel-Lynch		Division: Metabolism and Endocrinology

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is September 29, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR Oct. 7, 2016
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 5 – New Formulation or New Manufacturer
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Actions and dates AP September 29, 2017 CR October 7, 2016
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included – included with action letter
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included- included with action letter
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included – included with action letter
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letters: June 6, 2017 December 21, 2016 July 28, 2016 May 5, 2016 Reviews: May 29, 2017 December 15, 2016 July 26, 2016 April 22, 2016
❖ Labeling reviews *(indicate dates of reviews)*	RPM: February 2, 2016 DMEPA: August 24, 2017 August 7, 2017 July 20, 2016 DMPP/PLT (DRISK): September 20, 2017 September 8, 2016 OPDP: September 20, 2017 September 8, 2016 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: DPMH May 9, 2016
Administrative / Regulatory Documents	

❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	February 1, 2016 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC August 24, 2016 If PeRC review not necessary, explain:	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	February 22, 2016
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	December 15, 2016
• Pre-NDA/BLA meeting *(indicate date of mtg)*	June 22, 2015
• EOP2 meeting *(indicate date of mtg)*	March 2, 2011
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	October 7, 2016
Cross-Discipline Team Leader Review *(indicate date for each review)*	September 27, 2017 October 7, 2016
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review see CDTL review
• Clinical review(s) *(indicate date for each review)*	September 22, 2017 October 7, 2016 February 16, 2016
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See clinical review page 21 dated October 7, 2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	September 6, 2017 September 29, 2016
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	August 15, 2016
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	September 2, 2016 February 3, 2016

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	September 6, 2017 September 8, 2016 February 11, 2016
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	July 12, 2017 September 20, 2016 August 29, 2016 January 27, 2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	August 17, 2017 September 9, 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	September 21, 2016
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See integrated quality assessment page 45
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable 8/23/16 and 9/28/17 Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	**N/A**
• Finalize 505(b)(2) assessment	**N/A**
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	N/A
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	**N/A**
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	**N/A**
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

From: CappelLynch, Callie
To: HCHN (Helen Guo Chen) (hchn@novonordisk.com)
Subject: NDA 208751 labeling comments
Date: Friday, September 08, 2017 5:09:00 PM
Attachments: 9.8.17 FDA edits prop-pi-tracked.doc

Hi Helen,

Please see the attached FDA labeling comments. We request that you provide revised labeling by COB Wednesday, September 13th.

Thanks,
Callie

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

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
09/08/2017

From: CappelLynch, Callie
To: "HCHN (Helen Guo Chen)"
Subject: RE: NDA 208751
Date: Friday, August 25, 2017 4:44:00 PM
Attachments: 8.25.17 FDA comments resubmission prop-pi.doc

Hi Helen,

Please see the attached PI with FDA edits. Please also replace TRADENAME with the conditionally approved proprietary name throughout. We ask that you return a revised label by COB Friday, September 1st.

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Friday, August 25, 2017 4:05 PM
To: CappelLynch, Callie
Subject: RE: NDA 208751

Dear Callie,

Just quick check in to follow up on the status of the PI comments from the Agency.

Let me know if any changes.

Thanks in advance!

KR
Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Tuesday, August 22, 2017 6:39 AM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751

Yes, our goal is to send out comment this Friday. If anything changes, I'll let you know.

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Monday, August 21, 2017 5:36 PM
To: CappelLynch, Callie
Subject: RE: NDA 208751

Just double check before I inform my team. You mean we can expect the PI comments by the end of this week, by this Friday, right?

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Monday, August 21, 2017 5:19 PM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751

We typically ask for response in 1 week.

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Monday, August 21, 2017 5:17 PM
To: CappelLynch, Callie
Subject: RE: NDA 208751

Thanks so much, Callie.

How soon do you expect us to send back our comments for the PI? just want to get an idea so the team is prepared.

Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Monday, August 21, 2017 5:13 PM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751

Hi Helen,

We aim to send the PI with FDA edits by the end of the week. We will follow up with edits on the PPI and IFU once the PI is in close to final form.

The PMR proposal is still under review. I don't have an update at this time.

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Monday, August 21, 2017 4:54 PM
To: CappelLynch, Callie
Subject: RE: NDA 208751

Hi Callie,

Just checking in to see if you have any update on the PMR discussion? Also I would like to know when you anticipate to send the Agency's labeling comments on the proposed PI, PPI and IFU?

If the Agency has any additional questions on the resubmission, please let me know as soon as possible.

Thanks so much for all your help!

KR
Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Monday, August 14, 2017 4:35 PM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 IR

Hi Helen,

The proposal is still under review. We don't have any comments at this time.

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Monday, August 14, 2017 2:21 PM
To: CappelLynch, Callie
Subject: RE: NDA 208751 IR

Hi Callie,

Just want to follow up to see if the Agency has agreed with our proposed timeline of February 2019 for the PMR study. Let me know if any additional comments/recommendations from your side.

Thanks so much!

BR

Helen

From: HCHN (Helen Guo Chen)
Sent: Monday, August 07, 2017 5:01 PM
To: 'CappelLynch, Callie'
Subject: RE: NDA 208751 IR

Hi Callie,

[redacted] (b) (4)

Let me know if you have any additional questions.

KR

Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Monday, August 07, 2017 4:43 PM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 IR

Hi Helen,

Do you have a copy of [redacted] (b) (4)? If you could email one that

would be helpful.

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Monday, August 07, 2017 10:26 AM
To: CappelLynch, Callie
Subject: RE: NDA 208751 IR

Hi Callie,

Hope you had a nice weekend!

(b) (4)

BR
Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Friday, August 04, 2017 3:19 PM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 IR

Hi Helen,

Since this will be the safety/efficacy study you are required under PREA to submit the FR as a part of a supplement. (b) (4)

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]

Sent: Friday, August 04, 2017 2:51 PM
To: CappelLynch, Callie
Subject: RE: NDA 208751 IR

Hi Callie,

A quick question on the PMR study.

(b) (4)

Thanks in advance.

BR

Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Friday, August 04, 2017 11:36 AM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 IR

Thanks Helen. Please see our attached revisions. Please send back a revised copy within 1 week.

Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Friday, August 04, 2017 10:18 AM
To: CappelLynch, Callie
Subject: RE: NDA 208751 IR

Hi Callie,

The study was initiated July last year and is currently close to completing enrollment. SAP was not submitted with the final protocol in December 2015. Please let me know if a SAP submission is required.

KR
Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Friday, August 04, 2017 10:11 AM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 IR

Hi Helen,

Can you confirm if the study has already started enrolling, and whether or not a SAP has been submitted?

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Friday, August 04, 2017 9:19 AM
To: CappelLynch, Callie
Subject: RE: NDA 208751 IR

Good morning, Callie.

Please find attached PMR with our track changes for the milestone timelines.

Can you confirm that the final approved proprietary name will be included in the PMR study to differentiate treatment arms with Fiasp from NovoLog arm since both are insulin aspart formulations? Thanks.

Let me know if you have any questions.

Have a great weekend!

Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Tuesday, August 01, 2017 9:57 AM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 IR

Hi Helen,

Please see the attached PMR list for NDA 208751. We ask that you return the document with your changes marked via tracked changes within 1 week.

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Monday, July 31, 2017 11:52 AM
To: CappelLynch, Callie
Subject: RE: NDA 208751 IR

Dear Callie,

Hope you had a nice weekend!

Just a quick follow-up to see if the Agency has reviewed the responses we submitted and whether there is any additional questions we need to address.

Please let me know. Thanks a lot.

KR,
Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Friday, July 21, 2017 10:45 AM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 IR

Hi Helen,

Confirming receipt of the responses. I'll let you know as soon as possible if we need further clarification.

At this time, I'm not aware of any upcoming information requests.

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Friday, July 21, 2017 10:40 AM
To: CappelLynch, Callie
Subject: RE: NDA 208751 IR

Hi Callie,

We submitted the data file response yesterday and the bioanalytical response today. Hope you have received both of them.

As stated in today's submission cover letter, if the Agency needs further clarification on the responses to the validation and bioanalytical questions, we can have our internal experts available to speak with the FDA reviewers. Please let me know as soon as possible if these responses are acceptable by the reviewers.

By the way, do you expect more questions from the reviewers for the resubmission after the mid-cycle meeting? It will be nice to know so we are prepared internally. I appreciate it very much for all your help and timely communications.

Have a great weekend! Stay cool!.

BR
Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Wednesday, July 19, 2017 12:39 PM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 IR

Hi Helen,

That sounds great thanks for the update.

Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Wednesday, July 19, 2017 11:12 AM
To: CappelLynch, Callie
Subject: RE: NDA 208751 IR

Hi Callie,

Just to give you an update on the response to the IR from last Friday. We plan to submit the regenerated PK and PD data files and the related response tomorrow. In this submission, in addition to ".xpt" files, ".csv" files will also be included for the Agency's reference. Since ".csv" file format could result in submission validation error, we 'd like to submit tomorrow just in case we have to re-send the submission without the .csv files later.

The response to the ELISA assay validation and bioanalytical reports will be submitted on Friday.

Let me know if you have any questions.

BR
Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Friday, July 14, 2017 3:08 PM
To: MTHL (Marty Himmel)
Cc: HCHN (Helen Guo Chen)
Subject: NDA 208751 IR

Hi Marty,

Please see the information request below for NDA 208751.

Data files

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For the dilution integrity assessment reported in the validation and bioanalytical reports specify what matrix was used to dilute the quality control (QC) samples back into the calibration curve range. Clarify whether clinical samples that were above the calibration curve range were processed in a similar manner to the dilution QC samples.

In Table 19 of the validation study number AA81208 you report the following "QC samples were stored at -80°C on 16-Dec-2009". We note that the QC samples were prepared on 01-Dec-2009. Since this assessment is for long term stability at -80°C, specify at what storage conditions the QC samples were maintained from 01-Dec-2009 until 16-Dec-2009. If QC samples were not maintained at -80°C provide an explanation as to why it wasn't.

In validation report number VCA20958 specify whether long-term, freeze/thaw, short-term stability QC samples were compared against freshly prepared calibration standards. If not, provide an explanation as to why freshly prepared calibration standards were not used in this stability assessment.

We request that you respond by COB next Friday July 21st.

Thanks,
Callie

-----Original Message-----
From: MTHL (Marty Himmel) [mailto:mthl@novonordisk.com]
Sent: Thursday, July 06, 2017 9:06 AM
To: CappelLynch, Callie
Subject: RE: NDA 208751 and IND 106878

Thank you. Appreciate the follow up. I'll look for your email.

-----Original Message-----
From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Thursday, July 06, 2017 9:03 AM
To: MTHL (Marty Himmel)
Subject: RE: NDA 208751 and IND 106878

Hi Marty,

We did have the meeting last week. We may be sending some minor information requests. I'll get those to you as quickly as possible.

Thanks,
Callie

-----Original Message-----
From: MTHL (Marty Himmel) [mailto:mthl@novonordisk.com]
Sent: Wednesday, July 05, 2017 8:12 AM
To: CappelLynch, Callie
Cc: HCHN (Helen Guo Chen)
Subject: Re: NDA 208751 and IND 106878

Good morning Callie,

Hope you had a nice July 4rth! Helen had indicated to me that the FDA team was meeting last week for the mid-cycle review meeting for NDA 208751. Would you be able to provide me with any further information regarding that meeting? Specifically had the meeting taken place and are there any information requests or comments that you can share coming out of the meeting?

Marty

On Jun 27, 2017, at 9:34 AM, CappelLynch, Callie <Callie.CappelLynch@fda.hhs.gov<mailto:Callie.CappelLynch@fda.hhs.gov>> wrote:

Hi Helen,

Thank you for providing this information. Enjoy your time off!

Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Tuesday, June 27, 2017 9:22 AM
To: CappelLynch, Callie
Cc: MTHL (Marty Himmel)
Subject: NDA 208751 and IND 106878
Importance: High

Dear Callie,

Hope you had a nice vacation!

As communicated before, I will be on vacation starting tomorrow (June 28) till July 13. During this period, my manager Marty Himmel will be covering for NDA 208751 and IND 106878. Please contact Marty for any IRs or questions regarding these two applications. Please find below Marty's contact information:

609-786-4748 (office)
(b) (6) (mobile)
mthl@novonordisk.com<mailto:mthl@novonordisk.com>

If there is any questions coming in today, you can still send to me. I will be back in the office on July 14 and we can resume our usual contact.

Thanks in advance.

KR

Helen

Helen Chen
MSc, RAC, Senior Manager Regulatory Affairs Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
USA
+1 609-987-5800 (phone)

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

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/s/

CALLIE C CAPPEL-LYNCH
08/25/2017

From: CappelLynch, Callie
To: HCHN (Helen Guo Chen) (hchn@novonordisk.com)
Subject: NDA 208751 Carton and Container Comments
Date: Tuesday, August 08, 2017 9:12:00 AM

Hi Helen,

Please see the labeling comments below for the carton and container labels for NDA 208751. Please send in revised labels within 2 weeks.

Carton Labeling and Container Labels:
Include the approved routes of administration to the vial carton and container labeling principal display panel per 21 CFR 201.100(b)(3).

Carton Labeling and Container Label for Professional Samples:
Increase the size and prominence of the "Sample. Not for Resale" statement on the drug sample's label and the "Sample" statement on the drug sample container's labeling so that it is clear that these are drug samples, per 21CFR 203.38(c). Consider using a different font color or a text box for improved differentiation.

Thanks,
Callie

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
08/08/2017

From: CappelLynch, Callie
To: "HCHN (Helen Guo Chen)"
Subject: RE: NDA 208751 IR
Date: Tuesday, August 01, 2017 9:57:00 AM
Attachments: NDA 208751 PMR-PMC list.doc

Hi Helen,

Please see the attached PMR list for NDA 208751. We ask that you return the document with your changes marked via tracked changes within 1 week.

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Monday, July 31, 2017 11:52 AM
To: CappelLynch, Callie
Subject: RE: NDA 208751 IR

Dear Callie,

Hope you had a nice weekend!

Just a quick follow-up to see if the Agency has reviewed the responses we submitted and whether there is any additional questions we need to address.

Please let me know. Thanks a lot.

KR,
Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Friday, July 21, 2017 10:45 AM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 IR

Hi Helen,

Confirming receipt of the responses. I'll let you know as soon as possible if we need further clarification.

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Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Friday, July 21, 2017 10:40 AM
To: CappelLynch, Callie

Subject: RE: NDA 208751 IR

Hi Callie,

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By the way, do you expect more questions from the reviewers for the resubmission after the mid-cycle meeting? It will be nice to know so we are prepared internally. I appreciate it very much for all your help and timely communications.

Have a great weekend! Stay cool!.

BR
Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Wednesday, July 19, 2017 12:39 PM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 IR

Hi Helen,

That sounds great thanks for the update.

Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Wednesday, July 19, 2017 11:12 AM
To: CappelLynch, Callie
Subject: RE: NDA 208751 IR

Hi Callie,

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Let me know if you have any questions.

BR
Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Friday, July 14, 2017 3:08 PM
To: MTHL (Marty Himmel)
Cc: HCHN (Helen Guo Chen)
Subject: NDA 208751 IR

Hi Marty,

Please see the information request below for NDA 208751.

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In validation report number VCA20958 specify whether long-term, freeze/thaw, short-term stability QC samples were compared against freshly prepared calibration standards. If not, provide an explanation as to why freshly prepared calibration standards were not used in this stability assessment.

We request that you respond by COB next Friday July 21st.

Thanks,
Callie

-----Original Message-----
From: MTHL (Marty Himmel) [mailto:mthl@novonordisk.com]
Sent: Thursday, July 06, 2017 9:06 AM
To: CappelLynch, Callie

Subject: RE: NDA 208751 and IND 106878

Thank you. Appreciate the follow up. I'll look for your email.

-----Original Message-----
From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Thursday, July 06, 2017 9:03 AM
To: MTHL (Marty Himmel)
Subject: RE: NDA 208751 and IND 106878

Hi Marty,

We did have the meeting last week. We may be sending some minor information requests. I'll get those to you as quickly as possible.

Thanks,
Callie

-----Original Message-----
From: MTHL (Marty Himmel) [mailto:mthl@novonordisk.com]
Sent: Wednesday, July 05, 2017 8:12 AM
To: CappelLynch, Callie
Cc: HCHN (Helen Guo Chen)
Subject: Re: NDA 208751 and IND 106878

Good morning Callie,

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Marty

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Hi Helen,

Thank you for providing this information. Enjoy your time off!

Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
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To: CappelLynch, Callie
Cc: MTHL (Marty Himmel)
Subject: NDA 208751 and IND 106878
Importance: High

Dear Callie,

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609-786-4748 (office)
(b) (6) (mobile)
mthl@novonordisk.com<mailto:mthl@novonordisk.com>

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Thanks in advance.

KR

Helen

Helen Chen
MSc, RAC, Senior Manager Regulatory Affairs Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
USA
+1 609-987-5800 (phone)

PMR list for NDA 208751
insulin aspart injection

While review of your application continues, we are sending you a draft list of PMRs based on the data and internal analyses available to date. These brief study/trial summaries are intended to describe the main objective and study/trial characteristics of interest.

Please submit by email a copy of the PMR studies/trials to us with milestone dates, which include **Draft Protocol Submission**,**Final Protocol Submission**, **Study Completion,** and **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA; you should plan on submitting your initial draft protocol at least 6 months prior to this date.

Postmarketing Requirements

1) Conduct a 26-week, randomized, controlled efficacy and safety study comparing insulin aspart administered at mealtime and insulin aspart administered postmeal to NovoLog administered at mealtime, in combination with insulin degludec, in pediatric patients with type 1 diabetes ages 1 to 17 years (inclusive).

   Draft Protocol Submission:
   Final Protocol Submission:
   Study Completion:
   Final Report Submission:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
08/01/2017

From:	CappelLynch, Callie
To:	"MTHL (Marty Himmel)"
Cc:	HCHN (Helen Guo Chen) (hchn@novonordisk.com)
Subject:	NDA 208751 IR
Date:	Friday, July 14, 2017 3:08:00 PM

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Subject: RE: NDA 208751 and IND 106878

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From: MTHL (Marty Himmel) [mailto:mthl@novonordisk.com]

Sent: Wednesday, July 05, 2017 8:12 AM

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Cc: HCHN (Helen Guo Chen)

Subject: Re: NDA 208751 and IND 106878

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Subject: NDA 208751 and IND 106878

Importance: High

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(b) (6) (mobile)

mthl@novonordisk.com<mailto:mthl@novonordisk.com>

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Thanks in advance.

KR

Helen

_____

Helen Chen

MSc, RAC, Senior Manager Regulatory Affairs Novo Nordisk Inc.

800 Scudders Mill Road

Plainsboro, NJ 08536

USA

+1 609-987-5800 (phone)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
07/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208751

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

ATTENTION: Robert B. Clark
Vice President, Regulatory Affairs

Dear Mr. Clark:

Please refer to the resubmission of your New Drug Application (NDA) dated and received March 29, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Aspart Injection, 100 units/mL.

We also refer to your correspondence, dated and received March 29, 2017, requesting review of your proposed proprietary names, Fiasp and Fiasp FlexTouch.

We have completed our review of the proposed proprietary names, Fiasp and Fiasp FlexTouch and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Callie CappelLynch, Regulatory Project Manager, in the Office of New Drugs at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
06/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208751

PROPRIETARY NAME ACKNOWLEDGEMENT

Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

ATTENTION: Robert B. Clark
Vice President, Regulatory Affairs

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) dated and received March 29, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Aspart Injection, 100 U/mL.

We acknowledge receipt of your March 29, 2017, correspondence, received March 29, 2017, requesting a review of your proposed proprietary names, Fiasp and Fiasp FlexTouch.

The user fee goal date is June 27, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Callie CappelLynch, Regulatory Project Manager, in the Office of New Drugs at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Terrolyn Thomas, MS, MBA
Senior Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TERROLYN THOMAS
04/26/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208751

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

Novo Nordisk Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
800 Scudders Mill Rd.
Plainsboro, NJ 08536

Dear Mr. Clark:

We acknowledge receipt of your March 29, 2017, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for insulin aspart injection, 100 units/mL.

We consider this a complete, class 2 response to our October 7, 2016, action letter. Therefore, the user fee goal date is September 29, 2017.

If you have any questions, call me at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Callie Cappel-Lynch, Pharm.D., RAC
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CALLIE C CAPPEL-LYNCH
04/10/2017

From: Thomas, Terrolyn
To: "HCHN (Helen Guo Chen)"
Bcc: Rashid, Nichelle E
Subject: RE: NDA 208751: proprietary name issue
Date: Monday, February 06, 2017 11:48:00 AM

Hello:

Due to the lack of response from the other affected application holder, we are unable to share any further information.

Regards,
Terrolyn

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Monday, January 30, 2017 4:35 PM
To: Thomas, Terrolyn
Subject: RE: NDA 208751: proprietary name issue

Dear Terrolyn,

Just want to follow up the email below I sent to you earlier this month regarding the name "(b) (4) Would you let me know whether the other company has submitted the disclosure authorization letter or whether they have withdrawn the similar name?

Thanks in advance for your help.

KR,
Helen

From: HCHN (Helen Guo Chen)
Sent: Thursday, January 12, 2017 4:23 PM
To: 'Thomas, Terrolyn'
Cc: 'CappelLynch, Callie'
Subject: RE: NDA 208751: proprietary name issue

Hi Terrolyn,

Just let you know that we are re-submitting the proprietary name "Fiasp" to the NDA today. We'd like to request "Fiasp" as the primary choice, and keep "(b) (4) as alternative choice.

I'd like to also follow up with you regarding the name "(b) (4) Could you let me know whether the other company who submitted a similar name submitted a disclosure authorization letter to the Agency?

Thanks in advance.

KR,

Helen

From: HCHN (Helen Guo Chen)
Sent: Monday, January 09, 2017 1:52 PM
To: 'Thomas, Terrolyn'
Cc: CappelLynch, Callie
Subject: RE: NDA 208751: proprietary name issue

Dear Terrolyn,

Thanks so much for your response. I will let you know when we plan to resubmit the name.

KR,

Helen

From: Thomas, Terrolyn [mailto:Terrolyn.Thomas@fda.hhs.gov]
Sent: Monday, January 09, 2017 1:47 PM
To: HCHN (Helen Guo Chen)
Cc: CappelLynch, Callie
Subject: RE: NDA 208751: proprietary name issue

Hi Helen:

The Office of Surveillance and Epidemiology does not have any objections with you resubmitting the name FIAsp for the insulin aspart product.

Thanks,
Terrolyn

Terrolyn Thomas, MS, MBA
Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Email: terrolyn.thomas@fda.hhs.gov
Office: 240.402.3981

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Thursday, January 05, 2017 4:17 PM
To: CappelLynch, Callie
Subject: NDA 208751: proprietary name issue

Dear Callie,

Happy New Year! Hope you had a nice holiday season!

I am not sure if you are aware that the conditionally accepted proprietary name "(b) (4) was recently denied by OSE. Please see attached denied letter and disclosure

authorization request letter. This is certainly very unfortunate for us. As you recall, it has been a challenge for us to secure a proprietary name since we submitted December 2015. Both of the 2 submitted alternate names ((b) (4) and (b) (4) were rejected because another company submitted a similar name. Therefore, we'd like to check with DMEP again regarding our originally submitted name "Fiasp". We understand the Division had some concerns before finishing the review of the clinical documents and we had to withdraw the name early last year. Since the name is now approved by EMA, the team really would like to have the same name for US. Would the Division recommend us to re-submit the name "Fiasp" under the NDA?

Thanks in advance.

Helen

From: Thomas, Terrolyn [mailto:Terrolyn.Thomas@fda.hhs.gov]
Sent: Friday, December 23, 2016 11:48 AM
To: HCHN (Helen Guo Chen)
Subject: NDA 208751: proprietary name letter

Hi,

Attached are courtesy copies of the following letters:

denial
disclosure authorization request

Thanks,

Terrolyn Thomas, MS, MBA
Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Email: terrolyn.thomas@fda.hhs.gov
Office: 240.402.3981

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/s/

TERROLYN THOMAS
02/08/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208751

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

ATTENTION: Helen Chen, MSc, RAC
Senior Manager, Regulatory Affairs

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) dated December 8, 2015, received December 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Aspart Injection, 100 U/mL.

We also refer to your June 10, 2016, correspondence, received June 10, 2016, requesting review of your proposed proprietary name, (b) (4)

Your proposed name was found conditionally acceptable on July 28, 2016. Since that time, we have determined that your proposed proprietary name, (b) (4) could result in medication errors due to confusion with another product that is currently under review. Therefore, the ultimate acceptability of your proposed proprietary name, (b) (4) is dependent upon which underlying application is approved first. If another product is approved prior to your product, with a name that would be confused with your proposed name of (b) (4) you will be requested to submit another name.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf)

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Callie CappelLynch, Regulatory Project Manager in the Office of New Drugs, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
12/21/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208751

PROPRIETARY NAME
DISCLOSURE AUTHORIZATION REQUEST

Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

ATTENTION: Helen Chen, MSc, RAC
Senior Manager, Regulatory Affairs

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) dated December 8, 2015, received December 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Aspart Injection, 100 U/mL.

We also refer to:

- Your correspondence, dated and received June 10, 2016, requesting review of your proposed proprietary name, (b) (4)
- Our December 21, 2016, correspondence informing you that your proposed proprietary name, (b) (4) is unacceptable.

You were notified in the above referenced unacceptable letter that your proposed proprietary name, (b) (4) could result in medication errors due to confusion with the proposed proprietary name of another product also under review. The ultimate acceptability of your proposed proprietary name is dependent upon which underlying application is approved first. If you would like the contact information of the other affected application holder or authorized representative that has submitted the conflicting name as part of a pending application, please complete and submit contact information (non-public information) within 14 business days from the date of this correspondence. Submit this information on your letterhead to your application as General Correspondence, and provide a courtesy copy via email to Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology (OSE), at Terrolyn.Thomas@fda.hhs.gov.

Attached is a suggested format for your authorization letter permitting FDA to disclose your non-public information to the other affected application holder(s).

If OSE receives written authorization from **all** application holders or authorized representatives, OSE will provide each applicant with the name, title, and contact information of the authorized representatives for the affected application holders for each affected application. OSE will not participate in any discussion between the application holders or authorized representatives. If all affected parties do not consent to disclosure of their contact information, OSE will not provide any further information to you about the product with the conflicting proposed proprietary name.

For more information, we refer you to the Manual of Policies and Procedures:
Procedures for Sharing Non-public Information on Pending Proposed Proprietary Names
http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM521551.pdf

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Callie CappelLynch, Regulatory Project Manager in the Office of New Drugs, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Attachment: Example Disclosure Letter

NDA/BLA/ANDA/IND #
[Insert FDA contact address]

RE: FDA sharing of non-public information concerning **[NDA/BLA/ANDA/IND #]** and regarding proposed proprietary name, **[enter proposed proprietary name]**

Dear [**FDA contact name (OSE SRPM)**]:

On behalf of **[NDA/BLA/ANDA/IND # application holder or authorized representative]**, I authorize the United States Food and Drug Administration (FDA) and its staff to disclose the information described below to the holder (or its authorized representative) of the pending application that contains a proposed proprietary name that CDER believes is in conflict with the proprietary name contained in a pending application **[NDA/BLA/ANDA/IND #]** submitted by **[NDA/BLA/ANDA/IND application holder]**. The information will be shared for the purpose of facilitating discussions between **[NDA/BLA/ANDA/IND application holder]** and the other affected application holder about the conflicting proposed proprietary names.

I understand that this information may constitute confidential commercial information that would ordinarily be protected from disclosure under FDA's regulations and relevant law. (This includes, without limitation, 21 C.F.R. §§ 20.61, 312.130, 314.430, 601.50, and 601.51; 18 U.S.C. § 1905 (the "Trade Secrets Act," and 5 U.S.C. § 552(b)(4) (the "FOIA."). I agree to hold FDA harmless for any injury caused by FDA disclosing the information to be shared.

To this end, I hereby authorize FDA to disclose the following information, understanding that doing so will also disclose the fact that **[NDA/BLA/ANDA/IND application holder]** has submitted as part of a pending application a proposed proprietary name that CDER believes is unacceptable due to potential confusion with a proprietary name proposed as part of one or more other pending applications: **Name, title, and contact information (address, telephone number, and email address) of authorized representative for NDA/BLA/ANDA/IND application holder**.

As indicated by my signature, I am authorized to provide this consent on behalf of **[NDA/BLA/ANDA/IND application holder]**, and my full name, title, address, telephone number, and email address are set out below.

Sincerely,
(Signature)
(Printed name)
(Title)
(Address, telephone number & email address)

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/s/

TODD D BRIDGES
12/21/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208751

MEETING MINUTES

Novo Nordisk Inc.
Attention: Helen Chen
Senior Manager, Regulatory Affairs
800 Scudders Mill Rd.
Plainsboro, NJ 08536

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for insulin aspart injection, 100 units/mL.

We also refer to the meeting between representatives of your firm and the FDA on December 15, 2016. The purpose of the meeting was to discuss the October 7, 2016, Complete Response letter for NDA 208751 and discuss a path forward.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type A
Meeting Category:	End of Review
Meeting Date and Time:	December 15, 2016, 2:00pm-3:00pm
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	NDA 208751
Product Name:	insulin aspart injection
Indication:	diabetes mellitus
Sponsor/Applicant Name:	Novo Nordisk Inc.
Meeting Chair:	Jean-Marc Guettier
Meeting Recorder:	Callie Cappel-Lynch

FDA ATTENDEES

Jean-Marc Guettier, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Lisa Yanoff, M.D.	Clinical Team Leader, DMEP
Hyon Kwon, Pharm.D.	Clinical Reviewer, DMEP
Julie Van der Waag, M.P.H.	Chief, Project Management Staff, DMEP
Callie Cappel-Lynch, Pharm.D.	Regulatory Project Manager, DMEP
Manoj Khurana Ph.D.	Team Leader, Office of Clinical Pharmacology (OCP)
Shalini Wickramaratne Senarath Yapa, Ph.D.	Reviewer, OCP
Steven Bowen	Microbiology Reviewer
Patricia Love, M.D.	Deputy Director, Office of Combination Products (OCP)

CDRH Participants:

Carolyn Cochenour	Reviewer, General Hospital Devices Branch (GHDB)
Patricia Beaston, M.D., Ph.D.	Medical Reviewer, GHDB

SPONSOR ATTENDEES

Alan Moses	Senior Vice President, Global Chief Medical Officer
Robin Evers	Senior Vice President, Medical Affairs, Regulatory and Safety
Finn Møllgaard	Corporate Vice President, Regulatory Affairs
Liselotte Hyveled	Project Vice President
Bob Clark	Vice President, Regulatory Affairs US
Marek Demissie	International Medical Director
Hanne Haahr	Senior Clinical Pharmacology Advisor
Julie Mangor Lovmand	Manager, Development Bioanalysis
Helene Solberg	Manager, Immunogenicity Assessment
Lars Erichsen	Principle Statistician
Magdalena Niepsuj Jayatissa	Director, Regulatory Affairs
Shawn Hoskin	Senior Director, Regulatory Affairs US
Helen Chen	Senior Manager, Regulatory Affairs US
Rachel Turow	US Regulatory Affairs

1.0 BACKGROUND

NDA 208751 for insulin aspart injection was submitted by Novo Nordisk on December 8, 2015. The Agency issued a Complete Response (CR) letter on October 7, 2016. On November 16, 2016, Novo Nordisk submitted a meeting request for an End-of-Review meeting. The meeting was scheduled for December 15, 2016.

For convenience, the proposed proprietary name, (b) (4) is used throughout this document. This proposed proprietary name had been found to be conditionally acceptable. However, as communicated in a letter dated December 21, 2016, it has since been determined that this proposed proprietary name, could result in medication errors due to confusion with another product that is currently under review.

FDA sent Preliminary Comments to Novo Nordisk on December 13, 2016.

2. DISCUSSION

2.1. Clinical Pharmacology

Question 1: Does the Agency agree to use the total insulin aspart ELISA assay for characterizing the PK properties for (b) (4) to support the NDA resubmission?

FDA Response to Question 1: Yes, we agree that your proposal to use the total insulin aspart ELISA assay to characterize the pharmacokinetics (PK) of (b) (4) for the planned NDA resubmission is reasonable. However, the acceptability of the data and the robustness of the bioanalytical method to quantify total insulin aspart concentrations as the primary PK assessment will be a review issue.

Meeting Discussion Question 1: Novo Nordisk confirmed that they will use the total insulin aspart assay for the NDA resubmission. Novo Nordisk stated that the total insulin aspart assay was used in the original NDA and was used to support other applications. Novo Nordisk requested feedback on whether FDA had specific concerns about the total insulin aspart assay which was submitted in the first cycle. FDA stated that it had no specific concerns at this time. However, during original NDA review, the main focus was on reviewing (b) (4) *, which was used to characterize the primary PK endpoints. FDA stated that the total insulin aspart assay will need to be re-reviewed (e.g. for accuracy, precision, reproducibility) when the NDA is resubmitted.*

Question 2: Does the Agency agree with Novo Nordisk's proposal for using the total insulin aspart measurements from trials 3978, 3891 and 3852 as a part of the clinical pharmacology package for the resubmission (CRL 9a)?

FDA Response to Question 2: Yes, overall, we agree that using total insulin aspart measurements from trials 3978, 3891, and 3852, as part of the clinical pharmacology package for resubmission, is reasonable. However, the adequacy of these data to characterize the PK of (b) (4) **and whether the proposed labeling claims are supported will be a review issue.**

Meeting Discussion Question 2: No discussion occurred.

Question 3: Does the Agency agree that the proposed ongoing trial 3922 is sufficient to provide the required PK information regarding mealtime dosing for (b) (4) for the resubmission?

FDA Response to Question 3: Overall, we agree that the proposed ongoing trial 3922 is sufficient to provide the required PK information regarding mealtime dosing for (b) (4) **for the resubmission. However, we have following comments:**

- **In addition to the PK endpoints specified in Section 17.4.1.2 of the study protocol (trial ID: NN1218-3922) we recommend that you report the total exposure, onset of appearance, and duration of exposure of** (b) (4) **and NovoRapid.**

- **In Section 8.4 of the study protocol (trial ID: NN1218-3922) you report that** (b) (4) **. Clarify if you plan to add the proposed assessment of total insulin aspart as an additional component to this protocol.**

- **We recommend that you conduct PK/pharmacodynamic (PD) modeling as proposed in Section 17.5 of the study protocol (trial ID: NN1218-3922) and use the PK/PD modeling and simulations to predict the PD response following postmeal dosing (also refer to Agency response for Question 6). This may help in bridging the information gap due to the missing PK data.**

Meeting Discussion Question 3: Novo Nordisk agreed with the first 2 bullets listed above and stated that they will follow-up accordingly. Novo Nordisk stated that they will not be able to utilize PK/PD modeling and simulation to predict PD response following postmeal dosing since there are many confounding factors in a post-meal setting that limit the establishment a PK/PD relationship. FDA clarified that the availability of the quantitative PK/PD relationship data would help in leveraging the comparative PD data from studies where PK data is unavailable (e.g. dose-response study) for a comprehensive review of the clinical pharmacology data. Novo Nordisk proposed to conduct PK/PD modeling utilizing data from the previously conducted euglycemic clamp study. FDA agrees with this alternative approach for the future resubmission.

Question 4: Does the Agency agree that the proposed ongoing trial 3922 is sufficient to provide the required PK information regarding dose-concentration relationship of faster aspart for the resubmission?

FDA Response to Question 4: Overall, we agree that the proposed ongoing trial 3922 is sufficient to provide the required PK information regarding dose-concentration relationship for (b) (4) for the NDA resubmission. However, we recommend that a comprehensive compartmental population PK modeling be conducted using combined data from the Phase 1 studies to support the dose-concentration relationship. Ensure that the dose-concentration relationship for NovoRapid will also be reported in the NDA resubmission. We recommend that statistical analysis of dose proportionality for the PK endpoints be assessed and included in the NDA resubmission.

Meeting Discussion Question 4: No discussion occurred.

Question 5: Does the Agency agree that the dose-response data in trial 3887 submitted in the original NDA is adequate to support dose response information in the PI?

FDA Response to Question 5: We agree that the dose-response data in trial 3887 submitted in the original NDA is adequate to support the dose-response relationship in the PI for total glucose lowering effect per unit dose of insulin. We recommend that statistical analysis of dose proportionality for the pharmacodynamic endpoints be assessed and included in the NDA resubmission.

Meeting Discussion Question 5: No discussion occurred.

Question 6: Does the Agency agree that a PK postmeal study is not necessary for the resubmission?

FDA Response to Question 6: Yes, we agree that a new PK postmeal study is not necessary for the NDA resubmission. However, see response to Question 3 (item 3 in additional responses regarding 3922 study protocol) with regards to the utility of the PK/PD modeling proposed under trial 3922 to fill the information gap created by missing PK data.

Meeting Discussion Question 6: See meeting discussion for Question 3.

Question 7: Does the Agency agree that the results from the reanalyzed samples from trial 3949 can be used to support the relevant PI sections for injection site regions?

FDA Response to Question 7: Yes, we agree that the results from the reanalyzed samples from trial 3949 can be used to support the relevant PI sections for injection site regions. We recommend that you submit the relevant long-term stability data to demonstrate that the quantified total insulin aspart concentrations in the reanalyzed samples are reliable.

Meeting Discussion Question 7: No discussion occurred.

Question 8: Does the Agency agree that the (b) (4) ?

FDA Response to Question 8: Yes, we agree that the (b) (4)

Meeting Discussion Question 8: No discussion occurred.

Question 9: Does the Agency agree that the proposed clinical pharmacology data package is sufficient for the Agency's comprehensive assessment of (b) (4) and provides adequate information for Section 12.3 Pharmacokinetics in the PI?

FDA Response to Question 9: Overall, we agree that the proposed clinical pharmacology data package for NDA resubmission is sufficient for a comprehensive assessment of (b) (4) and to provide adequate information for Section 12.3 of the PI. Also see responses for questions 1, 2, 3, 4, 5, 6, 7, 8, 14, and 16.

Meeting Discussion Question 9: No discussion occurred.

2.2. Immunogenicity

Question 10: Does the Agency agree that the proposed justifications and data to be submitted in the resubmission are sufficient to address the Agency's concerns in the CRL issues 10-13, 16 to 19 for the NDA resubmission?

FDA Response to Question 10: The adequacy of the supporting data to address the concerns expressed in the CR letter will be a review issue. However, based on the information provided in the Briefing Package we have the following concerns with your proposal:

1. **You indicate that patient serum samples are not diluted prior to testing. However, an assessment of matrix effects on assay performance was not provided. Provide in your NDA resubmission an assessment of matrix effects on the selectivity of the assay as described in section IV. D. of the draft Guidance for Industry: Assay**

Development and Validation for Immunogenicity Testing of Therapeutic Protein Products, found at http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm192750.pdf.

2. **You propose that the assay precision for the D-F and F-E series was demonstrated by the performance of the positive suitability controls during the testing of clinical samples from trial 3852. However, the concentration of the positive suitability controls that were used for routine sample testing was close to the upper quantitative range of the assay, and therefore may not accurately represent the variability in the in the lower range of the assay. Assay precision should be evaluated using positive control concentrations that will capture assay variability at multiple points of the dose response curve.**

3. **Regarding CR letter comment 16, it should be noted that various assay parameters including, but not limited to assay precision, robustness, and on-board drug tolerance should be validated using the all three of your proposed ADA measurements (D-E, D-F, and F-E). This validation information should be provided with the NDA resubmission.**

Meeting Discussion Question 10: No discussion occurred.

Question 11: Does the Agency agree that the provided information is adequate to support the use of the %B/T value as a quantitative measure of anti-drug antibodies in the clinically relevant range?

FDA Response to Question 11: We agree that information provided in Figures 2 and 3 of the briefing package suggests linearity of the assays between 0%-30% B/T for the X14-6 F34 antibody and 0%-50% B/T for the GP□-insulin antibody. These ranges appear to be appropriate to quantitatively capture the levels of ADA observed in the clinical samples. However, the dose-response data for X14-6 F34 provided in Figure 2 of the Briefing Package appear to be inconsistent with the dose-response data provided in Table 9, Appendix B of Validation Report 215373. In your NDA resubmission provide an explanation for this discrepancy.

Meeting Discussion Question 11: No discussion occurred.

Question 12: Does the Agency agree that the information provided substantiates that the assay adequately detects low levels of ADA in accordance with the current FDA guidelines?

FDA Response to Question 12: Yes, we agree. It should be noted for future immunogenicity analysis that all routine testing of clinical samples should include a low positive control at a concentration close to the assay sensitivity that is predicted to fail the assay (i.e. test below the assay cutpoint) 1% of the time.

Meeting Discussion Question 12: No discussion occurred.

Question 13: Novo Nordisk proposes to submit the responses to the questions posed in the CRL relevant to immunogenicity under IND 106878 when available. Novo Nordisk would like to request the Agency to provide the feedback on these documentations within a 90-day review timeline. Does the Agency Agree?

FDA Response to Question 13: No, we do not agree. Re-validation data will be reviewed as part of the NDA resubmission. However, if you determine during re-validation that the assay used to test clinical samples was invalid, you may submit re-validation data to IND 106878 for review prior to the re-testing of clinical samples. We will provide feedback in as timely a manner as possible but cannot currently commit to a 90-day review timeline.

Meeting Discussion Question 13: No discussion occurred.

2.3. IV Route of Administration

Question 14: Does the Agency agree that the outlined data and considerations provide sufficient evidence to support the systemic and local safety of longer-term I.V. infusion of (b) (4)

FDA Response to Question 14: We agree that the outlined data and considerations provide sufficient information to support review of the safety of longer term I.V. infusion of (b) (4) such that no additional data are needed for the NDA resubmission. Adequacy of the data will be a review issue.

Meeting Discussion Question 14: No discussion occurred.

(b) (4)

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2.5. Planned Resubmission Documentation

Question 18: Does the Agency agree with the proposed plan for the documentation to be included in the NDA resubmission?

FDA Response to Question 18: Yes, we agree.

Meeting Discussion Question 18: No discussion occurred.

Question 19: Novo Nordisk proposes using the same structure and overall content as for the 120-Day Safety Update submitted under the NDA (located in Module 5.3.5.3). The resubmission Safety Update provides an overview of the (b) (4) safety profile based on all trials from the NDA as well as all ongoing and completed trials before the resubmission. Does the Agency agree with the proposal for resubmission Safety Update?

FDA Response to Question 19: Yes, we agree.

Meeting Discussion Question 19: No discussion occurred.

2.6. Data Format

Question 20: Does the Agency agree to the proposal of submitting the new PK dataset for trial 3949 and the datasets for trial 3922 in legacy format for the resubmission?

FDA Response to Question 20: Yes, we agree that the new PK dataset for trial 3949 and 3922 can be submitted in the legacy format during the NDA resubmission.

Meeting Discussion Question 20: No discussion occurred.

2.7. Timing of Resubmission

Question 21: Does the Agency agree with the proposal to resubmit as a Class II resubmission within the first half of 2018?

FDA Response to Question 21: **Your proposal is acceptable.**

Meeting Discussion Question 21: Novo Nordisk proposed to resubmit the NDA in March or April of 2017 (b) (4). *They will then* (b) (4) *FDA agreed to this proposal.*

4.0 ISSUES REQUIRING FURTHER DISCUSSION

FDA will continue to develop an approach for (b) (4). Novo Nordisk will also submit an additional meeting request to discuss this topic with FDA.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
(b) (4)		

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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/s/

JEAN-MARC P GUETTIER
01/12/2017

From: CappelLynch, Callie
To: "HCHN (Helen Guo Chen)"
Subject: RE: NDA 208751: Novo Nordisk alternative approach proposal for PK analysis data
Date: Wednesday, September 21, 2016 2:48:00 PM

Hi Helen,

We have reviewed your proposal and we do not find it acceptable. Additional information will be forthcoming.

Thanks,
Callie

-----Original Message-----
From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Wednesday, September 21, 2016 7:25 AM
To: CappelLynch, Callie
Subject: Re: NDA 208751: Novo Nordisk alternative approach proposal for PK analysis data

Thanks a lot, Callie.

Have a great day!

Helen

Sent from my iPhone

> On Sep 21, 2016, at 6:36 AM, CappelLynch, Callie <Callie.CappelLynch@fda.hhs.gov> wrote:
>
> Hi Helen,
>
> I'm hoping to get back to you by tomorrow. If anything changes, I'll update you.
>
> Thanks,
> Callie
>
> -----Original Message-----
> From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
> Sent: Tuesday, September 20, 2016 3:55 PM
> To: CappelLynch, Callie
> Subject: RE: NDA 208751: Novo Nordisk alternative approach proposal for PK analysis data
>
> Dear Callie,
>
> Sorry to disturb you again. I know you are very busy. I am just wondering whether there is any update from you regarding our proposal. You know we are planning to submit the proposed major amendment as soon as the Agency agrees. We have originally planned to submit by this Friday or latest next Monday. It would be very nice if you can inform me when the Agency plans to respond and whether our proposal for the amendment is adequate.
>
> Thanks so much for everything. Feel free to call me.
>
> KR,
> Helen
>
>
>
> -----Original Message-----

> From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
> Sent: Thursday, September 15, 2016 8:19 AM
> To: HCHN (Helen Guo Chen)
> Subject: RE: NDA 208751: Novo Nordisk alternative approach proposal for PK analysis data
>
> Hi Helen,
>
> I'll follow up with the team again.
>
> Thanks,
> Callie
>
> -----Original Message-----
> From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
> Sent: Thursday, September 15, 2016 7:27 AM
> To: CappelLynch, Callie
> Subject: Re: NDA 208751: Novo Nordisk alternative approach proposal for PK analysis data
>
> Good morning, Callie!
>
> Just a quick follow-up to see if you have any update regarding our request for T-con to discuss the alternative approach I sent on Monday. If you can provide a timeframe on getting back to us, it will be also very helpful.
>
> Have a great day!
> Helen
>
> Sent from my iPhone
>
> On Sep 12, 2016, at 1:45 PM, CappelLynch, Callie <Callie.CappelLynch@fda.hhs.gov<mailto:Callie.CappelLynch@fda.hhs.gov>> wrote:
>
> Hi Helen,
>
> Confirming receipt of your response. I'll let you know something as soon as possible.
>
> Thanks,
> Callie
>
> From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
> Sent: Monday, September 12, 2016 12:59 PM
> To: CappelLynch, Callie
> Subject: NDA 208751: Novo Nordisk alternative approach proposal for PK analysis data
> Importance: High
>
> Dear Callie,
>
> Hope you had a nice weekend!
>
> Thanks again for arranging the teleconference last Thursday and sending the IR afterwards.
>
> After evaluation of the Agencies concerns relayed to us, we believe we have a viable proposal of an alternative approach to move the NDA review forward within the current review cycle. Please find attached a brief document that summarizes the overall approach and the regulatory pathway. We'd like to request a short teleconference with the Agency (including you, Dr. Guettier, Dr. Yannof, and the clinical pharmacology reviewer as deemed relevant) as soon as possible to discuss the adequacy of our proposal.
>
> We highly appreciate all your help in this matter.
>

> Feel free to contact me anytime at (b) (6) (text or call).
>
> Kind regards,
>
> Helen
>
>
>
>
> _____
>
> Helen Chen
> MSc, RAC, Senior Manager Regulatory Affairs Novo Nordisk Inc.
> 800 Scudders Mill Road
> Plainsboro, NJ 08536
> USA
> +1 609-987-5800 (phone)
>

>
>

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/s/

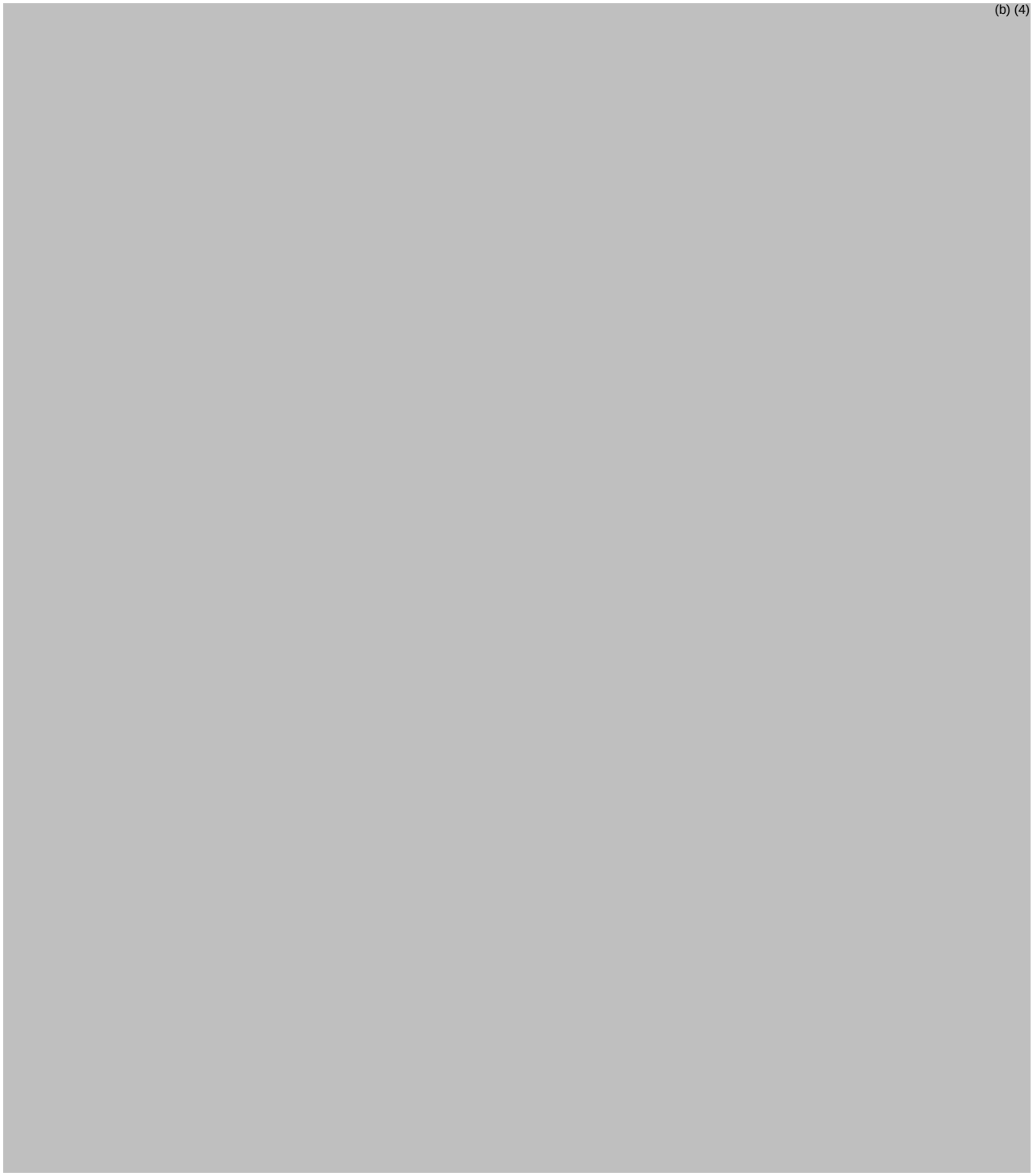
CALLIE C CAPPEL-LYNCH
10/06/2016

From: CappelLynch, Callie
To: "HCHN (Helen Guo Chen)"
Subject: RE: NDA 208751 IR Response
Date: Thursday, September 08, 2016 1:19:00 PM

Hi Helen,

We have reviewed your response and have the following concerns with regard to your bioanalytic method:

(b) (4)



(b) (4)

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Friday, August 12, 2016 3:39 PM
To: CappelLynch, Callie
Subject: RE: NDA 208751 IR

Hi Callie,

Please find attached a copy of the response. This is also submitted to the NDA today.

Let me know if any questions.

Have a nice weekend!

Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Thursday, August 11, 2016 8:39 AM
To: HCHN (Helen Guo Chen)
Subject: NDA 208751 IR
Importance: High

Hi Helen,

Please see the information request below for NDA 208751.

(b) (4)

We are requesting response by COB tomorrow.

If you have any questions, please let me know.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
09/08/2016

From: CappelLynch, Callie
To: "HCHN (Helen Guo Chen)"
Subject: RE: NDA 208751 information request
Date: Wednesday, September 07, 2016 8:25:00 PM

Hi Helen,

Please refer to your New Drug Application (NDA) dated and received December 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for insulin aspart injection, 100 units/mL.

We also refer to our February 16, 2016, letter in which we notified you of our target date of September 9, 2016, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2013 Through 2017."

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

Please contact me if you have questions.

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Friday, September 02, 2016 11:59 AM
To: CappelLynch, Callie
Subject: RE: NDA 208751 information request

Hi Callie,

Just let you know that we will submit the response to this IR by Tuesday September 13th.

In addition, can you confirm we are still on track to receive the Agency's labeling comments for the PI next Friday, September 9th?

I will be in Denmark next week. Feel free to call my cell at [redacted] (b) (6) if you need me urgently.

Thanks.

Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]

Sent: Thursday, September 01, 2016 9:51 AM
To: HCHN (Helen Guo Chen)
Subject: NDA 208751 information request

Hi Helen,

Please see the information request below for NDA 208751.

(b) (4)

Please respond within 2 weeks.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
09/07/2016

From: CappelLynch, Callie
To: HCHN (Helen Guo Chen) (hchn@novonordisk.com)
Subject: NDA 208751 information request
Date: Thursday, September 01, 2016 9:50:00 AM

Hi Helen,

Please see the information request below for NDA 208751.

(b) (4)

Please respond within 2 weeks.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
09/03/2016

From: CappelLynch, Callie
To: HCHN (Helen Guo Chen) (hchn@novonordisk.com)
Subject: NDA 208751 IR
Date: Thursday, August 11, 2016 8:39:00 AM
Importance: High

Hi Helen,

Please see the information request below for NDA 208751.

The ELISA assay used to [redacted] (b) (4)

Provide clarification as to [redacted] (b) (4)

Please include in your response [redacted] (b) (4)

We are requesting response by COB tomorrow.

If you have any questions, please let me know.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
08/11/2016

From: CappelLynch, Callie
To: "HCHN (Helen Guo Chen)"
Subject: RE: NDA 208751 labeling comments
Date: Wednesday, August 03, 2016 6:45:00 AM

Hi Helen,

Please see additional comments below regarding the carton and container.

(1) Include quality ingredient statement to your carton labels for vial and pen presentations.

(2) Include in-use storage statement after first use for both vial and pen carton labels. "After first use store at 2°-30°C (36°-86°F)".

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Tuesday, August 02, 2016 2:48 PM
To: CappelLynch, Callie
Subject: RE: NDA 208751 labeling comments

Hi Callie,

We will be ready to submit the updated carton and container labels tomorrow with all comments implemented. Can you confirm the reviewers are OK with the vial container and carton labels I sent to you except the quantities of the inactive ingredients?

Thanks.

Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Monday, August 01, 2016 12:12 PM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 labeling comments

Hi Helen,

We are reviewing the labels and have the following comment:

Quantitative inactive ingredient composition is missing on the carton labels.

Please send revised copies by the end of the week.

Thanks,

Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Thursday, July 28, 2016 9:52 AM
To: CappelLynch, Callie
Subject: RE: NDA 208751 labeling comments

Hi Callie,

Good morning!

We just realized there was a mistake in the vial trade container and vial sample container labels sent to you. Please ignore the 2nd page of both labels which were not supposed to be part of the label.

I think I forgot to mention that "Tradename" has replaced the original proposed proprietary name since we have no accepted name yet.

Let me know if any questions.

Have a good day!

Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Wednesday, July 27, 2016 2:31 PM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 labeling comments

Thanks Helen. These have been forwarded to the team. I'll let you know if/when you can formally submit.

Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Tuesday, July 26, 2016 4:46 PM
To: CappelLynch, Callie
Subject: RE: NDA 208751 labeling comments

Hi Callie,

Please find attached labels for vial. Please note, for the vial container labels, in addition to moving the net quantity away from the strength, the storage condition that was part of the label originally is deleted due to space limitation. For all the labels, (b) (4)

The (b) (4) change will also apply to the pen carton labels.

Let me know if these are acceptable.

KR,
Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Tuesday, July 26, 2016 3:28 PM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 labeling comments

Hi Helen,

Yes email copies work.

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Tuesday, July 26, 2016 2:30 PM
To: CappelLynch, Callie
Subject: RE: NDA 208751 labeling comments

Hi Callie,

I have the updated label mock-ups available now. Will it be OK for me to send you the vial carton and container labels via email so the reviewers can take a look see if they are satisfactory before we officially submit? These are the ones that were requested to move the net quantity away from the product strength.

Please advise.

Thanks.

Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Thursday, July 21, 2016 11:04 AM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751 labeling comments

Hi Helen,

Please send back revised copies within 2 weeks.

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Thursday, July 21, 2016 10:52 AM
To: CappelLynch, Callie
Subject: RE: NDA 208751 labeling comments

Thanks, Callie. Do you have a timeline for us to send back the revised label mock-ups?

BR

Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Thursday, July 21, 2016 10:49 AM
To: HCHN (Helen Guo Chen)
Subject: NDA 208751 labeling comments

Hi Helen,

Please see the labeling comments below regarding the carton and container labeling for NDA 208751.

A. Carton and Sample Carton Labeling and Container and Sample Container Label for Pen

1. Ensure container labels and carton labeling includes NDC numbers.

B. Carton and Sample Carton Labeling and Container and Sample Container Label for Vial

1. Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.

2. See A.1.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
08/03/2016

From: CappelLynch, Callie
To: HCHN (Helen Guo Chen) (hchn@novonordisk.com)
Subject: NDA 208751 Information Request
Date: Monday, August 01, 2016 4:40:00 PM

Hi Helen,

Please see the information request below for NDA 208751:

1. The levels of total anti-drug antibodies (ADA), insulin aspart-specific antibodies, and antibodies cross-reactive with human insulin are quantitated using the percentage of total radiolabeled tracer (insulin aspart) that is co-precipitated with Ig (%B/T). However, there is insufficient data in the Validation Reports to demonstrate that the assay is quantitative. One approach to address this deficiency and support the use of the %B/T value as a quantitative measure of antibodies in patient samples would be to demonstrate that there is a linear relationship between the positive control antibody concentration and the %B/T signal. Include a graphical and tabular analysis for each series (D, E, F) and the subtracted (D-E, D-F, F-E) values.

2. Section 2.7.1 Table 1-6 indicates that the two positive suitability controls used for analysis of clinical samples were QC2 (monoclonal anti-insulin aspart, 560 ng/ml) and QC3 (guinea pig polyclonal anti-human insulin antibody, 23-230 ng/ml). The results of the suitability controls during clinical testing were not provided, however during validation the results for QC2 and QC3 were substantially above the levels observed in your clinical samples. This raises concerns that your suitability controls are inadequate to ensure the detection of low levels of ADA. Low positive controls should be set to have a 1% failure rate based on the assay cutpoint. Indicate how the detection of low levels of ADA was demonstrated during clinical testing. For guidance refer to FDA Draft Guidance: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (2016).

3. According to Validation Report 215373, 50 normal human serum samples were used to establish a fixed cutpoint for total ADA (D-E, 1.9% B/T), insulin aspart-specific antibodies (F-E, 1.9% B/T), and antibodies cross-reactive with human insulin (D-F, 0.7% B/T). Fixed cutpoints are appropriate only if the mean values and variances are not statistically different between runs and analysts. Provide a mathematical justification for the use of fixed cutpoints in your analysis. Refer to the FDA Draft Guidance noted in Comment 2.

4. It is unclear how the fixed cutpoints were applied in your analysis of clinical samples from study NN1218-3852. Table 14.3.6.18 in the Clinical Study Report for trial NN1218-3852 indicates the overall mean %B/T values for each group at each time point. However, it is not clear whether the mean %BT value is representative of all of the collected samples, or only of the samples that were positive (i.e. above the cutpoint) for ADA. Indicate how patient serum samples were selected for the calculation of the mean %B/T values shown in Table 14.3.6.18. Indicate for each treatment group the number and percentage of patients that tested positive (above the assay cutpoint) for ADA at each sampling time point.

5. Section 2.7.1 of your application notes that most patients were positive for ADA at baseline and that no cutpoints were established to evaluate treatment-boosted ADA responses. In order to compare the immunogenicity of “faster aspart” and NovoRapid® the frequency of patients with treatment-emergent and treatment-boosted ADA should be determined. Therefore, develop an approach to identify treatment-induced and treatment-boosted patients in your clinical trials. In your response provide a detailed description of how treatment-emergent and treatment-boosted patients are mathematically defined as well as

the frequency of patients in each treatment group with treatment-induced or treatment-boosted ADA. Refer to the FDA Draft Guidance noted in Comment 2.

6. In order to assess the performance of the ADA assay during the testing of clinical material, provide a table (preferably in Excel format) with immunogenicity testing results for each individual patient enrolled in NN1218-3852. The table should contain the following information:
    a. Patient ID
    b. Treatment group
    c. Sampling visit
    d. Run ID
    e. %B/T results for series D
    f. %B/T results for series E
    g. %B/T results for series F
    h. Subtractive results for D-E
    i. ADA status for D-E (positive or negative based on the assay cutpoint)
    j. Subtractive results for D-F
    k. ADA status for D-F (positive or negative based on the assay cutpoint)
    l. Subtractive results for F-E
    m. ADA status for F-E (positive or negative based on the assay cutpoint)

Also provide a table containing the results for all suitability controls throughout the testing of clinical material from NN1218-3852.

Provide a response by August 26, 2016.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
08/01/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208751

PROPRIETARY NAME REQUEST CONDITIONALLY ACCEPTABLE

Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

ATTENTION: Helen Chen, MSc, RAC
Senior Manager, Regulatory Affairs

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) dated December 8, 2015, received December 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Aspart Injection, 100 U/mL.

We also refer to your June 10, 2016, correspondence, received June 10, 2016, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your June 10, 2016 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Callie CappelLynch, Regulatory Project Manager, in the Office of New Drugs at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
07/28/2016

From: CappelLynch, Callie
To: HCHN (Helen Guo Chen) (hchn@novonordisk.com)
Subject: NDA 208751 labeling comments
Date: Thursday, July 21, 2016 10:48:00 AM

Hi Helen,

Please see the labeling comments below regarding the carton and container labeling for NDA 208751.

A. Carton and Sample Carton Labeling and Container and Sample Container Label for Pen

1. Ensure container labels and carton labeling includes NDC numbers.

B. Carton and Sample Carton Labeling and Container and Sample Container Label for Vial

1. Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.

2. See A.1.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
07/21/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208751

PROPRIETARY NAME ACKNOWLEDGEMENT

Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

ATTENTION: Helen Chen, MSc, RAC
Senior Manager, Regulatory Affairs, Novo Nordisk Inc.

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) dated December 8, 2015, received December 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Aspart Injection, 100 U/mL.

We acknowledge receipt of your June 10, 2016, correspondence, received June 10, 2016, requesting a review of your proposed proprietary name, (b) (4)

The user fee goal date will be September 8, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Callie CappelLynch, Regulatory Project Manager, in the Office of New Drugs at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Terrolyn Thomas, MS, MBA
Senior Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TERROLYN THOMAS
07/15/2016

From: CappelLynch, Callie
To: HCHN (Helen Guo Chen) (hchn@novonordisk.com)
Subject: NDA 208751 IR
Date: Thursday, July 14, 2016 7:33:00 AM
Attachments: image001.png
image002.png

Hi Helen,

We are continuing to review NDA 208751 and have the following request for information:

In the validation of device use report for NDA 208751 submitted on December 9, 2015, you report the following failures. The report did not indicate at which step (i.e. step 1 pick the correct pen injector or step 3 verification via label and cartridge holder that it is the correct pen) the failures occurred. Please provide this information by July 20, 2016.

Task failure occurrences

For the trained and untrained participants, 8 participants committed 15 non-serious use errors (S3) which potentially can be associated with a non-serious adverse event and therefore a task failure:

- **Selected Incorrect Pen-injector Carton**
  - 4 untrained, pen-injector experienced participants (A6, A9, E11, E14)
  - 3 untrained, pen-injector naïve participants (A5, E8, E9)
  - 1 trained, pen-injector experienced participant (C10)

- **Selected Incorrect Pen-injector**
  - 4 untrained, pen-injector experienced participants (A6, A9, E11, E14)
  - 2 untrained, pen-injector naïve participants (A5, E8)
  - 1 trained, pen-injector experienced participant (C10)

Notably, each of these participants selected the same pen-injector as the carton they selected during Task 1 (Carton retrieval). For example, a participant who selected the Humalog® Mix 75/25™ KwikPen® carton during Task 1 also selected the Humalog® Mix 75/25™ KwikPen® pen-injector during Task 2. Per the protocol, the participant was not told that s/he selected the incorrect product during Task 1.

Step 1: Pick the correct carton/pen-injector

Step 2: Pen cap removal

Step 3: Verification via label and cartridge holder that it is the correct pen

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
07/14/2016

From: CappelLynch, Callie
To: "HCHN (Helen Guo Chen)"
Subject: RE: NDA 208751 IR
Date: Wednesday, July 06, 2016 7:25:00 PM

Hi Helen,

Please see additional IR below for NDA 208751.

At this time DMEP is considering (b) (4) [redacted]

We have the following additional specific comments:

Please clarify (b) (4) [redacted]

1. (b) (4) [redacted].

2. (b) (4) [redacted].

Please respond to this IR within 1 week. If you have any questions, please contact me.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
07/06/2016

From: CappelLynch, Callie
To: HCHN (Helen Guo Chen) (hchn@novonordisk.com)
Subject: NDA 208751 IR
Date: Thursday, June 30, 2016 3:33:00 PM

Hi Helen,

Please see the IR below for NDA 208751:

We continue to review the ELISA assay used to (b) (4)

We acknowledge that (b) (4) If available, submit any relevant data to support your response to above identified concerns.

Please respond to this information request by COB, July 8, 2016.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
06/30/2016

From: CappelLynch, Callie
To: "HCHN (Helen Guo Chen)"
Subject: RE: NDA 208751: Mid-cycle response to device questions submitted
Date: Friday, June 17, 2016 3:24:00 PM

Hi Helen,

In regard to your response to question 10, can you please clarify:

1. (b) (4)
2.
3.

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Friday, June 17, 2016 2:06 PM
To: CappelLynch, Callie
Subject: NDA 208751: Mid-cycle response to device questions submitted

Hi Callie,

Just let you know that we have submitted the response to the device questions (Q10-12) from the Mid-cycle IR today. A copy of the response is also attached.

Let me know if you have any questions.

Have a nice weekend.

Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Friday, June 10, 2016 9:35 AM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751: proprietary name Fiasp

Hi Helen,

Please see the attached information request for NDA 208751. If you have any questions, please contact me.

Thanks,

Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Thursday, June 09, 2016 3:41 PM
To: CappelLynch, Callie
Subject: RE: NDA 208751: proprietary name Fiasp

Thanks, Callie. Great to know that. Looking forward to the responses.

We are planning to submit the request for alternate proprietary name review tomorrow. Should we wait for your responses before making submission? Since if the Division is OK with Fiasp, we don't have to submit new names for review. We just need to resubmit Fiasp. It saves time for both ends.

Appreciated very much if you can let me know.

Thanks for all your help.

Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Thursday, June 09, 2016 3:16 PM
To: HCHN (Helen Guo Chen)
Subject: RE: NDA 208751: proprietary name Fiasp

Hi Helen,

I hope to have our responses finalized tomorrow.

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Thursday, June 09, 2016 3:02 PM
To: CappelLynch, Callie
Cc: Thomas, Terrolyn
Subject: RE: NDA 208751: proprietary name Fiasp

Dear Callie,

Sorry for pushing you again. Any update on this?

KR
Helen

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Monday, June 06, 2016 9:34 AM
To: HCHN (Helen Guo Chen)
Cc: Thomas, Terrolyn
Subject: RE: NDA 208751: proprietary name Fiasp

Hi Helen,

We have received your email and will respond as soon as possible.

Thanks,
Callie

From: HCHN (Helen Guo Chen) [mailto:hchn@novonordisk.com]
Sent: Thursday, June 02, 2016 3:19 PM
To: CappelLynch, Callie
Cc: Thomas, Terrolyn
Subject: NDA 208751: proprietary name Fiasp
Importance: High

Hi Callie,

Hope everything is going fine for you.

As recommended by the Agency at the February 10, 2016 T-con with FDA on the originally proposed proprietary name “Fiasp”, I am checking in with you to see whether the Agency has completed the evaluation of the submitted clinical data in the NDA and determined whether the faster PK/PD profile of faster-acting insulin aspart translates into a clinical benefit. If so, then the name Fiasp would not be misleading from a promotional perspective. Please let me know if “Fiasp” can be resubmitted under the NDA and can be acceptable as the proprietary name for this product.

As you may know, the alternate name we submitted on February 29 was not accepted by the Agency due to potential concern on medication error. We are currently planning to submit an alternate name for FDA’s review. Since we are approaching end of month 6 of the NDA review, securing a proprietary name for this product is quite urgent from our perspective. Your timely response is highly appreciated.

Thanks in advance for your help. Feel free to contact me if any questions.

KR,

Helen

Helen Chen
MSc, RAC, Senior Manager Regulatory Affairs
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
USA
+1 609-987-5800 (phone)

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/s/

CALLIE C CAPPEL-LYNCH
06/17/2016

From: CappelLynch, Callie
To: HCHN (Helen Guo Chen) (hchn@novonordisk.com)
Subject: NDA 208751 Information Request
Date: Thursday, June 16, 2016 10:07:00 AM

Hi Helen,

We are continuing to review NDA 208751 and have the following request for information:

Please provide clarification on your pattern mixture model algorithm and program code for studies 3852 and 3853. We are not able to discern how withdrawn subjects in the meal time faster-acting insulin aspart group are assumed to be switched to a treatment inferior to NovoRapid. You may want to also separate out the sub-macros.

Also please provide or direct us to the location of the dataset and programs used to estimate the rate ratios for severe or BG confirmed hypoglycemia within 1 hour and within 2 hours of meal for studies 3852 and 3853.

Please submit a response to this information request by COB Friday, June 24, 2016.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
06/16/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208751

INFORMATION REQUEST

Novo Nordisk Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
800 Scudders Mill Rd.
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) dated and received December 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for insulin aspart injection, 100 units/mL.

We also refer to your amendments submitted December 9, 2015, February 11, 19, and 29, March 3, 10, 21, and 24, and April 4, 2016.

We are providing these comments and requests for information to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. If you respond to these issues during this review cycle, depending on the timing of your response, we may or may not be able to consider your response before we take an action on your application during this review cycle.

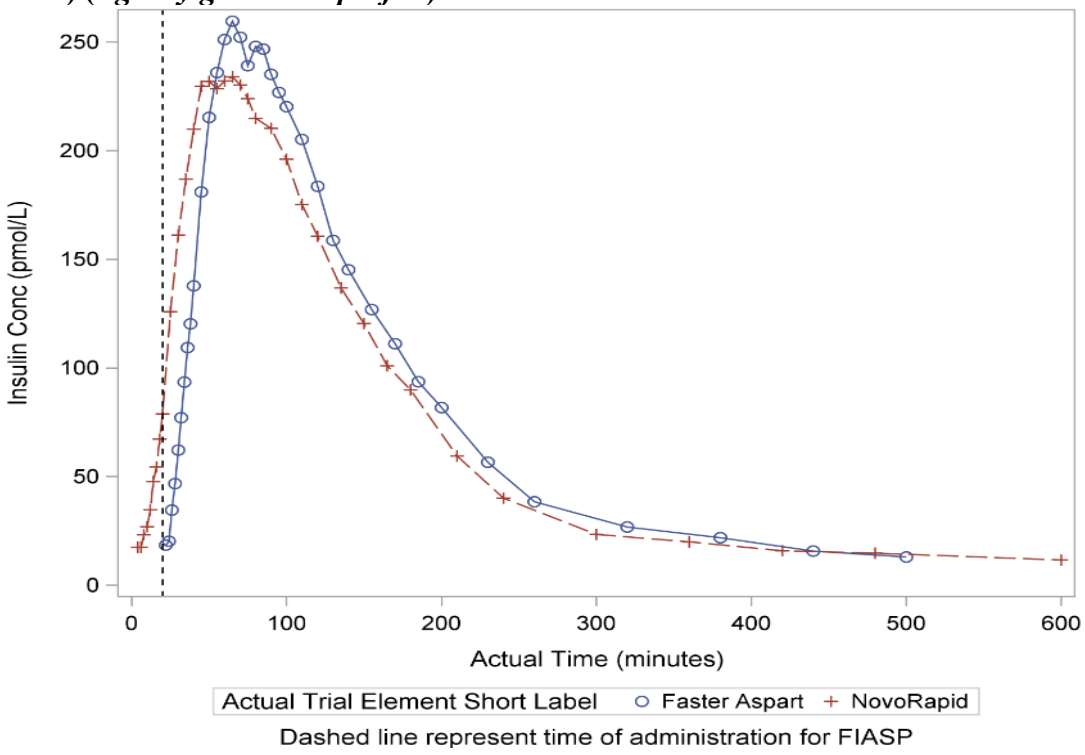
In this letter we refer to your proposed product under NDA 208751 as insulin aspart and the approved insulin aspart product under NDA 020986 as NovoLog.

Clinical Pharmacology

1. Clarify your position on either lack of difference (meal-time dosing) or higher post-prandial glucose (PPG) (post-meal dosing) in PPG data between insulin aspart and NovoLog in meal-challenge studies given that euglycemic clamp studies indicated differences in PK/PD during the initial 2 hours of the profile. Clarify if you have attempted to understand the relationship between the magnitude of PK/PD difference from euglycemic clamp studies and the translation to clinical scenarios in meal-challenge PK/PD studies. If not, consider utilizing quantitative analysis linking PK/PD data from the euglycemic clamp to the meal-challenge study results to explain this behavior of your product, and submit this information for review along with your rationale.

2. In the meal challenge study (3921), insulin aspart and NovoLog were administered 20 minutes post-meal and immediately before meal, respectively. PPG excursion was higher (poorer control) than meal-time administration of NovoLog (the recommended clinical use scenario of NovoLog). We believe that the plasma profile of insulin aspart over time shows that the absorption characteristics of insulin aspart following post meal dosing is not rapid enough to match the plasma profile of NovoLog given at meal time (Figure 1). Following post meal dosing of insulin aspart the baseline adjusted plasma glucose concentrations were higher (average plasma glucose 0-6 hr, $PG_{av,0\text{-}6hr}$ 13% higher) when compared to meal time dosing of NovoLog. You should explain how these data do or do not support a recommendation for post-meal dosing of insulin aspart.

Figure 1: Mean profiles for observed serum insulin aspart by treatments (Study: NN1218-3921) (*Agency generated profile*)



3. Because there is no PK/PD study conducted in T2DM subjects, it is uncertain if the PK/PD differences noted in T1DM patients in the euglycemic clamp studies are preserved in patients with T2DM. As you have noted, patients with T2DM are considered to be the less sensitive patient population to detect differences in postmeal response due to insulin resistance when compared to patients with T1DM. You assert in your NDA that PPG results from the Phase 3 trial in T2DM (particularly with 1 hour PPG) reflect the preserved PK/PD profile in T2DM. We are still reviewing these data; however, any PK/PD difference in insulin aspart versus NovoLog was not reflected in the 26-week HbA1c comparison.

4. In your analyses, early partial AUC estimates used predicted concentration time profile for data below the lower limit of quantification which can add uncertainty to conclusions drawn from these data. If you have any information to support this approach, please provide.

5. Clarify which data files contain dose versus time data (total, bolus, and basal dose) for the Phase 3 studies (Study number: NN1218-3852, NN1218-3853).

6. Provide a summary, stratified by treatment group (i.e. table format), of the additional/extra bolus insulin doses that were administered in the Phase 3 studies (Study number: NN1218-3852, NN1218-3853). Indicate what proportion of subjects required additional/extra bolus doses and also specify the number of additional/extra bolus doses by treatment. Indicate the exact location of this information if you already included this information in the original NDA submission.

Clinical/Statistical

We have the following comments based on our preliminary review of the trial results:

7. *Trial 3852-T1DM Pre-meal dosing*

   a. For the primary analysis of 26-week reduction in HbA1c, and using the MMRM analysis, insulin aspart was noninferior to mealtime NovoLog. Statistical superiority was also achieved, although superiority was not pre-specified. Therefore, we are considering whether a superiority claim in labeling would be appropriate.

   b. You state that superiority was achieved for change from baseline in 2-hour PPG increment after 26 weeks (although sensitivity analyses conducted to date do not appear to support the superiority claim). Further, similar outcomes were not observed for PPG excursion in the clinical pharmacology meal challenge studies. If possible, please provide unified explanation for the discordant study findings. See also comment 1.

   c. The observed superior reduction in HbA1c may be due to a better reduction of PPG with insulin aspart than NovoLog both administered at mealtime, but this remains uncertain, and review of trial conduct issues that may alter confidence in conclusions, including analyses addressing missing data, are ongoing. Any additional analyses you provide to explore this further may be considered. Please note that analyses based on PPG may be considered in regulatory action, but will not likely be acceptable for labeling. The regulatory basis for approval is reduction in the surrogate marker HbA1c and the clinical significance of reduction of PPG in and of itself with regard to important (hard) clinical outcomes is unclear.

d. If you have not already in your submission, please provide a summary of insulin dosing by week in each of the three study arms. Provide in graphical form with study week on the x axis and insulin dose on the y axis. Provide graphs for both basal and bolus dosing and total insulin dose. Provide information as when insulin dose stabilized in each study arm.

8. *Trial 3852-T1DM Post-meal dosing*

In the T1DM trial, for HbA1c, post meal insulin aspart was non-inferior to NovoLog. However, the proportion of subjects achieving HbA1c of <7% at week 26 is lower for the postmeal arm, and 2 hour PPG appears worse for post-meal dosing vs. pre-meal dosing. Further, as noted above we are not certain that the PK/PD differences observed in clamp studies in T1DM would also apply to T2DM, and there is no postmeal arm in the T2DM Phase 3 study. Providing different dosage instructions for T1DM and T2DM would be confusing to providers. For these reasons taken together we continue to question whether recommending post-meal dosing of insulin aspart is acceptable.

9. *Trial 3853-T2DM*

a. For the primary analysis of 26-week reduction in HbA1c, and using the MMRM analysis, meal time insulin aspart was non-inferior to NovoLog. There is no statistically significant difference in PPG excursion between mealtime insulin aspart and NovoLog; however, there appears to be a trend towards a greater reduction in the insulin aspart arm, and 1-hour PPG was statistically significantly reduced in favor of insulin aspart compared to NovoLog. A higher rate of hypoglycemia with insulin aspart than with NovoLog was observed in this trial. We also note that daily insulin use is slightly higher in the insulin aspart arm (4 units more of bolus insulin per day and 2 units more of basal insulin per day). Please provide your explanation for this constellation of findings. For example, were subjects in the insulin aspart arm administering their doses earlier than recommended? Were subjects permitted to use extra bolus doses after meals?

b. If you have not already in your submission, please provide a summary of insulin dosing by week in each of the two study arms. Provide in graphical form with study week on the x axis and insulin dose on the y axis. Provide graphs for both basal and bolus dosing and total insulin dose. Provide information as to when prandial insulin dose stabilized in each study arm.

Device

10. (b) (4)

11. *PDS290 Pen-Injector Design Verification*
In the Design Verification Report, you state: "PDS290 pen-injectors U100 1U have been used in this study as a representative of the PDS290 platform." It is unclear if any changes were made between the version of the pen-injector used in the design

verification activities versus the pen-injector you intend to market. Please provide a detailed history of all design changes between the test article and the commercial device. Additionally please provide a risk analysis for the impact of each of these changes. This information is needed to determine if the performance data provided is applicable to the commercial version of the device.

12. PDS290 Pen-Injector Biocompatibility

a. You have stated that the blue housing and cap of the PDS290 'Faster Aspart' pen injector consists of identical materials ((b) (4) including the colour masterbatch (b) (4)) as the housing of the currently marketed prefilled disposable FlexPen® and FlexTouch® pen-injectors. Please clarify if the FlexPen and FlexTouch pen-injectors are your own predicate devices with the same type of patient contact and duration. If so, in lieu of performing new biocompatibility testing for these device components, you may provide a material certification statement using the language as recommended below.

The [polymer/metal/ceramic/composite name] [component name] of the [subject device name] is identical to the [component name] of the [predicate device name] as it was approved/cleared in [PMA/510k/IDE number/NDA number, approval date] in formulation, processing, and sterilization, and no other chemicals have been added (e.g., (b) (4) , etc.).

If the FlexPen and FlexTouch pen-injectors are not your own devices with the same type of patient contact and duration or you cannot provide a material certification statement as shown above, biocompatibility testing based on the final finished proposed device components is considered necessary.

b. You have added new materials for the cartridge holder, dial, and dose button components. The biocompatibility evaluation of the delivery device referenced testing conducted on the raw material. However, medical device manufacturing processes can adversely affect biocompatibility by altering the chemical and physical properties of materials. Therefore, FDA and the ISO10993-1 recommend that biocompatibility testing is performed on the final finished device or component. Please provide cytotoxicity, sensitization, and irritation testing on the final finished components that have changed from your previous device.

Regulatory

13. Regarding the proposed proprietary name, FIAsp, the Division has not yet determined whether the faster PK/PD profile of insulin aspart translates into a clinical benefit. We agree with your plan to submit an alternate name for FDA's review.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JEAN-MARC P GUETTIER
06/10/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208751

PROPRIETARY NAME REQUEST UNACCEPTABLE

Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

ATTENTION: Helen Chen, MSc, RAC
Senior Manager, Regulatory Affairs

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) dated December 8, 2015, received December 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Aspart Injection, 100 units/mL.

We also refer to your February 29, 2016, correspondence, received February 29, 2016, requesting review of your proposed proprietary name, (b) (4) and (b) (4) FlexTouch.

We have completed our review of the proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

> This name could result in medication errors due to confusion with another product that is also under review. Therefore, the ultimate acceptability of your proposed proprietary name, (b) (4) is dependent upon which underlying application is approved first. If another product is approved prior to your product, with a name that would be confused with your proposed name of (b) (4) you will be requested to submit another name.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names

(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 240-402-3981. For any other information regarding this application, contact Callie Cappel-Lynch, Regulatory Project Manager in the Office of New Drugs, at 301-796-8436.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
05/05/2016

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 10, 2016
TIME: 9:00 AM (EST)
LOCATION: White Oak, Building 22, Room 3157
APPLICATION: NDA 208751
DRUG NAME: Fiasp (insulin aspart [rDNA origin])
TYPE OF MEETING: Teleconference

MEETING CHAIR: Jean-Marc Guettier
MEETING RECORDER: Terrolyn Thomas

FDA ATTENDEES:
Jean-Marc Guettier, Division Director, Division of Metabolism and Endocrinology Products
Lisa Yanoff, Medical Officer, Division of Metabolism and Endocrinology Products
Julie Van der Waag, Chief, Regulatory Project Management Staff, Division of Metabolism and Endocrinology Products
Callie CappelLynch, Regulatory Project Manager, Division of Metabolism and Endocrinology Products
Lubna Merchant, Deputy Director, Division of Medication Error Prevention and Analysis
Yelena Maslov, Team Leader, Division of Medication Error Prevention and Analysis
Ariane Conrad, Reviewer, Division of Medication Error Prevention and Analysis
Hyon Kwon, Medical Officer, Division of Metabolism and Endocrinology Products
Terrolyn Thomas, Senior Safety Project Manager, Office of Surveillance and Epidemiology

SPONSOR ATTENDEES:
Finn Møllgaard, Corporate Vice President Regulatory Affairs
Liselotte Hyveled, Project Vice President
Marek Demissie, International Medical Director
Magdalena Niepsuj Jayatissa, Regulatory Department Director
Wasim Anwar, Safety Surveillance Specialist
Shawn Hoskin, Senior Director Regulatory Affairs US
Helen Chen, Senior Manager Regulatory Affairs US

BACKGROUND: The sponsor submitted a request for proprietary name request on December 9, 2015 to review the proposed proprietary name, Fiasp. The sponsor previously noted that the name FIAsp was derived from Faster-acting insulin aspart.[1] DMEP disagreed with the proprietary name Fiasp because they do not believe a determination has been made yet regarding the faster onset of this insulin and therefore are unable to determine if there is any clinical benefit as compared to the marketed insulin aspart.

MEETING OBJECTIVES: The purpose of this meeting is to inform the sponsor of FDA's concern regarding the proposed proprietary name, Fiasp.

[1] Novo Nordisk Response: Faster-acting insulin aspart-IND 106878. Response to FDA Information Request Dated February 8, 2013.

DISCUSSION

FDA referred to the Sponsor's explanation on the name FIAsp, noting that it is intended to convey Faster-acting insulin aspart. DMEP noted although the sponsor intends to convey that the proposed product is "faster" than the currently marketed insulin aspart, however FDA has not made that determination. Since FDA is still reviewing the data and at this time is unable to determine if this has a faster onset or if there is any clinical benefit as compared to the marketed insulin aspart, we cannot reach a determination on the acceptability of the name.

The Applicant understood FDA's concern regarding the proposed proprietary name Fiasp. The Applicant will inquire, as recommended by FDA, whether to resubmit this proposed proprietary name for review at a later stage of the NDA review, when the relevant data has been reviewed by FDA. The applicant plans to submit an alternate proprietary name to NDA 208751 in the near future.

REGULATORY OPTIONS

DMEPA posed the following options to the sponsor:

- To withdraw the request for proprietary name review for Fiasp.
- To submit an alternative proprietary name for review
- If they intend to pursue the proprietary name Fiasp then the sponsor can resubmit the proposed proprietary name, Fiasp, for review at a later stage of the NDA review.

ACTION ITEMS

- Applicant agreed to withdraw proprietary name review request for Fiasp.

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/s/

TERROLYN THOMAS
02/22/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208751

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Novo Nordisk Inc.
Attention: Robert B.Clark
Vice President, Regulatory Affairs
800 Scudders Mill Rd.
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) dated and received December 8, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for insulin aspart injection, 100 units/mL.

We also refer to your amendments dated December 9, 2015 and February 11, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 8, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 9, 2016.

During our filing review of your application, we identified the following potential review issues and have the following requests for information:

Chemistry Manufacturing and Controls

1. Please provide the following information:
    a. Letters of authorization to access DMFs associated with primary container components.

b. A statement regarding availability of samples for FDA method validation. Include information, lot number, and standards information etc. under Section 3.2.R.

c. Certificates of analysis for representative lots of excipients used for manufacturing registration stability batches.

d. Temperature cycling data and data to support the stability of the finished product and intermediates during shipping and handling.

2. Your proposed analytical methodology is intended for measuring (b) (4) . Provide an assessment of the extent of (b) (4) present in stressed, accelerated, long-term stability and in-use stability samples.

Clinical Pharmacology

3. For study NN1218-3852 specify the location of the data files or submit the relevant data files pertaining to the population PK modeling described in the study report (Section 9.7.6).

4. Specify the location of the data files and output files pertaining to the population PK analysis conducted to determine the effect of age/BMI on the insulin exposure of this product.

Clinical

5. Provide justification for the applicability of study results to the US population for the trials conducted outside the US.

Device

6. You have provided (b) (4) This information alone will not be adequate to support a safety and effectiveness decision because, as a combination product, the PDS290 Pen-Injector is being reviewed as part of the NDA. Our expectation is that the design documentation included in the NDA will support this review, which should include design requirements specifications, device risk analysis, and design verification / validation data. Please remove (b) (4) from your application. You may opt to keep certain sections (b) (4) of the submission which are still relevant and supportive to the NDA submission. Additionally, please reframe your application for the PDS290 Pen-Injector as one for a New Drug Application with supporting evidence towards a determination of safe and effective.

7. (b) (4)

8. We were unable to locate where the PDS290 Pen-Injector was used in clinical studies. Please provide information regarding the clinical use of the proposed pen-injector including adverse events.

9. For the PDS290 Pen-Injector, you have provided a risk analysis, identification and verification of safety and essential performance characteristics, including test protocols. There is compliance with all the specifications and test methods according to ISO 11608-1. However, the submission does not appear to contain information supporting a conclusion that the dose accuracy requirements proposed in ISO 11608-1 do not present any additional risks for this particular drug product. Please provide a justification as to why the dose accuracy requirements in the ISO11608-1 standard are applicable to the PDS290 Pen-Injector and your drug product.

10. You state that the pen-injector dose accuracy was tested at min, mid and max doses for the PDS290 Pen-Injector (1, 40, 80 units respectively). However, we can only find where you report compliance with the specification limits of (b) (4) at dose level 50 units fulfilled. Please provide the test methods and reports for dose accuracy testing of the PDS290 Pen-Injector for the min, mid and max doses. Please provide this information for both time zero product and aged product part of shelf life testing.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

On December 4, 2014, the Food and Drug Administration published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR went into effect on June 30, 2015. According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

Together with submission of the proposed labeling for PLLR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).

During our preliminary review of your submitted labeling you did not provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made.

Submit the following information on insulin aspart use in pregnant and lactating women by March 11, 2016:

a) A review and summary of all available published literature regarding insulin aspart,
b) A review and summary from your pharmacovigilance database,
c) Interim ongoing or final report on a closed pregnancy registry (if applicable),
d) A revised label, if appropriate, incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Instructions for Use (IFU), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Instructions for Use (IFU), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
02/16/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208751

NDA ACKNOWLEDGMENT

Novo Nordisk Inc.
Attention: Robert B.Clark
Vice President, Regulatory Affairs
800 Scudders Mill Rd.
Plainsboro, NJ 08536

Dear Mr. Clark:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: insulin aspart injection

Date of Receipt: December 8, 2015

Our Reference Number: NDA 208751

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 6, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Callie Cappel-Lynch, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
12/10/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106878

MEETING MINUTES

Novo Nordisk, Inc.
Attention: Helen Chen, MSc
Manager, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Ms. Chen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NN1218 FIA (insulin aspart).

We also refer to the meeting between representatives of your firm and the FDA on June 22, 2015. The purpose of the meeting was to discuss filing and formatting issues for your planned NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Jean-Marc, Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 22, 2015 11:00am- 12:00pm
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: 106878
Product Name: NN1218 FIA (insulin aspart)
Indication: improve glycemic control in adults (b) (4) with diabetes mellitus.
Sponsor/Applicant Name: Novo Nordisk

Meeting Chair: Jean-Marc Guettier
Meeting Recorder: Callie Cappel-Lynch

FDA ATTENDEES

Office of New Drugs

Jean-Marc Guettier, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Hyon Kwon, Pharm.D., MPH	Clinical Reviewer, DMEP
Lisa Yanoff, M.D.	Clinical Team Leader, Acting, DMEP
Stephanie Leuenroth-Quinn, Ph.D.	Non-Clinical Team Leader, Acting, DMEP
Callie Cappel-Lynch, Pharm.D.	Regulatory Project Manager, DMEP
Pamela Lucarelli	Chief, Project Management Staff, DMEP
Jennifer Pippins, M.D.	Deputy Director for Safety, DMEP

Office of Biostatistics

Jiwei He, Ph.D.	Statistics Reviewer
Gregory Levin, Ph.D.	Statistics Team Leader, Acting

Office of Pharmaceutical Quality

Suong Tran, Ph.D.	CMC Team Leader

Office of Translational Science

Manoj Khurana, Ph.D.	Clinical Pharmacology Team Leader

Office of Biotechnology Products

Daniela Verthelyi, Ph.D.	Team Leader
Mohanraj Manangeeswaran, Ph.D.	Reviewer

Office of Surveillance and Epidemiology

Sarah Vee, Pharm.D.	Safety Evaluation (DMEPA)

Office of Combination Products

Bindi Nikhar, M.D.	Associate Clinical Director

Office of Regulatory Policy

Janice Weiner, J.D., M.P.H.	Senior Regulatory Counsel, Division of Regulatory Policy I (DRP I)

Center for Devices and Radiological Health

Ryan McGowan	Reviewer

SPONSOR ATTENDEES

Alan Moses	Senior Vice President, Global Chief Medical Officer
Finn Møllgaard	Corporate Vice President Regulatory Affairs
Liselotte Hyveled	Project Vice President
Mari-Anne Gall	International Medical Vice President
Bob Clark	Vice President Regulatory Affairs US
Marek Demissie	International Medical Director
Hanne Haahr	Senior Clinical Pharmacology Advisor
Søren Can Tamer	Principle Statistician
Aage Hvass	Principal Scientist Diabetes Analytical Development
Wasim Anwar	Safety Surveillance Specialist
Rasmus Klinck	Medical Technical Writer Prefilled Device Department
Magdalena Niepsuj Jayatissa	Regulatory Department Manager
Shawn Hoskin	Senior Director Regulatory Affairs US
Helen Chen	Senior Manager regulatory Affairs US

1.0 BACKGROUND

NN1218 FIA (insulin aspart) is an insulin analogue under development for improvement of glycemic control in adults (b) (4) with diabetes mellitus. IND 106878 was submitted on February 1, 2010. On March 2, 2011, an End-of Phase 2 meeting was held with the sponsor.

At this time the sponsor has completed 13 of 14 clinical trials and is planning to submit their NDA in December of 2015. They have requested this Pre-NDA meeting to discuss the content and formatting of their NDA.

FDA sent Preliminary Comments to Novo Nordisk on June 19, 2015.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing, and Controls

Question 1: Presuming the acceptance of the data conclusions in the NDA, can the Agency comment on the proposed strategy to support the proposed 30 month drug product shelf life for the 3 ml cartridge, the PDS290 Faster Aspart pen-injector and 10 ml vial?

FDA Response to Question 1: The proposed availability of stability data is adequate for NDA filing. The product shelf life will be determined as part of our review of the complete NDA. In the Quality Overall Summary of the NDA, provide tabulated information that clearly identifies all product batches submitted in the NDA as clinical, nonclinical, and/or stability batches, and pertinent information such as their manufacturing dates, sites, processes, scales, container closure systems, and clinical, nonclinical, and/or stability studies. Any difference in formulation, site, process, scale, or container closure system between the primary stability batches and the commercial product should be fully explained with supporting comparability information as appropriate.

Meeting Discussion: No discussion occurred.

Question 2: Does the Agency agree that additional 6 months of primary stability data for the 10 ml vials can be submitted within 6 months of the NDA filing?

FDA Response to Question 2: No, we do not agree to the proposed amendment. We expect you to submit a complete NDA for filing and we do not commit to reviewing additional stability data during the review cycle.

Meeting Discussion: No discussion occurred.

2.2. Clinical Pharmacology

Question 3: Does the Agency have any comments to the proposed presentation of clinical pharmacology data to be included in Summary of Clinical Pharmacology Studies in the NDA?

FDA Response to Question 3: Your proposal to include the PK/PD results of the individual studies and the pooled analysis in Summary of Clinical Pharmacology Studies in the NDA is acceptable from a NDA filing perspective. However, the utility of pooled analysis (e.g. any intended labeling claim based on pooled analysis) in the context of FIAsp PK/PD results may be limited, primarily due to the cross-study comparison nature of such analysis and variable nature of insulin PK/PD.

To facilitate an efficient and comprehensive review of your planned NDA submission, we request that you submit the individual level study data for all PK/PD studies as electronic data sets (SAS transport file). The PK/PD data sets should include, at a minimum, the following information:

For PK/PD studies conducted using a euglycemic clamp procedure:

1. **PK Data - Time, Insulin concentrations, c-peptide concentration (as applicable), adjusted insulin concentration (if applicable), actual treatment, sequence, period.**
2. **PD Data - Time, actual treatment, sequence, period, raw glucose infusion rate (GIR) and smoothed GIR, baseline adjusted GIR (if applicable), and blood glucose over the experiment duration.**
3. **Provide figures displaying overlay of insulin and c-peptide (if applicable) versus time plots over the euglycemic clamp duration by subject and treatment in the study report.**
4. **Provide figures displaying overlay of GIR and glucose versus time plots over the euglycemic clamp duration by subject and treatment in the study report.**

For PK/PD studies conducted using a meal challenge procedure:

1. **PK Data - Time, Insulin concentrations, c-peptide concentration (as applicable), adjusted insulin concentration (if applicable), actual treatment, sequence, period.**
2. **PD Data - Time, actual treatment, sequence, period, actual glucose, and baseline adjusted glucose (if applicable).**
3. **Provide figures displaying overlay of insulin and c-peptide (if applicable) versus time plots over the treatment duration by subject and treatment in the study report.**
4. **Provide figures displaying glucose and baseline adjusted glucose (if applicable) versus time plots by subject and treatment.**

Meeting Discussion: No discussion occurred.

2.3. Clinical

Question 4: Does the Agency agree with the proposed cut-off date (10 March 2015) for trials and safety data to be included in the NDA?

FDA Response to Question 4: Yes, we agree.

Meeting Discussion: No discussion occurred.

Question 5: Does the Agency agree that the number of exposed subjects and the duration of exposure in the therapeutic confirmatory trials evaluating efficacy and safety to be included in the NDA are adequate to support the NDA submission?

FDA Response to Question 5: We agree that your proposed number of exposed subjects and the duration of exposure would be sufficient to support the filing of the NDA based on the currently available information for your product.

Meeting Discussion: No discussion occurred.

Question 6: Does the Agency agree that the trials included adequate exposure for the various races and ethnicities and are sufficiently representative of the US patient population?

FDA Response to Question 6: We cannot agree at this time, and this will be a review issue. We do note that non-White subjects appear to be relatively underrepresented in the trials (e.g., African-Americans, Hispanics). For the trials conducted outside the US, you should provide justification for the applicability of study results to the US population.

Meeting Discussion: No discussion occurred.

Question 7: Does the Agency agree to the proposed approach for presentation of efficacy results in the ISE?

FDA Response to Question 7: Yes, your approach for presentation of the primary efficacy results appears acceptable. See also our response to Question 8.

Meeting Discussion: No discussion occurred.

Question 8: Does the Agency have additional comments to the analysis of PPG and hypoglycemia across trials 3852 and 3853?

FDA Response to Question 8: Our evaluation of efficacy and what would be included in the label will be based on the results from the individual confirmatory efficacy and safety trials. Integrated analyses will not replace the individual trial results when evaluating the collective evidence of efficacy. In addition, we note that 1-hour PPG was a supportive secondary endpoint in both studies and was not included in the multiple testing hierarchy to control the type I error rate. Analyses of such endpoints are generally considered exploratory and are unlikely to be included in product labeling. Hypoglycemia is considered a safety endpoint. See our response to question 10.

Meeting Discussion: No discussion occurred.

Question 9: Does the Agency agree with the proposal to (b) (4) in the faster aspart product label?

FDA Response to Question 9: No, we do not agree. This endpoint was not included in the hierarchy to control type I error rate across the multiple comparisons. Analyses of such endpoints are generally viewed as exploratory and are unlikely to be included in the product label.

Meeting Discussion: No discussion occurred.

Question 10: Does the Agency agree with the proposed strategy for pooling of the faster aspart trials and the plan for presenting safety data in the ISS?

FDA Response to Question 10: No, we do not agree. It appears that some of the integrated safety analyses you may carry out will be based on a simple pooling of data from studies with different randomization ratios and potentially also different adverse event rates. Such an approach is subject to confounding by study (e.g., Simpson's Paradox).[1] You should appropriately account for study differences through stratification by study or adjustment for study in integrated analyses.

[1] Chuang-Stein, C. and Beltangady, M. (2011). Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies. *Pharmaceutical Statistics*, 10: 3–7.

In addition, from a clinical perspective the safety data in type 1 and type 2 should be presented separately as they are different patient populations. Hypoglycemia should be evaluated at the individual trial level.

Meeting Discussion: The sponsor stated that the safety data at the individual trial level will be presented and will provide the core of the safety evaluation. In addition, in order to evaluate safety events that may occur with less frequency, the sponsor proposed to pool four studies (3852, 3853, 4049 and 3931) for presenting safety data in the ISS. (b) (4) *. To address FDA's concern about confounding by study, the sponsor proposed to stratify by study in integrated analyses using the Cochran-Mantel-Haenszel method to estimate rates and proportions. Hypoglycemia will be presented at the individual trial level, and results based on both the sponsor's and ADA's definitions will be presented in the NDA. FDA agreed to this approach.*

Question 11: Does the Agency agree with the proposal for the safety data presentation in the ISS?

FDA Response to Question 11: See our response to Question 10 regarding pooling data for safety. Tabulation of adverse events by MedDRA system organ class, high-level group term, and preferred terms are acceptable. Summary and tabulation of adverse events at a frequency of ≥1% are acceptable. However, you should also summarize and present safety data for events that may occur with lesser frequency but are serious in sequelae (e.g., hypersensitivity).

Meeting Discussion: Please see meeting discussion for Question 10.

Question 12: Can the Agency confirm that the proposal for presentation of antibody data and adverse events is acceptable?

FDA Response to Question 12: No, the proposal is not adequate. With your NDA you should submit a complete description of the assays used and the data validating their suitability. Assessment of immunogenicity only at 26 weeks is not adequate. You should submit all of the data for week 12 and 26. The format for the presentation of antibody data and adverse events for immunogenicity is acceptable. However, in addition you should provide a summary of total antibodies specific for insulin aspart and antibodies cross-reacting with human insulin in tabular form. The table should specify patient treatment, raw antibody levels, PK, PD and adverse events. A sortable table in excel format (or similar) is preferred.

Additional Comment:
We recommend you submit all SOPs and the assay development and validation reports of the immunogenicity assay/s including cut point determination for the assay to the agency prior to submission of your NDA. Until assays have been validated and assessed by the Agency you should bank sera under appropriate conditions and in sufficient quantities to allow for re-testing if deemed necessary after review of the assays.

Meeting Discussion: The sponsor stated that the immunogenicity assay used was the same as the assay used for Novolog and the assay development and validation reports of the immunogenicity assay will be submitted to the agency before the NDA submission. The sponsor also agreed to provide antibody data for week 12 along with week 26. The sponsor will provide ADaM data sets that can be used to get raw sample level data on immunogenicity. If requested, the sponsor will also provide a sortable spreadsheet (Excel or any other format) with raw antibody data at the sample level.

Question 13: Does the Agency agree with the proposed approach to present safety areas of special interest?

FDA Response to Question 13: In addition to raw cumulative incidence proportions, also provide exposure-adjusted incidence rates. Include in your tables the exposure years for each adverse event. For all analyses, report estimated differences (or ratios) to compare treatment groups, along with confidence intervals to convey the statistical uncertainty in the comparison. Also see response to Question 10 regarding appropriate statistical approaches for pooling data from multiple studies.

Meeting Discussion: The sponsor agreed to present total exposure years and estimated differences (or ratios) comparing treatment groups, along with the corresponding confidence intervals, in the tables for MACE, injection site/infusion site reactions, medical errors and allergic reactions.

Post-meeting comment: The sponsor should present total exposure years and estimated differences (or ratios) comparing treatment groups, along with the corresponding confidence intervals, in tables for all adverse events of interest, including hypoglycemia.

Question 14: Does the Agency agree with the proposed subgroups for the safety evaluation?

FDA Response to Question 14: We agree.

Meeting Discussion: No discussion occurred.

Question 15: Does the Agency agree on the proposed database cut-off for 120-day safety update?

FDA Response to Question 15: We agree.

Meeting Discussion: No discussion occurred.

Question 16: Does the Agency agree to the proposal for presenting safety data from the additional treatment period in trial 3852 in the NDA and 120-day safety update?

FDA Response to Question 16: We agree.

Meeting Discussion: No discussion occurred.

Question 17: Does the Agency agree with the proposal for inclusion of CRFs and Narratives?

FDA Response to Question 17: Your approach seems reasonable. In addition, we ask that you also submit narratives for adverse events of special interest (e.g., hypersensitivity/allergic reactions, injection site reactions, severe hypoglycemic events, etc). All narratives should be well-written and manually-generated narratives.

For ease of review, individual CSR sections (i.e., data tables/figures) should contain hyperlinks to narratives.

For ease of review, create a list of patients for whom narratives are provided with hyperlinks to the narrative. The list should be in the following format:

Patient ID (Hyperlink to narrative)	***Reason(s) for Narrative (i.e., Death; SAE, SAE leading to treatment discontinuation, Severe hypoglycemia, etc)***	***Preferred term(s) (PT) associated with the event***	***Assigned treatment group***

Organize the table according to "Reason for narrative" (i.e., categories) and identify patients who fall in multiple categories for a narrative.

In your presentations for discontinuation in your individual CSRs and in the integrated summaries, the category of "other" without further explanation is not acceptable. In your report you should provide a table with patient ID and verbatim terms for all discontinuations due to "other".

Meeting Discussion: *No discussion occurred.*

2.4. Regulatory/Administrative

Based on our understanding of the guidance and the recent FDA Type C Written Responses on the planned data standards for the NDA (dated July 28, 2014) Novo Nordisk's understanding of section §4.1.2.8 of the guidance is that software programs for the table and figure creation which are relevant for the key efficacy and safety analyses should be submitted. However, our ADaM dataset creation programs, especially those that perform specialized imputations and derivations are very large and complex. They use standard processes and components that are used to implement Novo Nordisk's business rules applicable across trials. Therefore Novo Nordisk intends to, instead, deliver Define.XML metadata and other supporting documentation that is both compliant and useful (ref: §8.1) in determining the source, traceability and derivation methods for ADaM datasets. Novo Nordisk also intends to deliver all SAS program code that can be used to confirm our analysis of key efficacy and safety data.

Question 18: Does the Agency concur to this approach?

FDA Response to Question 18: This approach appears reasonable. We also have the following general comments for a future NDA submission:

1. **Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.**

2. **Please provide the location of the SAS dataset, the names of the variables used, and the programs used to get every new value that will be appearing in the label.**

3. **For each phase 3 study, in addition to the electronic datasets, you should submit study protocols and statistical analysis plans, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).**

Meeting Discussion: *No discussion occurred.*

Question 19: Does the Agency accept this update to the Study Data Standardization Plan?

FDA Response to Question 19: Yes.

Meeting Discussion: No discussion occurred.

Question 20: With reference to §4.1 and §4.1.1.2 (Adjudication Data), does the Agency accept the format and structure of the standardized SDTM data?

FDA Response to Question 20: Yes.

Meeting Discussion: No discussion occurred.

Question 21: Does the Agency accept the format and structure of the standardized ADaM data?

FDA Response to Question 21: Yes.

Meeting Discussion: No discussion occurred.

Question 22: Does the Agency agree that it is acceptable not to submit the individual patient data listings in the NDA?

FDA Response to Question 22: Yes.

Meeting Discussion: No discussion occurred.

Question 23: Does the Agency agree that it is appropriate and beneficial to the patient's safety to use (b) (4) in the faster aspart labeling and packaging material including Physician Insert (PI), Patient Package Insert (PPI), cartons and container labels?

FDA Response to Question 23: FDA agrees that your proposed product should be distinguished from the currently marketed NovoLog (insulin aspart) to help ensure safe use. However, the approach to distinguishing between products will be a review issue. Your planned NDA submission should use the nonproprietary name "insulin aspart."

Meeting Discussion: The sponsor requested input from FDA regarding distinguishing between products at the nonproprietary name level. FDA clarified that its response regarding product differentiation was not directed to the nonproprietary name. FDA's current recommendation is that the planned NDA should be submitted with the nonproprietary name "insulin aspart", and that the sponsor should consider other approaches to distinguish its proposed product from NovoLog. The sponsor should submit appropriate data or justification supporting its proposed approach to product differentiation in the NDA.

Question 24: Does the Agency agree with use of the generic name (b) (4) ?

FDA Response to Question 24: No, FDA does not agree with the proposed nonproprietary name (b) (4) See response to Question 23.

Meeting Discussion: No discussion occurred.

Question 25: Does the Agency agree that an Advisory Committee Meeting would not be needed for faster aspart NDA?

FDA Response to Question 25: This will be a review issue; therefore, we cannot agree at this time. Based on the currently known information an Advisory Committee Meeting is not anticipated.

Meeting Discussion: No discussion occurred.

Additional Clinical Comment:
To facilitate review, we ask that you present laboratory results in conventional units as well as in SI units.

Meeting Discussion: No discussion occurred.

Additional Statistical Comment:
In 4.6.3 Conclusion on efficacy results, you state that "the reduction in HbA1c with mealtime faster aspart was statistically significantly greater compared to mealtime Novolog". This conclusion is questionable because a superiority test for comparing mealtime faster aspart and Novolog in terms of change in HbA1c was not pre-specified.

Meeting Discussion: No discussion occurred.

Additional Comments Regarding Delivery Devices:

1. **Within the briefing package, you reference (b) (4) drug delivery devices for the administration of faster-acting insulin aspart 100U/ml drug product: pre-filled and co-packaged with PDS290 Faster Aspart pen-injector (b) (4) . As part of the meeting discussion, please clarify what information you intend to provide within the NDA to support each drug delivery device presentation. Please note that the Agency expects that the planned NDA submission will contain sufficient information for each drug delivery device constituent part.**

2. **Within your description of stability study for the PDS290 Faster Aspart pen-injector, you indicate that "dose accuracy" will be the primary assessment. Within the planned NDA, the Agency expects that you will present information that supports that each essential device performance requirement of the PDS290 Faster Aspart pen-injector device will perform as expected at the end of the labeled expiration period.**

3. **The briefing package presented two tables containing overviews of drug product stability data (Section 9, Table 3 and Section 10.1, Table 5). Table 5 appears to reference an assessment of "Dose accuracy data at end of shelf life and end of in-use for primary 3 ml cartridge batches assembled in PDS290 Faster Aspart pen-injector" for 28 days at 5°C. Table 3 does not appear to contain this assessment. Please state if such an assessment will be presented within the planned NDA.**

4. **For the in-use assessments of the PDS290 Faster Aspart pen-injector, the Agency expects that the device will be repeatedly accessed via a needle and activated over the in-use study period, commensurate with expected clinical use.**

Meeting Discussion: The sponsor clarified that (b) (4) *devices i.e., the prefilled PDS 290 pen injector,* (b) (4) *would be included in the NDA and are meant for commercialization.*

See also additional meeting discussion below.

Additional Combination Product comments:
The proposed insulin aspart drug product that is to be used with a pen-injector is a combination product subject to 21 CFR Part 4 requirements.

eCTD comments for combination products:

Other than data analogous to batch records, all device constituent and combination product information data should be integrated in the eCTD with conceptually similar drug constituent information. The data should be organized based on the following principles:

1. **For eCTD format and use of the electronic submission system, please adhere to eCTD headings as defined per ICH and FDA specifications. In the specifications, these may be identified as leaf nodes or elements. Specifically, any title that is associated with a numerical item should not change; i.e., Item 3.2.P.7 should say "Container Closure System."**

2. **Do not use "node extensions" to create new elements. Although this is described in the eCTD specification, and may be acceptable in some regions, it is not acceptable in submissions to FDA.**

3. **When including and referencing device information, we recommend the following:**

   3.1. **You may reference files under 3.2.P.7, which are not currently listed as numerical items in ICH and FDA specifications and guidance.**
   3.2. **In Module 3.2.P.7, you could include a leaf titled similar to the following, "Table of Contents for Drug-Device pen-injector. This leaf/document could provide reference links to the other files in module 3.2.P.7.**
   3.3. **The leaf titles should be clear, concise, and indicative of the document's content.**

4. **Module 1.4.4 "Cross-reference to other applications" is a location where you can provide references to other applications and you can include copies of an application's table of contents, reference tables, or other similar documents. If you are cross referencing another company's application or master file, include the appropriate letters of authorization from the other companies in modules 1.4.1 - 1.4.3 (1.4.1 "Letter of authorization", 1.4.2 "Statement of right of reference," 1.4.3 "List of authorized**

persons to incorporate by reference"). If there are standards you will reference in the Performance Specifications which also meet these criteria, then please put them in module 1.4.4. The Performance Specifications section should link to this information.

5. **All device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with 21 CFR Part 4 and the applicable 21 CFR part 820 regulations should be located in Section 3.2.P.3.**

   5.1. **The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site involved with the device constituent part.**
   5.2. **Suggestions on the types of documents to submit for review of required sections of 21 CFR Part 820 (based upon the combination product 21 CFR Part 4 GMP operating system at the facility) can be found in the guidance document titled "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," issued on February 3, 2003. The complete document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm.**

6. **We recommend that you provide an "Information to Reviewers" or "Reviewers Guide" document in Module 1.2 Cover letters. This document would be separate from the cover letter and placed after the cover letter and should provide a high level overview (with reference links) of the submission's content and list where the information is located in the eCTD. For example, it should identify where drug, device and combination product is located.**

Meeting Discussion: No discussion occurred.

Additional Meeting Discussion:

Device: Additional discussion occurred regarding the sponsor's plan to (b) (4) [redacted]

(b) (4) [redacted]

(b) (4)

(b) (4)

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U

CM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

5.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided

in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

6.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

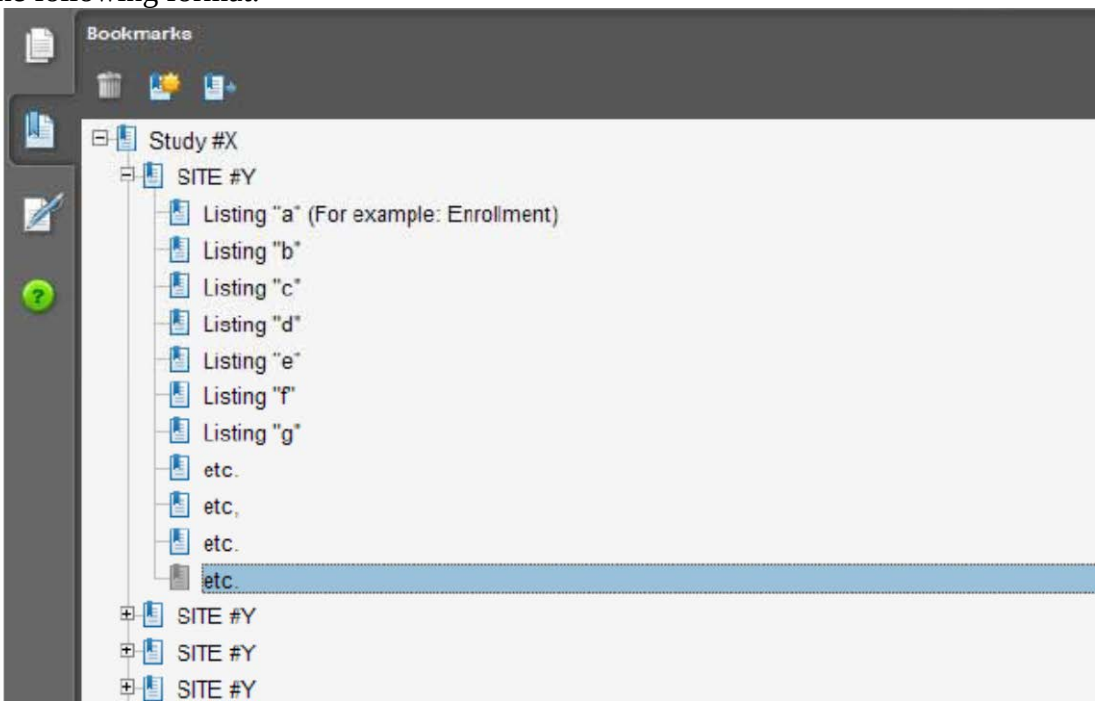
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:

a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
b. Subject listing for treatment assignment (randomization)
c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

The sponsor presented slides which are attached to this document.

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

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
07/13/2015

From: CappelLynch, Callie
To: HCHN (Helen Guo Chen) (hchn@novonordisk.com)
Subject: NDA 208751
Date: Monday, May 02, 2016 11:22:00 AM

Hi Helen,

On March 10, 2016, you submitted a response to our 74 day letter which included required PLLR information. You submitted the following information as part of this response:

The publications described below provide results from 2 RCTs sponsored by Novo Nordisk (Trial IDs ANA-1474 and ANA-2067)1-3; the data from these trials have previously been submitted to the agency (NovoLog®: NDA 20986/S-037).

Two publications described the primary results of a single RCT in women with type 1 diabetes mellitus (T1DM), who were pregnant (gestational age below 10 weeks) or planning pregnancy, and who were randomized 1:1 to insulin aspart or regular human insulin as the bolus component in a basal-bolus regimen (with NPH insulin) in an open-label, parallel-group trial.1, 2 In total, 322 subjects (insulin aspart, 157; human insulin, 165) were pregnant during the trial. Subjects were followed up to 6 weeks post-partum. One publication presented data on maternal hypoglycemia, glycemic control and safety,1 and the other publication presented data on fetal and perinataloutcomes.2 The overall safety and efficacy of insulin aspart were shown to be similar to that of human insulin and did not indicate any adverse effect of insulin aspart on pregnancy or on the health of the fetus/newborn. Publications providing data on secondary or exploratory analyses of this RCT are presented separately below.

One publication provided results of another RCT in which 27 women with gestational diabetes mellitus (GDM) were randomized 1:1 to receive insulin aspart or regular human insulin as the bolus component in a basal-bolus regimen (with NPH insulin) in an open-labelled, parallel-group trial3. The trial period extended from diagnosis of GDM (18–28 weeks) to 6 weeks postpartum. The efficacy and safety, including immunogenicity, of insulin aspart versus human insulin were investigated. Overall, the safety and efficacy of insulin aspart were comparable to human insulin in pregnant women with GDM in this study.

Can you please clarify which trial number applies to each of the 2 studies, one with 323 subjects, one with 27 subjects.

Thanks,
Callie

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
05/02/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106878

MEETING MINUTES

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NN1218 FIA (faster-acting insulin aspart).

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on March 2, 2011.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**B**
Meeting Category:	**End of Phase 2**
Meeting Date and Time:	**March 2, 2011 (12:00 – 1:00pm)**
Meeting Location:	**10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903**
Application Number:	**IND 106878**
Product Name:	**NN1218 FIA (faster-acting insulin aspart).**
Indication:	**treatment of diabetes mellitus**
Sponsor/Applicant Name:	**Novo Nordisk**
Meeting Chair:	**Mary H. Parks, M.D.**
Meeting Recorder:	**Rachel Hartford**

CDER participants: (tentative) (alphabetic)

Jeanine Best, MSN, RN, PNP	Senior Clinical Analyst, Pediatric and Maternal Health Staff
Sally Choe, Ph.D.	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCP II)
Samantha Cotter	Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)
Karen Davis Bruno, Ph.D.	Supervisory Pharmacologist, Division of Metabolism and Endocrinology Products (DMEP)
Rachel Hartford	Regulatory Health Project Manager, DMEP
Ilan Irony, M.D.	Diabetes Team II Leader, DMEP

Manoj Khurana, Ph.D.	Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II (DCP II)
Hyon Kwon, Pharm.D., M.P.H.	Clinical Reviewer, DMEP
Joe Leginus, Ph.D.	Chemist, Branch VII, DNDQA-III, ONDQA
Lee Pian, Ph.D.	Statistician, Division of Biometrics II
Mary H. Parks, M.D.	Director, DMEP
Todd Sahlroot, Ph.D.	Statistics Team Leader, Division of Biometrics II
Kellie Taylor, Pharm.D.	Deputy Director, DMEPA, OSE
Suong Tran, Ph.D.	Chemistry, Manufacturing, and Controls Lead, DNDQAIII, ONDQA
Miyun Tsai-Turton, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP

SPONSOR ATTENDEES

Dejgaard Anders	CVP, Insulin and Device projects
Demissie Marek	International Medical Director
Fischer Robert	Senior Director, Regulatory Affairs, US
Haahr Hanne	Director of Insulin Clinical Pharmacology
Henriksen Hanne	Senior Regulatory Project Manager
Hyveled Liselotte	Project Vice President
Jensen Steen	Senior CMC Project Manager
Kristensen Peter	Senior Vice President, Global Development
Lynggaard Helle	Principal Statistician, International Project Statistician
Mollgaard Finn	Corporate Vice President, Regulatory Affairs
Olsen Kristensen Anette	Senior Non-clinical Project Manager

Sturis Jeppe	Vice President, Diabetes Research Unit
Tan Elizabeth	Director, Regulatory Affairs, US

1.0 BACKGROUND

The Faster Acting Insulin Aspart (FIA) IND 106878 was submitted on February 1, 2010. Novo Nordisk requested this End-of-Phase 2 meeting on December 23, 2010. FDA granted the meeting on January 20, 2011. The briefing package was received via the gateway on January 27, 2011.

Insulin aspart is the drug substance used in NovoLog NDA 020986, NovoLog Mix 50/50 NDA 021810, and NovoLog Mix 70/30 NDA 021172. FIA is insulin aspart formulated to achieve an earlier absorption than NovoLog. It contains three new excipients (nicotinamide, L-arginine hydrochloride, (b) (4) .

The briefing package contained the following two protocol synopses:

Trial NN1218-3852: A 26-week randomised, treat to target, multicenter, controlled, 3- arm parallel, efficacy and safety basal-bolus trial comparing administration of doubleblind meal-time FIA, double-blind meal-time NovoRapid®/NovoLog® and open-label post-meal FIA, all in combination with Levemir® in adult subjects with type 1 diabetes followed by an additional 26-week treatment period in the double-blind arms of the trial.

Trial NN1218-3853: A 26-week randomised, double-blind, treat to target, multicentre, controlled, parallel, efficacy and safety basal-bolus trial comparing administration of FIA to Novo Rapid®/NovoLog® both in combination with insulin glargine and metformin in adult subjects with type 2 diabetes.

2. DISCUSSION

Preliminary responses to the questions enclosed in the meeting package were sent to you via email on March 1, 2011. We have renumbered the questions so that each question has a unique number. Your original number follows ours in brackets. Your questions appear below followed by our preliminary responses in **bold**. A summary of the discussion at the meeting is shown in ***bold italics***. Post-meeting comments are shown in underlined regular font. For questions where no additional discussion is indicated, neither Novo Nordisk nor FDA raised any additional issues pertaining to the questions.

CMC

1. [1] Does the Division agree with the proposed drug product specification for FIA?

FDA Response: The proposed formulation of FIA (G) differs from the approved formulation for NovoLog® in several ways. These include a) (b) (4) e) addition of L-arginine hydrochloride as a stabilizing agent, and f)

addition of nicotinamide as an absorption modifier. Due to changes in the formulation of FIA (G) compared to NovoLog, provide experimental evidence in the NDA to support your assertion that the test parameters of identity of insulin aspart, identity and content of (b) (4), identity and content of (b) (4) pH, freezing point depression and (b) (4) are not stability indicating parameters which, and if shown, would then require testing only at release.

We do <u>not</u> agree with your proposal not to include a bioactivity assay as part of the drug product specifications. A bioactivity assay should be used for release and stability testing for the drug product. However, alternate approaches are available. One example would be to confirm a relationship between biological activity and an orthogonal analytical method, e.g., content by RP-HPLC assay using non-degraded as well as degraded samples of insulin aspart drug substance and drug product. The objective would be to provide experimental evidence to allow a conclusion that a second analytical method can offer a reliable indication of the biological activity of insulin aspart, thereby precluding the requirement to conduct a biological assay on the drug product at release.

<u>Discussion:</u> The main point of discussion centered on the need for a bioactivity assay as part of the drug product specifications. The sponsor stated that in previous applications with the same drug substance (e.g., Novolog), a bioactivity assay was conducted on the drug substance, but was not required for the drug product. FDA stated that FIA is a new drug product with a new formulation compared to Novolog, therefore, a bioactivity assay would be required. However, if a complementary analytical method (e.g., content by HPLC) could be shown to have a direct correlation with bioactivity of the FIA drug product (using non-degraded and degraded samples of FIA), then results from the analytical method could be presented as quantitative measures of bioactivity, which would preclude the necessity to conduct a bioactivity assay on the drug product.

(b) (4)

(b) (4)

Nonclinical

3. [3] For the purpose of NDA approval, does the Division agree that safety of the excipients (L-arginine hydrochloride, nicotinamide and (b) (4) for chronic subcutaneous injection can be based on a combination of literature review, their use in currently marketed products, and local tolerance studies of FIA (A-D, G) without additional nonclinical investigations?

FDA Response: Based on your PK and local tolerance studies with all FIA formulations (A-D, G) and literature review of these added excipients (L-arginine, nicotinamide, and (b) (4) no additional animal study is needed at this time to assess the safety of these three excipients in FIA (G) formulation. Final decision will rely on your study reports upon submission.

4. [4a] Does the Division agree that the above described nonclinical safety program is sufficient to support initiation of the proposed Phase 3a program?

FDA Response: see response to question 5.

5. [4b] Does the Division agree that the above described nonclinical safety program is sufficient to support approval of the NDA?

FDA Response: Since insulin aspart, the active drug substance, is an approved product, local tolerance studies with the FIA (G) formulation would be sufficient to initiate Phase IIIa clinical study and to support NDA approval, assuming there would be no impurities/degradant issues raised by CMC and no unfavorable risk / benefit profile uncovered in the clinical review.

Clinical Pharmacology

6. [5a] Does the Division agree that the proposed NN1218-3872 clinical pharmacology trial with FIA (G), in addition to the trials conducted with FIA (A-D) and existing knowledge with NovoLog®, are adequate to initiate the phase 3a program?

FDA Response: Yes, we agree.

7. [5b] To date, trials with FIA (A-D) have, in patients with type 1 diabetes, shown marked differences in onset of appearance and action, early exposure and early glucose lowering effect compared to NovoLog® as seen from preliminary data from NN1218-3808 and NN1218-3824. Novo Nordisk anticipates similar results with FIA (G). Would a difference within the same magnitude (as shown in Table 1 and Table 2 below and further described in Section 10.3.1.1) be acceptable for differentiating from the adjacent product, NovoLog®, in Novo Nordisk's rapid-acting insulin product line?

FDA Response: Appropriateness of any claims for differences of FIA from Novolog based on PK and PD properties depends on comprehensive review of results from euglycemic clamp studies as well as meal challenge PKPD studies. In addition, keep in mind that any claim on difference should be supported by your Phase 3 trial results. Based on your meeting package, we understand FIA to be a standalone insulin product, not in the same line as Novolog and the Novolog pre-mixes. Therefore, FIA is not subject to the demonstration of "sufficient distinctiveness" from products in the same line as described in the Diabetes Draft Guidance.

8. [5c] Does the Division agree that the proposed confirmatory clinical pharmacology program is adequate to support NDA approval and that FIA is a distinct product from NovoLog®?

FDA Response: We agree that the planned clinical pharmacology program is adequate to support your NDA submission. However, clarify if you plan to rotate the injection sites in your proposed Phase 3 trials. Please refer to our response to Question 7, regarding the lack of requirement to demonstrate "sufficient distinctiveness" for a standalone insulin product such as Novolog FIA.

Discussion: The sponsor indicated plans to only use the abdomen as the site of injection to reduce the variability in the Phase 3 trial and asked if they can keep the flexibility of injection sites the same as Novolog language of "can be injected at arm, thigh or

abdomen" in the final FIA label. The FDA responded that a clinical pharmacology PKPD evaluation is necessary to support this type of injection site interchangeability claim.

Clinical

9. [6a] Does the Division agree that the proposed number of exposed subjects (755 subjects) and the duration of exposure (up to 6 months) in the proposed phase 3a program for FIA together with the safety database for NovoLog® are sufficient to support market approval given the extensive clinical experience with insulin aspart as NovoLog®?

FDA Response: Provided there are no safety concerns related to the product formulation or unexpected safety findings identified prior to NDA submission, we agree that your proposed number of exposed subjects and the duration of exposure in the proposed 3a program are sufficient to support the NDA submission.

10. [6b] Does the Division agree that demonstration of non-inferiority of HbA1c (0.4% limit) for post-prandial dosing of FIA compared to dosing of FIA immediately before the meal would be adequate to add a post-prandial dosing regimen in the label?

FDA Response: We agree that demonstration of non-inferiority of HbA1c at 0.4% margin is acceptable. We recommend that the primary comparison be the glycemic effect of post-prandial dosing of FIA against dosing of Novolog before the meal, to avoid a bio-creep whereby post-prandial administration of Novolog FIA may be statistically non-inferior to pre-prandial Novolog FIA, but be statistically inferior to the reference comparator in the study, Novolog. In addition, you state in your submission that the meal-time dosing in this trial is defined as injecting immediately before the meal, while post-meal dosing is defined as injection (b) (4) **20 minutes after the start of a meal,** (b) (4) **.** (b) (4) **Instruct investigators to have the patients in the post-prandial FIA group wait a full 20 minutes after initiation of the meal before injecting the post-prandial dose of FIA.**

11. [6c] In the T1DM trial, patients with a pre-trial QD or BID basal insulin (Levemir® or insulin glargine) regimen will be allowed and will be asked to maintain a QD or BID frequency of dosing with Levemir during the maintenance phase of the trial. In the T2DM trial, only patients on insulin glargine QD are eligible to enter the trial and they will be asked to maintain this basal insulin regimen throughout the trial.

    Does the Division agree to the proposed basal insulin comparators, including dosing regimen, in the proposed phase 3a program e.g. Levemir® in the T1DM trial and insulin glargine in the T2DM trial?

FDA Response: Yes, we have no objections. It is not clear why you propose different basal insulin comparators in T1DM and T2DM; please provide a rationale.

You state that after 8-week basal insulin titration period, the investigator should focus on optimizing the bolus insulin doses individually in a treat-to-target fashion based on the clinical response and safety according to the pre-meals and bedtime glucose levels following developed algorithms. You state that further up- or down-titration of basal insulin doses can be done at the discretion of the Investigator, if dictated by the patient's safety. We concur with your proposal, because changes in dosing of basal insulins or in the algorithms for bolus insulins may affect the interpretability of trial results. Please emphasize to investigators to minimize changes to basal insulin doses during the treatment period that are unrelated to treatment or prevention of hypoglycemia, as well as changes to bolus insulins algorithms unrelated to severe or recurrent episodes of hypoglycemia.

Discussion: ***The sponsor clarified that they would like to obtain clinical data on using both basal insulin (Levemir® and insulin glargine) with FIA, and they chose one basal insulin product for each trial for consistency. Insulin glargine was chosen for T2DM trial since this basal insulin is used more often in patients with T2DM.***

12. [6d] Does the Division agree that it is acceptable to advise patients included in the T1DM and T2DM trials to follow their normal injection routine?

FDA Response: Yes.

13. [7a] Does the Division agree that the statistical hierarchical testing procedure for the confirmatory secondary endpoints will support inclusion of significant p-values in the clinical studies section of the label?

FDA Response: See response to question 14.

14. [7b] Does the Division agree that the (b) (4)

FDA Response: This will be a review issue. We object, however, to the 2-hour post prandial glucose (PPG) being based on SMPG. These measurements are not as reliable as lab-based, plasma glucose measurements, and the values are affected by non standardized meals with different caloric composition. In addition, the timing of these samplings depends on patient reporting . A reduction in meal carbohydrate intake at home for one of the groups may bias the 2-hour PPG results and their interpretability, in contrast to ingestion of a standard meal with collection of blood samples at pre-specified times. This may be accomplished in trial subjects by conducting a rigorous MMTT or OGTT 2-hour PPG based on in clinic lab-based glucose measurements.

(b) (4)

(b) (4)

(b) (4)

16. [9] Does the Division agree that antibody measurements at 0, 3, 6 and 12 months in the basal/ bolus trial (NN1218-3852) in subjects with type 1 diabetes is sufficient to evaluate the potential risk of immunogenicity by the FIA formulation?

FDA Response: Yes. In addition to antibody assessment, correlate selected Adverse Events (ranging from local irritation to loss of glycemic effect to anaphylaxis) to antibody titers in your safety analyses.

17. [10] Does the Division agree that (b) (4)

FDA Response: This will be a review issue. Because you claim that FIA has different pharmacokinetic and pharmacodynamic properties from NovoLog®, (b) (4) **will be determined based on the findings from your trials upon submission.**

Discussion:
FDA expects adequate representation of the target population in the Phase 3 trials, but does not require that separate, dedicated trials in specific populations be conducted. However, because (b) (4)

18. [11] Does the Division agree that including injection site reactions as a Medical Event of Special Interest (MESIs) with additional tracking and follow-up of patients in the clinical program provides a sufficient level of safety assessment for local tolerability of FIA?

FDA Response: Yes.

19. [12a] Due to the significant NovoLog® clinical experience, does the Division agree that the proposed clinical program sufficiently investigates the cardiovascular risk profile of FIA?

FDA Response: At this time, we do not require the development of parenteral insulins to rule out a specified threshold of increased cardiovascular risk as described in the *Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf). However, you should still collect and analyze the cardiovascular data from your clinical trials as outlined in that guidance document, perform statistical testing on your cardiovascular data, and report the relative cardiovascular risk in your NDA submission.

20. [12b] Does the Division agree that this will be sufficient?

FDA Response: See response to Question 19. The NDA should include a detailed description of your methodology for these analyses of major adverse cardiovascular events (MACE), including narratives of these events

21. [13] (b) (4)

FDA Response: The Pediatric Research and Equity Act (PREA) of 2007 requires that you address dosing, safety, and efficacy for faster-acting insulin aspart in the pediatric population. (b) (4) **You must address dosing and safety with faster-acting insulin aspart in the pediatric population in the context of a clinical trial in pediatric subjects with type 1 diabetes. In addition, you must submit a Pediatric Plan for faster-acting insulin aspart that covers all pediatric age groups. We recommend that you conduct the adult trial in type 1 diabetes, to determine the best timing of Novolog FIA administration** (b) (4)

(b) (4)

(b) (4)

Regulatory

24. [15a] Provided that the Usability Test results validate the market's ability to differentiate between NovoLog® and FIA, does the Division agree that only two attributes, (1) color branding of pen and cartons and (2) tradename, are sufficient to test for market approval?

FDA Response: FDA does not agree that only two attributes, (1) color branding of pen and cartons and (2) tradename, are sufficient to test for market approval. Although we have concern that the introduction of FIA will lead to errors with other marketed insulin products and recommend that this risk be included as a component of your human factors testing, we recommend that you conduct a comprehensive risk analysis identifying the use-related risks with the FIA / pen injector combination product. As a general recommendation, you should perform such risk analysis for all drug/ device combination products.

We are unclear with your statement "Provided that the Usability Test results validate the market's ability to differentiate between NovoLog® and FIA…" The intent of Human Factors testing is not to make such a distinction. Rather, the purpose of a human factors study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users.

We ask that you explicitly demonstrate that all of the use-related risks for this combination product have been successfully mitigated. In this capacity, if you utilize existing testing (i.e. testing from previous NDA submissions where this particular autoinjector was the device constituent) to demonstrate the safe and effective use of the FIA / pen injector (subject device of IND 106878), then you should clearly explain how this testing mitigates the specific use risks as associated with the FIA/ pen injector combination product. However, if FDA disagrees on whether the existing testing appropriately addresses a particular use-related risk, you may have to perform additional testing to demonstrate that the use-related risks associated with THIS combination product have been mitigated.

We expect that the human factors testing that you perform will be aligned with the Human Factors / Usability Testing recommendations, as explained in our Guidance, *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management* (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf).

25. [15b] Does the Division have any comments to the proposed tradename of (b) (4)

FDA Response: We recommend that (b) (4) be used for the FIA insulin product and that you (b) (4) Our reasons are as follows:

A) (b) (4)

B) (b) (4)

26. [16a] Does the Division agree to the proposal that the FIA NDA will extensively cross-reference the NovoLog® NDA whenever applicable?

FDA Response: Yes. Clearly indicate what you are bridging to in the NovoLog NDA and include submission dates.

27. [16b] If the Division is agreeable to the proposal, are there any special considerations which Novo Nordisk should be aware of to make the Division's review easier and more efficient?

FDA Response: You have submitted several NDA and IND submissions where a pen injector was utilized to deliver a particular formulation of insulin. It is unclear whether there are unique characteristics of the pen injector utilized to deliver FIA (versus other pen injectors submitted as part of previous NDA submissions). Please provide a table that compares the physical, material, and functional characteristics of the pen injector used to deliver FIA with the Pen Injectors that have been the subject of previous NDA submissions (i.e. PDS-290). This information would assist the FDA to perform a comprehensive review of your combination product.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

4.0 ACTION ITEMS

There are not any action items.

5.0 ATTACHMENTS AND HANDOUTS

There are not any attachments or handouts.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHEL E HARTFORD
03/29/2011