CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209637Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION¹

<table>
<thead>
<tr>
<th>NDA #</th>
<th>209637</th>
<th>NDA Supplement #</th>
<th>If NDA, Efficacy Supplement Type: N/A (an action package is not required for SE8 or SE9 supplements)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLA #</td>
<td></td>
<td>BLA Supplement #</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Proprietary Name:</th>
<th>Ozempic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established/Proper Name:</td>
<td>semaglutide</td>
</tr>
<tr>
<td>Dosage Form:</td>
<td>injection</td>
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</table>

<table>
<thead>
<tr>
<th>Applicant:</th>
<th>Novo Nordisk Inc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent for Applicant (if applicable):</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RPM:</th>
<th>Peter Franks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Division:</td>
<td>DMEP</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>NDA Application Type:</th>
<th>☒ 505(b)(1)</th>
<th>☐ 505(b)(2)</th>
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</thead>
<tbody>
<tr>
<td>Efficacy Supplement:</td>
<td>☐ 505(b)(1)</td>
<td>☐ 505(b)(2)</td>
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</tbody>
</table>

<table>
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<tr>
<th>BLA Application Type:</th>
<th>☐ 351(k)</th>
<th>☐ 351(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy Supplement:</td>
<td>☐ 351(k)</td>
<td>☐ 351(a)</td>
</tr>
</tbody>
</table>

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

- Review the information in the 505(b)(2) Assessment and submit the draft² 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 December 5, 2017

<table>
<thead>
<tr>
<th>AP</th>
<th>TA</th>
<th>CR</th>
</tr>
</thead>
</table>

- Previous actions (specify type and date for each action taken)

| None |

**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](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf)). If not submitted, explain __________

| Received |

**Application Characteristics³**

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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 1 (New Molecular Entity)
(confirm chemical classification at time of approval)

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

(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)
☐ 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

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

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)
  ☐ Yes ☐ No
  - Office of Executive Programs (OEP) liaison has been notified of action
  - 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)?
    - No ☐ Yes
  - If so, specify the type

- 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) (link)
  - Included

Documentation of consent/non-consent by officers/employees (link)
  - Included
### Action Letters

- Copies of all action letters *(including approval letter with final labeling)*  
  - Action(s) and date(s)  
  - Approval 12/5/2017

### 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  
    - See labeling attached to approval 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)*  
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*  
    - Included  
    - See labeling attached to approval 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  
    - See labeling attached to approval letter

- **Proprietary Name**  
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*  
  - Review(s) *(indicate date(s))*  
  - Conditional approval letters: 2/27/2017  
  - Review: 2/17/2017 (NDA)  
  - 10/9/2015 (IND)

- **Labeling reviews** *(indicate dates of reviews)*

### Administrative / Regulatory Documents

- RPM: 4/19/2017
  - DMEPA: [ ] None 11/24/2017; 12/1/2017; 12/4/2017  
  - DMPP/PLT (DRISK): 11/9/2017  
    - None
  - OPDP: [ ] None 11/13/2017  
  - SEALD: [X] None
  - CSS: [X] None  
  - Product Quality 7/25/2017; see Chapter 2 of integrated quality assessment
  - Other: [ ] None

Reference ID: 4191977
<table>
<thead>
<tr>
<th>Topic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPM Filing Review/Memo of Filing Meeting</td>
<td>4/20/2017</td>
</tr>
<tr>
<td>All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee</td>
<td>Not a (b)(2)</td>
</tr>
<tr>
<td>NDAs/NDA supplements only: Exclusivity Summary</td>
<td>Completed (Do not include)</td>
</tr>
<tr>
<td>Application Integrity Policy (AIP) Status and Related Documents</td>
<td></td>
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<tr>
<td>Applicant is on the AIP</td>
<td>Yes</td>
</tr>
<tr>
<td>This application is on the AIP</td>
<td>Yes</td>
</tr>
<tr>
<td>If yes, Center Director’s Exception for Review memo</td>
<td>Not an AP action</td>
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<tr>
<td>If yes, OC clearance for approval</td>
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<tr>
<td>Pediatrics (approvals only)</td>
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<tr>
<td>Date reviewed by PeRC</td>
<td>11/1/2017</td>
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<tr>
<td>If PeRC review not necessary, explain:</td>
<td></td>
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<tr>
<td>Breakthrough Therapy Designation</td>
<td>N/A</td>
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<tr>
<td>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</td>
<td></td>
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<tr>
<td>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes)</td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td>Included</td>
</tr>
<tr>
<td>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)</td>
<td>Included</td>
</tr>
<tr>
<td>Minutes of Meetings</td>
<td></td>
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<tr>
<td>If not the first review cycle, any end-of-review meeting</td>
<td>N/A or no mtg</td>
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<tr>
<td>Pre-NDA/BLA meeting</td>
<td>No mtg 8/2/2016</td>
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<tr>
<td>EOP2 meeting</td>
<td>No mtg 6/9/2010</td>
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<tr>
<td>Mid-cycle Communication</td>
<td>N/A 6/1/2017</td>
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<tr>
<td>Late-cycle Meeting</td>
<td>N/A 9/19/2017</td>
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<tr>
<td>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings)</td>
<td>N/A</td>
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</tbody>
</table>

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

Reference ID: 4191977
| Advisory Committee Meeting(s) | □ No AC meeting |
| Date(s) of Meeting(s) | 10/18/2017 |

## Decisional and Summary Memos

| Office Director Decisional Memo (*indicate date for each review*) | □ None 12/1/2017 |
| Division Director Summary Review (*indicate date for each review*) | □ None 12/2/2017 |
| Cross-Discipline Team Leader Review (*indicate date for each review*) | □ None 12/2/2017 |
| PMR/PMC Development Templates (*indicate total number*) | □ None 12/4/2017 (4) |

## Clinical

| Clinical Reviews |
| Clinical Team Leader Review(s) (*indicate date for each review*) | □ No separate review |
| Clinical review(s) (*indicate date for each review*) | 11/16/2017; 11/27/2017 |
| 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 page 447 of Clinical Review; 11/27/2017

### Clinical reviews from immunology and other clinical areas/divisions/Centers (*indicate date of each review*)

| 5 |

### Controlled Substance Staff review(s) and Scheduling Recommendation (*indicate date of each review*)

| □ None |

### 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*)

| 12/5/2016 |

### OSI Clinical Inspection Review Summary(ies) (*include copies of OSI letters to investigators*)

| □ None requested |

8/1/2017 (Interim Summary)  
11/13/2017 (Final Summary)

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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).
<table>
<thead>
<tr>
<th>Category</th>
<th>Summary</th>
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<tbody>
<tr>
<td><strong>Clinical Microbiology</strong></td>
<td>□ None</td>
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<tr>
<td></td>
<td>▪ Clinical Microbiology Team Leader Review(s) <em>(indicate date for each review)</em></td>
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<td></td>
<td>▪ Clinical Microbiology Review(s) <em>(indicate date for each review)</em></td>
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<tr>
<td></td>
<td>▪ See integrated quality assessment</td>
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<tr>
<td><strong>Biostatistics</strong></td>
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<td></td>
<td>▪ Statistical Division Director Review(s) <em>(indicate date for each review)</em></td>
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<td>▪ Statistical Team Leader Review(s) <em>(indicate date for each review)</em></td>
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<tr>
<td></td>
<td>▪ Statistical Review(s) <em>(indicate date for each review)</em></td>
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<td></td>
<td>Safety Statistics (CVOT study): 8/29/2017</td>
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<td><strong>Clinical Pharmacology</strong></td>
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<td></td>
<td>▪ Clinical Pharmacology Team Leader Review(s) <em>(indicate date for each review)</em></td>
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<td></td>
<td>▪ Clinical Pharmacology review(s) <em>(indicate date for each review)</em></td>
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<tr>
<td></td>
<td>▪ OSI Clinical Pharmacology Inspection Review Summary <em>(include copies of OSI letters)</em></td>
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<tr>
<td><strong>Nonclinical</strong></td>
<td>□ None</td>
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<tr>
<td></td>
<td>▪ Pharmacology/Toxicology Discipline Reviews</td>
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<td>▪ ADP/T Review(s) <em>(indicate date for each review)</em></td>
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<td></td>
<td>▪ Supervisory Review(s) <em>(indicate date for each review)</em></td>
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<td></td>
<td>▪ Pharm/tox review(s), including referenced IND reviews <em>(indicate date for each review)</em></td>
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<td>▪ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <em>(indicate date for each review)</em></td>
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<td></td>
<td>▪ Statistical review(s) of carcinogenicity studies <em>(indicate date for each review)</em></td>
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<tr>
<td></td>
<td>▪ ECAC/CAC report/memo of meeting</td>
</tr>
<tr>
<td></td>
<td>▪ OSI Nonclinical Inspection Review Summary <em>(include copies of OSI letters)</em></td>
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<tr>
<td>Product Quality</td>
<td>None</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
</tr>
<tr>
<td><strong>Product Quality Discipline Reviews</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
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</tr>
<tr>
<td>• Tertiary review <em>(indicate date for each review)</em></td>
<td>None</td>
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<tr>
<td>• Secondary review (e.g., Branch Chief) <em>(indicate date for each review)</em></td>
<td>None</td>
</tr>
<tr>
<td>• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <em>(indicate date for each review)</em></td>
<td></td>
</tr>
</tbody>
</table>
| **Drug Product** 7/25/2017  
**Primary Process:** 7/26/2017  
**Primary Facilities:** 7/23/2017  
**Microbiology:** 7/25/2017  
**Integrated Quality:** 7/27/2017 |
| **Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)* | None |
| **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 chapter 2, integrated quality assessment |
| ☐ Review & FONSI *(indicate date of review)* | |
| ☐ Review & Environmental Impact Statement *(indicate date of each review)* | |
| **Facilities Review/Inspection** | |
| ✗ Facilities inspections *(indicate date of recommendation)* *(within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter)* *(only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)* | Acceptable 7/23/2017  
See Integrated Quality Assessment  
 ☐ Withhold recommendation  
 ☐ Not applicable |

<sup>6</sup> Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.
### Day of Approval Activities

- **For all 505(b)(2) applications:**
  - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)
    - No changes
    - New patent/exclusivity (Notify CDER OND IO)
- Finalize 505(b)(2) assessment
  - Done
- **For Breakthrough Therapy (BT) Designated drugs:**
  - Notify the CDER BT Program Manager
    - Done
    - Send email to CDER OND IO
- **For products that need to be added to the flush list (generally opioids):**
  - Flush List
  - Notify the Division of Online Communications, Office of Communications
    - Done
- 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
  - Done
- 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
- Take Action Package (if in paper) down to Document Room for scanning within two business days

Reference ID: 4191977
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PETER D FRANKS
12/07/2017
Hello Stephanie,

The IFUs submitted 11/30/2017 are acceptable. Please submit the final versions to the NDA.

Thanks,
Pete

Hi Pete,

Attached are Novo Nordisk’s response to FDA’s comments on the IFU. We have accepted all FDA’s comments and updated the requested figures.

If you have any questions, please let me know.

Thanks,
Stephanie

Hello Stephanie,

Please refer to your New Drug Application (NDA 209637), dated December 5, 2016, and received December 5, 2016, for semaglutide injection.

Attached are the second round of FDA edits of the draft Instructions For Use (IFU) for both pen injectors. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review and consideration.

We do not have any further comments on the Medication Guide at this time, and the previous round of comments provided by Novo Nordisk are acceptable.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of
labeling negotiations in the label. When you add a comment bubble, please state "NN response to FDA change or NN comment."

We ask that you complete your review and return comments as soon as possible or **by 10 am on Friday, December 1, 2017**. You can return the updated labeling via email as the updated versions of the labeling need not be submitted to the NDA until final agreed labeling has been reached.

Please acknowledge receipt of this email and let me know if you have any questions.

Sincerely,

Pete

---

**Peter Franks, M.S.**  
*Regulatory Project Manager*  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
U.S. Food and Drug Administration  
Tel: 240-402-4197  
Peter.Franks@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
PETER D FRANKS
12/04/2017
Hello Stephanie,

The carton/container pieces submitted on November 30 (via the email below), are acceptable. Please submit clean versions of the carton/container pieces to the NDA.

Thanks,
Pete

**Peter Franks, M.S.**  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
U.S. Food and Drug Administration  
Tel: 240-402-4197  
Peter.Franks@fda.hhs.gov

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**From:** SDEC (Stephanie DeChiaro) [mailto:sdec@novonordisk.com]  
**Sent:** Thursday, November 30, 2017 4:58 PM  
**To:** Franks, Peter <Peter.Franks@fda.hhs.gov>  
**Subject:** RE: NDA 209637 semaglutide injection: Round 2 carton/container FDA comments

Hi Pete,

We have accepted all of FDA’s revisions. Per your instructions, I am attaching a “clean” word documents and a PDF proof for the following:

- 1 mg container label
- 1 mg carton
- 0.25/0.5 mg carton (sample and trade)

Please let me know if you were able to receive the e-mail with the 8 attachments.

Thanks,
Stephanie
Hello Stephanie,

Please refer to your New Drug Application (NDA 209637), dated December 5, 2016, and received December 5, 2016, for semaglutide injection. Below please find the second round of edits to the carton/container labeling. We will respond to the electronic/pharmacy systems submission separately. Let me know if you have any questions on the changes below.

We recommend the following be implemented prior to approval of this NDA:

1. Container Label for Pen-injector that Doses 1 mg – To mitigate confusion regarding the strength and concentration of semaglutide, remove [涉密信息]

2. Carton Labeling for Pen-injector that Doses 0.25 mg or 0.5 mg
   a. For added clarity and better readability, revise the following statements:
      i. Change [涉密信息] to “I injected my weekly 0.25 mg dose on the dates below.”
      ii. [涉密信息] to “I injected my weekly 0.5 mg dose on the dates below.”

3. Carton Labeling for Pen-injector that Doses 1 mg
   a. For better readability, revise the following statement:
      Change [涉密信息] to “I injectedAPPEARS THIS WAY ON ORIGINAL

Please submit the revised “clean” versions of each labeling piece for the carton and container labels (i.e., don’t submit annotated versions).

We ask that you complete your review and return comments and labeling pieces as soon as possible or by noon on Friday, December 1, 2017. You can return the updated labeling via email as the updated versions of the labeling need not be submitted to the NDA until final agreed labeling has been reached.

Please acknowledge receipt of this email.

Sincerely,

Pete
Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PETER D FRANKS
12/04/2017

Reference ID: 4189911
Hi Stephanie,

In regards to NDA 209637 semaglutide injection, please see the attached draft PI, which includes grammatical edits in section 13. We remind you that these edits do not reflect the final regulatory decision for this application.

Please accept the tracked changes and submit a clean version of the PI to the NDA by 2pm today.

Please acknowledge receipt of this email and let me know if you have any questions.

Thanks,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PETER D FRANKS
12/04/2017

Reference ID: 4189811
Hello Stephanie,

Attached are the fifth round of FDA edits of the draft PI for NDA 209637 semaglutide injection. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review and consideration.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "NN response to FDA change or NN comment."

We ask that you complete your review and return comments as soon as possible or by EOB today, 12/1/2017. You can return the updated label via email as the updated versions of the label need not be submitted to the NDA until final agreed labeling has been reached.

Please acknowledge receipt of this email and let me know if you have any questions.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

Reference ID: 4189189
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/s/

PETER D FRANKS
12/01/2017
Hello Stephanie,

In regards to NDA 209637 semaglutide injection, please see the recommendations below in response to the submission received on 11/30/2017, pertaining to the electronic/pharmacy systems.

We recommend the following be implemented prior to approval of this NDA:

1. Figure 1 Example Screenshots of How Requested Naming Convention May Appear in an EHR – For added clarity and to mitigate any confusion, revise the following statements:
   a. Screenshot Example 1
      i. Revise “” to “Ozempic 0.25 mg or 0.5 mg doses,...”
   b. Screenshot Example 3
      i. Remove (i.e., change “” to “1”).

Once these revisions are made, please submit the final version with the screenshots to the NDA.

Please acknowledge receipt of this email and let me know if any questions.

Thanks,
Pete

---

**Peter Franks, M.S.**

*Regulatory Project Manager*

Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
12/01/2017
Hello Stephanie,

Attached are the fourth round of FDA edits of the draft PI for NDA 209637 semaglutide injection. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review and consideration.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "NN response to FDA change or NN comment."

We ask that you complete your review and return comments as soon as possible or by noon tomorrow, Dec 1, 2017. You can return the updated label via email as the updated versions of the label need not be submitted to the NDA until final agreed labeling has been reached.

Please acknowledge receipt of this email and let me know if you have any questions.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

Reference ID: 4188396
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/s/

PETER D FRANKS
11/30/2017
Hello Stephanie,

Please refer to your New Drug Application (NDA 209637), dated December 5, 2016, and received December 5, 2016, for semaglutide injection. Below please find the second round of edits to the carton/container labeling. We will respond to the electronic/pharmacy systems submission separately. Let me know if you have any questions on the changes below.

We recommend the following be implemented prior to approval of this NDA:

1. Container Label for Pen-injector that Doses 1 mg – To mitigate confusion regarding the strength and concentration of semaglutide, remove ________________.

2. Carton Labeling for Pen-injector that Doses 0.25 mg or 0.5 mg
   a. For added clarity and better readability, revise the following statements:
      i. Change ________________ to “I injected my weekly 0.25 mg dose on the dates below.”
      ii. Change ________________ to “I injected my weekly 0.5 mg dose on the dates below.”

3. Carton Labeling for Pen-injector that Doses 1 mg
   a. For better readability, revise the following statement:
   Change ________________ to “I injected APPEARS THIS WAY ON ORIGINAL

Please submit the revised “clean” versions of each labeling piece for the carton and container labels (i.e., don’t submit annotated versions).

We ask that you complete your review and return comments and labeling pieces as soon as possible or by noon on Friday, December 1, 2017. You can return the updated labeling via email as the updated versions of the labeling need not be submitted to the NDA until final agreed labeling has been reached.

Please acknowledge receipt of this email.

Sincerely,

Pete

Peter Franks, M.S.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PETER D FRANKS
11/30/2017
Hello Stephanie,

Please refer to your New Drug Application (NDA 209637), dated December 5, 2016, and received December 5, 2016, for semaglutide injection.

Attached are the second round of FDA edits of the draft Instructions For Use (IFU) for both pen injectors. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review and consideration.

We do not have any further comments on the Medication Guide at this time, and the previous round of comments provided by Novo Nordisk are acceptable.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "NN response to FDA change or NN comment."

We ask that you complete your review and return comments as soon as possible or by 10 am on Friday, December 1, 2017. You can return the updated labeling via email as the updated versions of the labeling need not be submitted to the NDA until final agreed labeling has been reached.

Please acknowledge receipt of this email and let me know if you have any questions.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
11/30/2017
Hello Stephanie,

Please refer to your New Drug Application (NDA 209637), dated December 5, 2016, and received December 5, 2016, for semaglutide injection.

Attached are the second round of FDA edits of the draft Instructions For Use (IFU) for both pen injectors. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review and consideration.

We do not have any further comments on the Medication Guide at this time, and the previous round of comments provided by Novo Nordisk are acceptable.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "NN response to FDA change or NN comment."

We ask that you complete your review and return comments as soon as possible or by 10 am on Friday, December 1, 2017. You can return the updated labeling via email as the updated versions of the labeling need not be submitted to the NDA until final agreed labeling has been reached.

Please acknowledge receipt of this email and let me know if you have any questions.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
Hi Pete,

Attached are Novo Nordisk’s revisions to the cartons, container labels, Medication Guide, Instructions for Use and Rx sticker.

I have included the following 16 attachments:

- Carton and Container labels (12 attachments, both a clean word document and also a clean PDF proof). A few comments on the cartons and containers:
  - We did not have space on the container labels to add
  - For the Quick Guide on the cartons, we added arrows between each task,.
    We did however add the text “Go to Give your injection (see opposite flap on box)”
- Rx sticker (1 attachment, word document with tracked changes)
- Instructions for Use (2 attachments, word documents with tracked changes)
- Medication Guide (1 attachment, word document with tracked changes)

Please let me know if you were able to receive the e-mail with the attachments.

Thanks,
Stephanie

Reference ID: 4188632

From: Franks, Peter [mailto:Peter.Franks@fda.hhs.gov]
Sent: Friday, November 24, 2017 1:40 PM
To: SDEC (Stephanie DeChiaro)
Subject: NDA 209637 semaglutide injection: Round 1 FDA comments on IFU, Med Guide, and Carton/Container labeling

Hello Stephanie,

Please refer to your New Drug Application (NDA 209637), dated December 5, 2016, and received December 5, 2016, for semaglutide injection.
Attached are the first round of FDA edits of the draft Instructions For Use (IFU), Medication Guide, and carton/container labeling for NDA 209637. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review and consideration. Please note that the IFU document contains comments on both pen injectors.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "NN response to FDA change or NN comment."

Please submit the revised “clean” versions of each labeling piece for the carton and container labels (i.e., don’t submit annotated versions).

We ask that you complete your review and return comments and labeling pieces as soon as possible or by the end of business on **Tuesday, November 28, 2017**. You can return the updated labeling via email as the updated versions of the labeling need not be submitted to the NDA until final agreed labeling has been reached.

Please acknowledge receipt of this email and let me know if you have any questions.

Sincerely,

Pete

---

**Peter Franks, M.S.**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov

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

PETER D FRANKS
11/30/2017
Hello Stephanie,

Attached are the third round of FDA edits of the draft PI for NDA 209637 semaglutide injection. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review and consideration.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "NN response to FDA change or NN comment."

We ask that you complete your review and return comments as soon as possible or by the end of business on **Tuesday, November 28, 2017**. You can return the updated label via email as the updated versions of the label need not be submitted to the NDA until final agreed labeling has been reached.

Please acknowledge receipt of this email and let me know if you have any questions.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager

Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
11/27/2017
Hello Stephanie,

Please refer to your New Drug Application (NDA 209637), dated December 5, 2016, and received December 5, 2016, for semaglutide injection.

Attached are the first round of FDA edits of the draft Instructions For Use (IFU), Medication Guide, and carton/container labeling for NDA 209637. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review and consideration. Please note that the IFU document contains comments on both pen injectors.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "NN response to FDA change or NN comment."

Please submit the revised “clean” versions of each labeling piece for the carton and container labels (i.e., don’t submit annotated versions).

We ask that you complete your review and return comments and labeling pieces as soon as possible or by the end of business on Tuesday, November 28, 2017. You can return the updated labeling via email as the updated versions of the labeling need not be submitted to the NDA until final agreed labeling has been reached.

Please acknowledge receipt of this email and let me know if you have any questions.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/
PETER D FRANKS
11/27/2017

Reference ID: 4186205
Hello Stephanie,

In regards to NDA 209637 semaglutide injection, we are requesting your assistance in populating the attached excel table.

As part of FDASIA 2012, information on demographic subgroups in clinical trials for newly approved drugs and biologics will be made publicly available on www.fda.gov/drugtrialssnapshot.

The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

1. Information written in consumer-friendly language
2. “MORE INFORMATION” sections that provide more technical, data-heavy information
3. Information that focuses on subgroup data and analyses
4. Links to the PI for the product and to the FDA reviews at Drugs@FDA

Please see the attached Word document for more detailed information and instructions pertaining to this IR. We are hoping to have this completed and returned by 11/30/2017. Let me know if there are questions. Please confirm receipt of this email.

Thanks very much,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
Please complete the shell table for HbA1c results by subgroup using the retrieved dropout analysis method in Section 14 of the proposed product label based on analyses in each of the following studies or combinations of studies:

- Placebo-controlled key efficacy studies 3623 and 3627 combined
- Active-controlled key efficacy studies 3626, 3624, 3625 individually

For the individual active-controlled studies, estimate the treatment effect of each of semaglutide 0.5 mg and semaglutide 1.0 mg relative to the active comparator within subgroups and test for the difference in overall treatment effect across subgroups. For the combination of placebo-controlled studies, estimate the treatment effect of each of semaglutide 0.5 mg and semaglutide 1.0 mg relative to the placebo within subgroups by combining the estimates for individual studies inversely weighted by their variances.

With respect to the interaction tests of the treatment effect by subgroup factor (e.g., race), for an individual study the ANCOVA model should include the factors/terms:

- race (as a categorical factor)
- treatment
- treatment by race interaction term
- the covariates used in the primary analysis

When performing an interaction test of the treatment effect by subgroup factor (e.g., race) for a combination of studies, additionally include the factors/terms:

- race by study interaction term
- treatment by study interaction term
- interaction terms with study for each covariate used in the primary analysis

In addition, please provide a forest plot for each set of subgroup analysis. An example forest plot may be found at: [https://www.fda.gov/Drugs/InformationOnDrugs/ucm532714.htm](https://www.fda.gov/Drugs/InformationOnDrugs/ucm532714.htm) under the MORE INFO section of the question addressing whether there were any differences in how well the drug worked in clinical trials among sex, race and age.

Please provide the code and a description of the statistical methods used to generate these analyses.
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<th>Demographic Parameters</th>
<th>Semaglutide 0.5 mg</th>
<th>Semaglutide 1.0 mg</th>
<th>Control</th>
<th>Treatment Difference (95% Confidence Interval) (Semaglutide 0.5 mg minus Control)</th>
<th>Test for Treatment by Subgroup Interaction (p-value)</th>
<th>Treatment Difference (95% Confidence Interval) (Semaglutide 1.0 mg minus Control)</th>
<th>Test for Treatment by Subgroup Interaction (p-value)</th>
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<td>N</td>
<td>LS Mean HbA1c at baseline</td>
<td>LS Mean Change from Baseline to End of Study</td>
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</table>
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/s/

PETER D FRANKS
11/21/2017
Hello Stephanie,

Attached are the second round of FDA edits of the draft PI for NDA 209637 semaglutide injection. We remind you that these edits do not reflect the final regulatory decision for this application and that portions of the label are still under review and consideration.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "NN response to FDA change or NN comment."

We ask that you complete your review and return comments as soon as possible or by the opening of business on Monday, November 13, 2017 (by 9am EST). You can return the updated label via email as the updated versions of the label need not be submitted to the NDA until final agreed labeling has been reached.

Please acknowledge receipt of this email and let me know if you have any questions.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
11/03/2017
Hello Stephanie,

Please see the attached draft PMR/PMC list for NDA 209637 semaglutide injection. Instructions are included in the first part of the document. The submission can be sent back either via email or as a formal submission to the application. Please respond by close of business on Thursday, 11/9/2017, with any edits marked via tracked changes. Let me know if you have any questions and please confirm receipt of this email.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

Reference ID: 4175934
PMR/PMC list for NDA 209637
OZEMPIC (semaglutide) injection

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

Please submit by email a copy of the PMR and PMC studies to us with the milestone dates indicated below.

- 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.
- For PMCs, include a statement that you agree to conduct these studies/trials.

Postmarketing Requirements

1) Conduct a 26-week, randomized, double-blind, placebo-controlled parallel group study of the safety and efficacy of Ozempic (semaglutide) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive), followed by a 26-week controlled extension. Background therapy will consist of either metformin, insulin, or metformin plus insulin.

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

2) Conduct a medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Ozempic (semaglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Ozempic (semaglutide).

Draft Protocol Submission:
Final Protocol Submission:
Interim Report Submissions:
Study Completion:
Final Report Submission:
**Postmarketing Commitments:**

3) Develop and validate a sensitive assay to assess the neutralizing activity of anti-semaglutide antibodies and its cross-neutralizing effect on native GLP-1.

   Final Report Submission:

4) Conduct a study to assess the incidence of neutralizing antibodies to semaglutide and GLP-1 in subjects treated with semaglutide using the assays developed under PMC #3. The samples may be derived from pre-existing clinical studies. Sample selection criteria will be submitted to and reviewed by the Agency prior to initiation of sample analysis.

   Final Protocol Submission:
   Final Report Submission:
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/s/

PETER D FRANKS
11/02/2017
PeRC Meeting Minutes  
November 1, 2017

PeRC Members Attending:
Lynne Yao  
George Greeley  
Meshaun Payne  
Gerri Baer  
Jacqueline Yancy  
Shrikant Pagay  
Susan McCune  
Lily Mulugeta  
Greg Reaman  
Raquel Tapia  
Thomas Smith  
Daiva Shetty  
Donna Snyder  
Barbara Buch  
Adrienne Hornatko-Munoz  
Robert “Skip” Nelson  
Susan Mccune  
Julia Pinto  
Jingjeng Ye  
Dionna Greene  
Victor Baum
## Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Reference ID: 4180964</th>
<th>NDA 209637</th>
<th>Semaglutide injection (Full Waiver/Partial Waiver/Deferral/Plan) with Agreed iPSP</th>
<th>DMEP</th>
<th>Peter Franks</th>
<th>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
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Semaglutide injection (Full Waiver/Partial Waiver/Deferral/Plan) with Agreed iPSP

- Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- This product triggers PREA as a new active ingredient and has a PDUFA goal date of December 5, 2017.
- The PeRC noted that the plan for this product follows a similar plan for many of the T2DM studies previously required for other products. Entry criteria have been modified to assist with enrollment for these studies.
- The division clarified that the study design for this product are consistent with the study design for other T2DM products (controlled trial with add-on to metformin,
with or without the use of insulin for a controlled period of 26 weeks and an open-label extension for safety of another 26 weeks).

- The division also noted that the required juvenile animal studies have been completed.
- The sponsor provided a study completion date of December 2026. However, the protocol submission and study submission dates were not provided. The protocol submission and study submission dates will need to be provided from the sponsor prior to approval.

- **PeRC Recommendations:**
  - The PeRC concurred with the division’s plan for a partial waiver in pediatric patients less than 10 years of age with T2DM because studies are impossible and highly impractical because there are too few patients and to the deferral in patients 10 to 17 years of age because the product is ready for approval in adults.
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/s/

MESHAUN L PAYNE
11/14/2017
Hello Stephanie,

In regards to NDA 209637 semaglutide injection, please see the information request from DMEPA below. Let me know if you have any questions and please confirm receipt.

We refer to your Amendment submitted on June 7, 2017, for Ozempic (semaglutide) 2 mg/1.5 mL (1.34 mg/mL) PDS290 pen-injector under NDA 209637 proposing to modify the flexible-dose pen-injector. We acknowledge the proposal to remove the 1 mg dose from the flexible-dose pen-injector, which may help to mitigate the selection errors seen in your differentiation study. However, there are other use-related risks that have not been addressed. Specifically, both proposed pen-injector variants have the same strength (2 mg/1.5 mL) and concentration (1.34 mg/mL), which may lead to confusion with regard to orders or prescriptions, and product selection. Please provide your strategies to overcome these use-related risks. We ask that you respond to this information request and return comments as soon as possible, but no later than close of business Monday, October 30, 2017.

Thanks very much,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
10/26/2017
Hello Stephanie,

In follow-up to the discussion at the late-cycle meeting today, we are submitting a formal information request below for the additional data discussed during the meeting.

Please provide the following information by Friday, September 22, 2017:

- Summary statistics for UACR (mg/g) as follows: median change from baseline, and interquartile range, by treatment group (semaglutide 0.5, semaglutide 0.1, and pooled comparator) over time (by study week) for each pool (phase 3, placebo, and CVOT).

- For the re-adjudicated events from open-label studies, the additional data (if any) available to the second adjudication committee and provide information on the number of cases for which additional data were available during the re-adjudication.

- Additionally, provide summary statistics for amylase (U/L) and lipase (U/L) as per the August 30, 2017 Information Request for the phase 3 incretin pool and for the phase 3 non-incretin pool.

Please let me know if any questions and please confirm receipt.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/
PETER D FRANKS
09/19/2017
Hello Stephanie,

In regards to NDA 209637 semaglutide injection, please see the information request below from DMEPA. We ask that you respond to this information request and return comments as soon as possible, but no later than close of business

**Wednesday, September 6, 2017.**

We have the following preliminary pen-injector recommendations and IR for the Applicant:

We reference your labeling submission for Ozempic (semaglutide) injection 1.34 mg/mL (2 mg/1.5 mL), under NDA 209637, on December 5, 2016, and June 19, 2017.

We are informing you of the following recommendations for the pen-injector at this time:

1. To mitigate confusion and prevent users from using the line markings to dial the dose, remove the line markings between doses in the pen-injectors.
2. For the pen-injector that provides doses of 1 mg only, we recommend removing [b] [4].

We may have additional recommendations for your container labels and carton labeling, which will be forthcoming.

In addition, please provide a response to the following information request:

1. We note that you have submitted a label for an “Rx Sticker” in your submission. Please clarify the purpose of the “Rx Sticker,” where it is intended to be placed, and who will place the sticker.

Let me know if you have any questions, and please confirm receipt of this email.

Thanks very much,

Pete

**Peter Franks, M.S.**
*Regulatory Project Manager*

**Division of Metabolism and Endocrinology Products**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation II**
**U.S. Food and Drug Administration**
Tel: 240-402-4197
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/s/

PETER D FRANKS
09/01/2017
Hello Stephanie,

In regards to NDA 209637 semaglutide injection, please see the clinical information request below. A response is needed as soon as possible, and no later than this Friday 9/1/2017. Let me know if you have any questions and please confirm receipt of this email.

Please provide tables with laboratory values (US units) over time [number of patients, mean (SD), median, min, max, change from baseline], for baseline, each subsequent visit, and follow-up visit, by treatment arm, for the following laboratory parameters:

- eGFR (MDRD)
- UACR (mg/g)
- Lipase
- Amylase
- LDL
- HDL
- Triglycerides
- Calcitonin
- AST
- ALT

The descriptive statistics should be presented for each of the three pools: placebo pool, phase 3 excluding CVOT, and CVOT.

Additionally, please provide similar tables for SBP, DBP, and HR.

The following shell table is provided as an example to be filled out.

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Thanks very much,
Pete

**Peter Franks, M.S.**
Regulatory Project Manager

Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/
PETER D FRANKS
08/30/2017
Hello Stephanie,

In regards to NDA 209637 semaglutide injection, please see the information request below from the OBP immunogenicity review team. A response is needed by September 8, 2017. Let me know if any questions, and please confirm receipt of this email.

Questions have been raised regarding the immunogenicity results that you have reported. In order to facilitate review, please provide the following information by September 8:

1) Confirm that the sensitivity of the NAB assay is 32ug/ml

2) Describe each dilution step during ADA testing and titer determination

3) A description of the outlier determination in the calculation of the cut point for the screening and confirmatory ADA assays

4) A sortable table (preferably in excel) that identifies:
   - individual patient that screened positive for ADA
   - individual patient that had confirmed ADA positive samples
   - the titer of each samples that was confirmed positive for ADA. Titers should be calculated considering every dilution step including the acid dissociation steps.
   - The crossreactivity with endogenous GLP-1
   Table format:
   
   Patient#  study #  Sample (week)  screening test result (pos/neg)  confirmatory test result  Titer  crossreactivity to GLP1

5) A summary table for each of the phase III studies with the:
   - number of samples tested for ADA at each time point,
   - number of samples that screened positive at each time point,
   - number of samples that were confirmed positive at each time point,
   - mean titer at each time point.
   - Number of confirmed ADA samples that crossreact with GLP1

Thanks very much,

Pete
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/s/

PETER D FRANKS
08/29/2017
Hello Stephanie,

Please refer to your New Drug Application (NDA 209637), dated and received December 5, 2016, for semaglutide injection.

We also refer to our February 15, 2017, letter in which we notified you of our target date of August 12, 2017, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the “PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017.”

Attached are the initial round of FDA edits of the draft labeling for the Prescribing Information (PI) for NDA 209637. These edits reflect changes made to the labeling that was received from you on March 1, 2017. We remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "Novo Nordisk response to FDA change" or "Novo Nordisk comment." Only use Word document tracked changes and comments. The resubmitted labeling will be used for further labeling discussions.

We ask the you complete your review and return comments by close of business on Friday September 8, 2017.

Please confirm receipt of this email, and let me know if you have any questions.

Kind regards,

Peter Franks

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
08/17/2017
Hello Stephanie,

Please see the Information Request below from our Clinical team which is a follow-up question to the previous IR that was handled via email. Please submit this response to the NDA by **August 8, 2017**, and let me know if you have any questions. Please confirm receipt of this email.

*Please explain why a decision was made not to have a Steering Committee for this application, and whether the role of a Steering Committee was undertaken by a different organization.*

Sincerely,

Pete

---

**Peter Franks, M.S.**  
*Regulatory Project Manager*

Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
U.S. Food and Drug Administration  
Tel: 240-402-4197  
[Peter.Franks@fda.hhs.gov](mailto:Peter.Franks@fda.hhs.gov)
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/s/

PETER D FRANKS
08/03/2017
Dear Ms. DeChiaro:

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

We also refer to the meeting between representatives of your firm and the FDA on August 2, 2016. The purpose of the meeting was to discuss the upcoming submission of your NDA.

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 Martin White, M.S., Regulatory Project Manager at (240) 402-6018.

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
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: August 2, 2016; 11:00 AM-12:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, MD 20903

Application Number: 079754
Product Name: semaglutide subcutaneous

Indication: As an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2D)

Sponsor: Novo Nordisk Inc.

Meeting Chair: Jean-Marc Guettier, M.D.
Meeting Recorder: Martin White, M.S.

FDA ATTENDEES
Division of Metabolism and Endocrinology Products
Jean-Marc Guettier, M.D., Director
William Chong, M.D., Clinical Team Leader
Mahtab Niyyati, M.D., Clinical Reviewer
Calvin (Lee) Elmore, Ph.D., Supervisory Pharmacologist
Pamela Lucarelli, Chief, Project Management Staff
Martin White, M.S., Regulatory Project Manager

Office of Biostatistics, Division of Biometrics II
Mark Rothmann, Ph.D., Statistical Team Leader
Anna Kettermann, Dipl. Math, M.A., Biometrics Reviewer
1.0 BACKGROUND

Semaglutide injection is a long-acting glucagon-like peptide-1 (GLP-1) agonist being developed for the treatment of type 2 diabetes mellitus. The sponsor proposes dosing as a subcutaneous once-weekly injection. Currently, semaglutide is under Phase 3 clinical development.

The initial IND was submitted to the FDA on September 19, 2008. The End of Phase 2 (EOP2) meeting was held on June 9, 2010, during which the Phase 3 development program was discussed.

The Agency provided Type C written responses on May 18, 2012. In the responses, the Agency provided feedback on changes to the sponsor’s CMC, preclinical and planned Phase 3 programs since the EOP2 meeting.

The Agency provided Type C written responses on March 25, 2013. In the responses, the Agency provided feedback on the semaglutide injection nonclinical development program.
The Agency provided Type C written responses on August 16, 2014. In the responses, the Agency provided feedback on the July 15, 2013, and February 17, 2014, FDA advice letters regarding NN9535-3744 (SUSTAIN 6), entitled, *A longterm, randomised, double-blind, placebo controlled, multinational, multicentre trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes.*

The Agency provided Type C written responses on June 12, 2015. In the responses, the Agency provided feedback on the data format and standards for the clinical and nonclinical data to be included in the semaglutide NDA.

The Agency provided Type C written responses on November 13, 2015. In the responses, the Agency provided feedback on the human factors/usability validation test protocol for the PDS290 semaglutide pen-injector.

The Agency provided Type C written responses on April 15, 2016. In the responses, the Agency provided feedback on your proposal to use semaglutide s.c. as starting material for the manufacture of semaglutide drug substance for an NDA scheduled for submission in December 2016.

FDA sent Preliminary Comments to Novo Nordisk Inc. on July 29, 2016.

2.0 DISCUSSION

2.1 Clinical

*Question 1:* Does the Agency agree to the April 18, 2016, safety database cut-off for the NDA?

*FDA Response to Question 1:* Your proposed safety database cut-off date is acceptable.

**Discussion:** No discussion occurred.

*Question 2:* Does the Agency agree to the proposal for inclusion of the safety data in the NDA as outlined above for the two ongoing trials?

*FDA Response to Question 2:* Your proposal for inclusion of the blinded safety data from trials 4215 and 4216 as of the April 18, 2016, NDA cut-off date is acceptable. If safety issues are identified that require an assessment of unblinded data from these trials, unblinding will be requested.

**Discussion:** No discussion occurred.

*Question 3:* Does the Agency agree with the Novo Nordisk proposal that the NDA will only include data from semaglutide s.c. once-weekly trials in T2DM?
**FDA Response to Question 3:** Clarify why data from once daily subcutaneous semaglutide, oral semaglutide, semaglutide for NASH, and semaglutide for obesity are not pertinent to the safety review of once weekly subcutaneous semaglutide.

**Discussion:**

The sponsor stated that the data from subcutaneous semaglutide for the treatment of NASH and for obesity would not be relevant as these are different indications. Some data from the oral semaglutide studies would be included (i.e., data from the subcutaneous semaglutide arm from an oral semaglutide trial). The Agency stated that this was acceptable.

**Question 4:** Does the Agency agree that the pre-specified primary and sensitivity analyses are adequate to demonstrate the effect and describe the effect size of semaglutide for both HbA1c and body weight?

**FDA Response to Question 4:** Our goal is to provide the most appropriate estimate of the treatment effect. We are interested in estimating the treatment effect based on the intent-to-treat (de facto) estimand. The analysis for change in HbA1c should account for missing data in a fashion consistent with what the measurement would have been, had it been measured. The MMRM used in your primary analysis likely does not appropriately address missing data as it treats the behavior of missing data for those patients who are off-treatment to be the same as that of observed data for those patients who are on-treatment in the same treatment arm. We generally consider it inappropriate to represent the missing data from subjects who do not adhere to therapy by the data from those subjects on the same arm who adhere to therapy. We recommend addressing missing data on the primary endpoint by having the missing data from subjects who do not adhere to therapy represented by the data from those subjects on the same arm that also did not adhere to therapy but had the measurement for the primary endpoint.

From the text of your briefing package, we note that for the missing data analysis, you are planning to utilize multiple imputations approach with 100 imputations. It is known that the precision of estimation depends on the number of imputations; therefore, we encourage you to explore the analysis utilizing a larger number of imputations.
We were not able to locate information about missing data on HbA1c and body weight. Please provide missing data and retrieved dropout rates by study and treatment group.

**Discussion:** The sponsor will include all collected primary endpoint data in an analysis. The analysis will utilize a multiple imputation approach based on a retrieved dropout model. More than 100 imputations will be used. The specific number of imputations will be based on the precision of the estimate; specifically, the goal is to achieve precision in the second decimal. The sponsor stated that the analysis would include all randomized and exposed subjects. This type of analysis will also be performed for secondary endpoints. These analyses will be performed for the SUSTAIN 1-5 studies. The sponsor will provide a summary in the NDA submission on the reasons for missing data.

During the meeting, the sponsor presented a table with data illustrating dropout by trial. The Agency asked whether the number of dropouts were similar between different arms within each trial, the sponsor stated that the numbers were similar between arms. During discussion, the Agency asked to clarify whether the trials were blinded. The sponsor stated that only SUSTAIN 3 and SUSTAIN 4 were open-label studies among all phase 3 trials and all other SUSTAIN trials were blinded. The sponsor also stated that very few subjects were not exposed to protocol treatment and that some had HbA1c data collected. The Agency stated that when the NDA is submitted, they would determine whether it was impact to exclude from the analysis subjects not exposed to protocol treatment.

**Question 5:** Does the Agency agree to the planned presentation for the completed phase 2 and 3a semaglutide s.c. trials in the Summary of Clinical Efficacy/ISE?

**FDA Response to Question 5:** We agree with your proposal of not pooling the efficacy data from the trials listed in your meeting package. We note that you intend to include the two Japanese studies (study 4091 and study 4092) in your analysis of efficacy. From review of the submitted meeting package, it appears that the primary objective of these studies is safety in the Japanese population. Explain your rationale for including these two studies as part of your efficacy analysis.

Novo Nordisk will address \((b)^{(4)}\) (glycemic control in T2D)\(^{(b)}\) (glycemic control in T2D) within a single SCE\(^{(b)}\). This is consistent with the ICH M4E guidance.

**Discussion:** The sponsor stated that the two Japanese studies were performed at the request of the Japanese regulatory authorities and that the required primary endpoint for these studies was treatment emergent adverse events. However, the studies were designed to also perform analyses for efficacy (i.e., glycemic lowering) similar to the SUSTAIN trials. The Agency asked whether the Japanese trials were reflective of medical practice in United States (e.g., whether doses of active comparators were consistent with U.S.-approved doses). The sponsor replied that
the sitagliptin in the comparator arm is not dosed differently in Japan compared to the U.S. Following this discussion, the Agency agreed that it was acceptable to submit the Japanese studies for review of glycemic efficacy.

**Question 6:** Does the Agency agree to the approach of submitting a single SCE?

**FDA Response to Question 6:** Your proposal of submitting a single SCE is acceptable. The data should be presented in a format that would allow for efficient review of the efficacy data.

**Discussion:** No discussion occurred.

**Question 7:** Does the Agency agree to the presentation and evaluation of safety in the ISS?

**FDA Response to Question 7:** For the summary of safety, you propose to present data for a pool of the five Phase 3 studies (studies 3623, 3624, 3625, 3626, 3627) and the two Japanese studies (4091, 4092). You also propose to present the cardiovascular outcome trial (study 3744) separately from the Phase 3 pool.

We agree that data from the cardiovascular outcomes study can be presented separately. To facilitate the safety review, we ask that you present the following additional pools:

1. A pool of placebo-controlled studies (i.e., studies 3623 and 3627);
2. A pool of the 5 multi-national Phase 3 studies (i.e., studies 3623, 3624, 3625, 3626, 3627);
3. A pool of the 2 Japanese safety studies (studies 4091, 4092).

When presenting the safety findings, we request that you present the findings by individual dose of semaglutide, pooled semaglutide, compared to placebo, compared to active comparator, and compared to all comparators (as applicable).

You mention that for certain safety parameters such as pancreatitis or hypoglycemia you may focus on individual trials (trial or subject sub-setting) rather than pooling due to confounding introduced by the comparator or the background medications in the trials. Explain your sub-setting strategy for these trials.

Please explain how you intend to characterize the efficacy and safety of adding semaglutide to sulfonylurea therapy without a dedicated trial to evaluate the effect of adding semaglutide to patients inadequately controlled on background sulfonylurea.

**Discussion:** The sponsor agreed with adding additional pools of placebo-controlled studies (i.e. SUSTAIN 1 and 5) and multi-national phase 3 studies (i.e. SUSTAIN 1-5). However, given differences between the 2 Japanese trials, Novo Nordisk
proposed not to submit a separate pool of these studies, but to provide the data as individual trials. The Agency found this acceptable.

The sponsor stated that they intend to further subset based on safety areas of special interest to avoid confounding by comparators (e.g., for adverse events such as pancreatitis a subset of the broad pool excluding incretin mimetics in the comparator arm would be used). For the hypoglycemia analysis, the sponsor intends to pool patients based on background therapy from different trials (i.e, add-on to sulfonylureas (SU), add-on to insulin, add-on to SU and insulin, add-on to oral antidiabetic (OAD [not SU]), and monotherapy).

The Agency inquired whether the sponsor has conducted any standalone trial with metformin as background medication. The sponsor said they have not studied a pure population on metformin. However, SUSTAIN 2 has largely metformin as background medication.

The Agency stated that the pooling strategy (to pool patients from different trials) seems confusing and asked the sponsor to clarify how they intend to pool subjects from trials with different trial lengths and randomization ratios. Also, the Agency stated that the approach that involves pooling of data from studies with different randomization ratios and potentially also different adverse event rates is subject to confounding (e.g., Simpson’s Paradox). The sponsor acknowledged that their suggested pools combined trials with different lengths.

The Agency commented that the subcutaneous semaglutide program is not typical for what is generally conducted for diabetes products. The Agency suggested that the sponsor consider a meta-analytical approach to analysis of such pools. The sponsor proposed that they intend to provide the results by trial and include only the final results using meta-data. The sponsor asked the Agency how they can further clarify their development program, to which the Agency replied that further comments may be given in post meeting minutes.

The sponsor inquired why the Agency requested inclusion of a placebo arm for the tables from the broad pool. The Agency stated that the placebo comparison is the most appropriate for assessing safety and that active comparators may mask events or issues. The Agency emphasized that our review of safety would focus on comparison to placebo, particularly in the assessment of common adverse reactions. The other pools which include active comparators would primarily be used by the Agency for rare adverse reactions.

The sponsor discussed how they intend to evaluate the efficacy and safety of semaglutide in combination with SUs. The sponsor explained that in the Phase 3 trials, more than 1,400 subjects were exposed to semaglutide on a background of SU (alone or in combination). Additionally, there were subjects on SU alone as background medication in the cardiovascular outcomes trial (i.e., SUSTAIN 6). The Agency asked if there was a period of time in the CVOT trial in which additional
antidiabetic drugs were not allowed to be added to which the sponsor responded that there was no period where additional antidiabetic drugs were prohibited. The Agency commented that this may make the interpretation of efficacy and safety of semaglutide in combination with SU from SUSTAIN 6 difficult given potential changes in medication. The sponsor was of the opinion that there would be minimal additional medications added to confound the analyses given an efficacy endpoint of 30 weeks.

**Question 8:** Does the Agency agree with the proposed subgroups for the evaluation of efficacy and safety?

**FDA Response to Question 8:** The proposed subgroups for the evaluation of efficacy and safety appear reasonable. For your HbA1c analysis, please include an analysis that examines treatment effect by baseline HbA1c. If needed, additional sub-group analyses may be requested.

**Discussion:** No discussion occurred.

**Question 9:** Does the Agency agree to the proposal for addressing the applicability of the non-US data for the US population?

**FDA Response to Question 9:** You have proposed to not perform analyses of the U.S. population but to perform analyses based on region. We ask that you provide a breakdown of which countries constitute the North America region in your studies, and the proportion of subjects that come from each country in this region.

The above would also be adequate for the assessment of the 1.8 risk margin based on the cardiovascular outcome trial SUSTAIN6 (Trial 3744).

**Discussion:** No discussion occurred.

**Post-meeting comment:** Following the meeting, the sponsor clarified that the North American region consisted of the United States and Canada. The table below provides the proportion of subjects that come from each country in the North American region. Of note, SUSTAIN 2 did not include any subjects from the North American region.

<table>
<thead>
<tr>
<th></th>
<th>SUSTAIN 1, 3, 4, and 5</th>
<th>SUSTAIN 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total N (%)</td>
<td>Semaglutide N (%)</td>
</tr>
<tr>
<td>North America</td>
<td>1157 (100)</td>
<td>875 (100)</td>
</tr>
<tr>
<td>United States</td>
<td>1118 (97)</td>
<td>852 (97)</td>
</tr>
<tr>
<td>Canada</td>
<td>39 (3)</td>
<td>23 (3)</td>
</tr>
</tbody>
</table>

As the North American region consists of nearly all United States subjects, the proposed approach of doing analyses by region seems reasonable.
**Question 10:** Does the Agency agree to the proposal for the 4 month safety update?

**FDA Response to Question 10:** The proposed contents of your 4 month safety update appear reasonable.

**Discussion:** No discussion occurred.

**Question 11:** Does the Agency agree that it is relevant to request a waiver not to conduct a trial in children and adolescents with T2D?

**FDA Response to Question 11:** Your proposal to request a waiver not to conduct a trial in children and adolescents with type 2 diabetes mellitus seems reasonable. The final determination of the acceptability of your request will occur during the review of your application.

**Discussion:** No discussion occurred.

### 2.2 Statistical

**Question 12:** Does the Agency agree to the planned ADaM domains that will be included for the phase 3a trials as part of the NDA?

**FDA Response to Question 12:** Your proposed ADaM domains appear reasonable; however, we note that you have not provided specific information on your cardiovascular outcome trial, Trial 3744. We request that you follow a similar format for the datasets for study 3744 as was requested in correspondence regarding the LEADER trial. Please refer to Attachment 2 for details.

**Discussion:** The sponsor stated that datasets will include all information collected according to protocol. “Clinical events” will be included in an adjudication dataset. “Deaths” will be included in an adjudication dataset. The sponsor stated that events adjudicated as “no” will be included in the adverse event dataset. Accidents, dyspnea, and orthostatic hypotension are found in the adverse event dataset. The standalone procedure dataset as requested by the Agency will not be provided. However, revascularization will be in the adjudication dataset and other procedures such as amputation, surgeries, and dialysis will be in the adverse event dataset. The sponsor stated that ECG metrics beyond an interpretation of the ECG test, were not measured in the SUSTAIN program. The Agency asked whether the sponsor will provide flags, such as the on-treatment, +7 day, and +30 days flags for the CVOT trial. The sponsor replied yes and added that they would provide the above flags for the Phase 3 global trials as well.

**Question 13:** Does the Agency agree to the suggested data format approach for phase 2?
FDA Response to Question 13: The suggested data format to provide SDTM data, define.xml, and an SDTM-annotated Case Report Form (CRF) along with legacy analysis data is acceptable as long as you provide the same unique subject identifier in both the SDTM and the legacy analysis data sets.

**Discussion:** No discussion occurred.

Question 14: Does the Agency have any comments on the format of the sample datasets provided?

FDA Response to Question 14 In general, the format of the sample datasets provided in your meeting package seems reasonable. We have the following comments:

1. Review of your sample data shows that there are inconsistencies across data-sets in providing study day as well as onset and end date of a variable. If applicable to the data-set, we ask you to be consistent in providing the study day and the start and end date, if relevant, across all the data-sets.

2. We ask that you provide a baseline flag, post-baseline flag, post-baseline grouping (for all relevant variables), baseline values, and change from baseline values as separate variables for all parameters.

3. Provide flags to designate type of specimen e.g. urine, plasma.

4. We request that you flag the subjects who are treated with sulfonylureas as background therapy (as sulfonylurea monotherapy and in combination with other antidiabetic drugs).

5. In order for us to conduct a comprehensive review of this submission we would need your analysis datasets. Based on our experience with your previous submissions, we would like you to make sure that analysis datasets are controlled for quality. Specifically, all observations excluded from the analysis need to be flagged and clarifications for those exclusions should be reflected in the dataset. Please make sure that visit numbers are congruent with chronological order of observations. The data issues described above could be a potential cause for us not being able to adequately evaluate the outcomes of your studies.

6. If variable naming across efficacy datasets differ between studies, please provide a table that clarifies those differences.

**Discussion:** The sponsor stated that they will incorporate lessons learned from previous applications and intends to submit a request for a dataset walkthrough once the NDA has been submitted.

Post-meeting comments: Following the meeting, the sponsor submitted a request for further clarifications:

For #1, the Agency commented there were inconsistencies across the sample data-sets in providing study day as well as onset and end date of a variable. Novo Nordisk
has re-reviewed the submitted sample datasets and is unable to locate the inconsistencies. 
For #2, the Agency requested a post-baseline grouping flag. 
For #6, the information will be provided in the NDA.

*Would the Agency be able to share specific details of the inconsistencies found in the datasets?*

**FDA Response:** The following inconsistencies were noted in review of the sample datasets submitted in the pre-NDA package:

For NN9535-3623:
- ADHYPO: Dose not have Analysis Relative Study Day of Event
- ADA1CEN: Dose not have Analysis Date of Measure Taken

For ISS:
- ADCM: Does not have Study Day of Start or End of Medication Use
- ADHYPO: Does not have Study Day of Event

*Would the Agency be able to clarify what is meant by ‘post-baseline grouping’?*

**FDA Response:** The phrase ‘post-baseline grouping’ was intended to refer to categorical variables. As an example, in your submitted ADSL sample data set you have provided categories for Body Mass Index (BMI) and baseline HbA1c.

It is unclear what additional categorical variables you will be analyzing, but we request that you also identify these categorical variables as baseline or post-baseline in your datasets.

*Question 15: Does the Agency have any comments on the excerpts from the Reviewer’s Guide?*

**FDA Response to Question 15:** We do not have comments on the Reviewer’s guide at this time.

The pooled trial database will be in CDISC ADaM standard covering all the analysis data from the phase 1 and 2 trials based on legacy analysis data and the phase 3a data based on ADaM data; all trials listed in the Study Data Standardization Plan will be included. The “source/derivations/comments” field in the define.xml will together with the Analysis Data Reviewers Guide explain how the technical pooling of the mixture between Legacy and ADaM data of a variable has been done. The full metadata documentation is specified for each individual trial for phase 3a in the define.xml. For phase 1 and 2 this will be covered in the define.pdf in accordance to the legacy standards. Novo Nordisk believes this is sufficient to ensure traceability from the pooled database towards the legacy and ADaM analysis data.
**Discussion:** No discussion occurred.

**Question 16: Does the Agency agree to this approach?**

*FDA Response to Question 16:* This approach seems reasonable. See our previous comments on ensuring that unique subject identifiers match across Legacy and SDTM datasets. We may request additional clarification if questions arise regarding traceability.

**Discussion:** No discussion occurred.

Additional FDA comments:

**Statistics:**

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. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

**Discussion:** No discussion occurred.

2. The analysis dataset documentation (Define.pdf) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables.

**Discussion:** No discussion occurred.

3. To improve reproducibility of your findings, please include a well-commented SAS codes for all primary and secondary endpoints. Please provide a separate code for each type of analysis. Also include in the submission the SAS programs that are used to create the derived datasets for the efficacy and safety endpoints and pooled data.

**Discussion:** No discussion occurred.

4. 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.

**Discussion:** No discussion occurred.

5. In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

**Discussion:** No discussion occurred.

**Clinical Pharmacology:**

6. Is the formulation of semaglutide used for the Phase 3 clinical trials identical to the to-be-marketed formulation of semaglutide? If not, you need to provide justification for the differences of the formulations before submission of the NDA for semaglutide.

**Discussion:** No discussion occurred.
7. Provide the information on the formulation of semaglutide used in all Phase 1, 2, and 3 studies (preferably in a tabular format) in the Summary of Biopharmaceutic Studies and Associated Analytical Methods section in future NDA submission.

   **Discussion: No discussion occurred.**


   **Discussion: No discussion occurred.**

9. Provide the following information in all datasets of Clinical Pharmacology studies in SAS transport files (.xpt):
   - Treatment
   - Sequence
   - Period

   **Discussion: No discussion occurred.**

**Immunogenicity:**

10. Until the validated Immunogenicity assays have been reviewed by the Agency, you should bank sera under appropriate conditions and in sufficient quantities to allow for re-testing if deemed necessary.

   **Discussion: No discussion occurred.**

**Combination Product:**

11. The proposed semaglutide drug product that is to be delivered via the PDS290 pen injector is a combination product subject to 21 CFR Part 4 “Current Good Manufacturing Practice Requirements for Combination Products” accessible at: [https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products](https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products).

   **Discussion: No discussion occurred.**


   **Discussion: No discussion occurred.**

13. Device data-related comments will be provided as post-meeting comments.

   **Discussion: No discussion occurred.**

Reference ID: 3980435
The future marketing application for this combination product should contain documentation to address the following:

1. A description of the complete system, including individual device components, configurations, and packaging in its final form within the co-labeled or co-packaged medication configuration;

2. Product labeling and instructions for use which describe the process of using the device to deliver the medication;

3. A complete description of device requirements and specifications, which fully describe the attributes of the system and their acceptability in the context of the intended use of the system and the medication being delivered;

4. Design verification and validation information in the form of test reports and other activities which verify the individual requirements and specifications for the system and validate the system is fit for its intended use within the context of the medication being delivered;

5. Risk analysis information which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states. Such an analysis should clearly describe system hazards, mitigations implemented to reduce the risk of those hazards, effectiveness of the mitigation, as well as conclusions of the acceptability of system risks within the final finished system;

6. Verification and validation of the following specific system attributes should be documented. Note that this is not a complete list, as it does not include device-specific requirements and hazards which will be associated with the specific system use, design, and risks:
   a. All critical system requirements;
   b. Adherence to standards, where appropriate (e.g. luer connections, needle design);
   c. Physical retention of device components and resistance to separation during use;
   d. Freedom from system leakage;
   e. Forces required to attach or detract system components;
   f. Accuracy of delivered dose when administered;
   g. Needle depth of delivered dose when administered (for injection systems);
   h. Sharpness/dimension of delivery needle bevel (for injection systems);
   i. Freedom from unacceptable damage to or loss of medication volume due to mechanical forces exerted by the system;
j. Freedom from unacceptable damage to or loss of medication volume due to materials used within the system;

k. Biocompatibility of system components, where required (i.e. fluid or tissue contact);

l. Resistance of system components to aging to a period equal to or greater than that labeled for expiration;

m. Resistance of system components to damage from shipping;

n. Verification of system attributes after preconditioning to sterilization, aging, and shipping;

7. The lot release criteria should include the essential performance requirements of the device constituent (e.g. dose accuracy, needle extension, activation force, audible and visual feedback mechanisms).

8. Please clarify if the PDS290 pen injector used in clinical studies is identical to the to-be marketed device. Please describe any differences and provide a justification for why the differences will not impact results of the validation of the device.

9. The biocompatibility evaluation should be performed on the final finished device. If you are leveraging biocompatibility information from a previous device, provide a certification statement that all materials, manufacturing and processing are identical between the two pens. If the to-be marketed device is a different please address the impact of this change on the applicable biocompatibility endpoints in your evaluation.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed during the meeting and agreed upon in the preliminary comments conveyed prior to the meeting. These agreements are noted above.
• All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

• In the background package, the sponsor stated that a Risk Evaluation and Mitigation Strategies (REMS) would be submitted. We expect that the NDA submission will include a REMS addressing the risk of MTC and aligned with the REMS for your other currently approved GLP-1 agonist products.

• Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

4.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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/UCM360507.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.
5.0 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 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 related to pregnancy, lactation, and females and males of reproductive potential
- 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 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft 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).

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

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.

7.0 ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

8.0 ACTION ITEMS
There were no action items.

9.0 ATTACHMENTS AND HANDOUTS

Attachment 1 - Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format
Attachment 2 – Statistical Comments
Attachment 3 - The attached slides were presented by Novo Nordisk Inc. at the meeting.
Attachment 1

Technical Instructions:
Subverting 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.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item¹</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
  ➜ [m5]
    ➜ datasets
      ➜ bimo
        ➜ site-level
```

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.

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

eCTD Backbone Specification for Study Tagging Files v. 2.6.1  

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

For general help with eCTD submissions:  ESUB@fda.hhs.gov
Attachment 2:

We request you follow a similar format for your submitted datasets for the subcutaneous semaglutide cardiovascular outcome study as was communicated in correspondence for the liraglutide cardiovascular outcome trial (i.e., LEADER). We suggest you provide a similar format, as applicable, for the Phase 3 studies as well.

**Demographic dataset:**
Age groups  
Region  
Duration of diabetes  
Smoking  
Population indicators  
Trial dates (e.g. randomization date, start of treatment, etc.)

Subject Disposition: This dataset should contain all subject disposition information (e.g. screened, enrolled, treated, discontinued treatment or trial and reasons for discontinuation).

**Clinical Events (CE) dataset:**
Date of CE onset  
Date CE resolved/worsened/ resulted in death  
Study Day CE Onset  
Study Day CE resolved/worsened/ resulted in death  
MACE  
MACE+  
Hypoglycemia Events  
Accidents (including falls)  
Dyspnea  
Orthostatic Hypotension  
Malignancy (thyroid, pancreas, breast)  
Adjudication Y/N; Investigator vs. Board  
On treatment flag  
On treatment +7 days flag  
On treatment +30 days flag

**Concomitant medication dataset (at randomization):**
Demographic Dataset concomitant medication at randomization/baseline-if not included in the demographic dataset  
Anti-hypertensive  
Statins  
Antidiabetic medications  
On treatment flag  
On treatment +7 days flag  
On treatment +30 days flag

**Hypoglycemia dataset:**
Hypoglycemia ADA categorization
Time of event (date)
Treatment-emergent flag

**Procedures dataset:**
Date of Procedure
Study Day of procedure
Reason for Procedure
Amputation
Surgeries
Dialysis
On treatment flag
On treatment +7 days flag
On treatment +30 days flag

**Death dataset:**
Date of Death
Study Day of Death
Cause of Death
Reported adverse event(s) results in death /before death
Adjudication Y/N; Investigator vs. board
Cardiovascular death
Treatment-emergent flag

**Adverse Events (AE):**
Date of Randomization
Date of treatment discontinuation
Date of trial discontinuation
Date of AE onset
Date of AE Resolution
AE ongoing at end of study
Study Day AE Onset
Study Day AE Resolved
Tox Grade
AE leading to discontinuation
Hospitalization Y/N
Hospitalization prolonged Y/N
Hospitalization for heart failure
Stroke type flag (ischemic or hemorrhagic)
Adjudication Y/N  Investigator vs. Board
On treatment flag
On treatment +7 days flag
On treatment +30 days flag
SMQ flag
Injection site flag
Allergic reaction flag
All MedDRA hierarchy terms (i.e. SOC, HLG, HLT, LLT, PT term, investigator reported term)

**Time to event dataset:** This dataset should contain all information relevant for time-to-event analyses of adjudicated endpoints, for example, subject identification, demographics, treatment group, population flags, cardiovascular composite endpoint(s), other adjudicated endpoints, individual components of composite endpoints, censoring flags and dates, event dates, and risk factors. All composite endpoints specified in the protocol (e.g. MACE), and their respective components, as well as all-cause mortality, should be accounted for in this dataset. This dataset should also contain variables relevant for subgroup analyses specified in the protocol. The structure of this dataset should be one record per subject per analysis population per event.

**SMQ dataset:**
- SMQ broad
- SMG narrow
- Custom SMQ (if any)

**Lab Data:**
- Study day specimen collected
- Baseline value for ALL laboratory measures
- Change from baseline value
- Change from previous value
- Baseline flag
- Post-Baseline Flag
- Tox Grade
- Baseline Tox Grade
- On treatment flag
- On treatment +7 days flag
- On treatment +30 days flag

**HbA1c Categories:**
- HbA1c Baseline Category
- HbA1c Post-Baseline Category

**eGFR: Categories (MDRD):**
- 15-29 mL/min/1.73m2
- 30-44
- 45-59
- 60-89
- 90 plus
- eGFR: Baseline Category
- eGFR: Post-Baseline Category

**Creatinine Categories:**
- Creatinine Baseline Category
- Creatinine Post-Baseline Category
ALBCREAT Categories:
<30 mg/g
>300 mg/g
ALBCREAT Baseline Category
ALBCREAT Post-Baseline Category

Microalbumin Categories:
Microalbumin Baseline Category
Microalbumin Post-Baseline Category
Normalized to upper limit laboratory values for all collected
Normalized to lower limit laboratory values for all collected

Vital signs:
Study Day of Test
Baseline value
Change from Baseline value
Change from Previous value
Baseline Flag
Post-Baseline Flag
Normal Range Reference Range Low
Normal Range Reference Range High
Treatment-emergent flag

ECG metrics beyond Interpretation of the ECG test:
QTcB - Bazett's Correction Formula (msec)
QTcF - Fridericia's Correction Formula (msec)
Summary (Mean) Heart Rate (BEATS/MIN)
Summary (Mean) PR Duration (msec)
Summary (Mean) QRS Duration (msec)
Summary (Mean) QT Duration (msec)
Summary (Mean) RR Duration (msec)

Additional comments:

1. **Documentation of how tables and figures were generated:**
In your study report, for all figures and tables, include a reference to the data-set name, variable name, inclusion/exclusion criteria (or flags) used to generate data. This information should be sufficient to re-generate the figure or table. If more than one data-set was used to create a table, for each data-set, specify the variables and the inclusion or exclusion criteria used. One suggestion is to have a hyperlink to this additional information at the end of each table in the CSR. See examples below:

Sample Table 1: Adjudicated adverse events by preferred term listing

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Semaglutide 0.5 mg</th>
<th>Semaglutide 1 mg</th>
<th>Comparator</th>
</tr>
</thead>
</table>
Sample Table 2: Adjudicated adverse events by preferred term listing for Males

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Semaglutide 0.5 mg</th>
<th>Semaglutide 1 mg</th>
<th>Comparator</th>
</tr>
</thead>
</table>

Consistency of counts across datasets: the adjudication flag in the adverse event dataset should match the adjudicated events in the Analysis Time to Event (ADTTE) dataset and the Adjudicated Events Analysis (ADADJ) dataset.

2. **Information about how outcome events were gathered, adjudicated, and presented in the datasets should be clear.**
   a. For those patients ill enough, or who died, who did not return for in-person visits, what process did your staff have to collect medical history, record and inform the adjudication committee about the outcome events of interest, namely CV death, non-fatal MI, and non-fatal stroke? Was there an algorithm for staff to follow regarding pursuing AE if in the initial phone call they heard that the patient had a suspicious symptom such as a hemiparesis? Were they instructed to follow-up and gathered appropriate source documents for all such cases so that the adjudication committee could arbitrate on all the cases that might have had a fatal or serious outcomes of interest such as fatal and non-fatal MI or stroke?
   b. When was the AE/outcome form filled out, at the time of the visit, or after the initial set of source documents arrived?
   c. For all no-accessible deaths, elaborate on the causes of these deaths and provide a breakdown in a table. An attempt to further classify “no-accessible deaths” that were deemed cardiovascular will be helpful as well as how they were distinguished from “non-CV causes of death.” Examples might include categories that would be useful to understanding the decision-making process. More than one category might be possible or may use other categories that better describe how the decision was adjudicated.
      - examination findings incompatible with Echo and ECG,
      - ECG not available to make determination, but other findings suggestive
      - Echo, physical examination not available to make determination
      - History inadequate, such as dead in bed, without other documentation or limited other information
      - limited or no medical records, but suggestive history
      - autopsy only
      - only death certificate available without even history
   d. How did the adjudication committed adjudicate the cause of death i.e. last cause that was documented? Was it an underlying cause/ contributing cause, etc.?
3. **Summary of regulatory history**: as part of your submission, please include a regulatory history including the dates of protocols and amendments that were submitted, the dates of meetings discussing the study, etc.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Hyperlink (if pertinent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Protocol finalized hyperlink</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>1st subject enrolled</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>1st subject randomized</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>Protocol amendment 1</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>FDA Meeting to discuss X</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>Event adjudication charter version change</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>Final database lock- database un-blinded</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>NDA submission to FDA</td>
<td></td>
</tr>
</tbody>
</table>

4. **DMC meeting minutes**: Please submit all DMC meeting minutes.

5. **Protocol submission**: As part of your NDA submission, please include ALL protocol versions and protocol amendments with track changes.
   a. Include a summary document that briefly describes the changes to this document

6. **Statistical analysis plan submission**: Please include the date of the original SAP and the dates of all the SAP amendments including the track changes of these documents.
   a. Include a summary document that briefly describes the changes to this document

7. **Event Adjudication Committee Charter**: Please include the original Clinical events committee charter and the dates of all subsequent modifications to charter. Submit all Charters to the NDA.
   a. Include a summary document that briefly describes the changes to this document

8. **Steering committee minutes**: Provide the steering committee meeting minutes.

9. **The following dates should be made clear in your submission. All of these dates should also be provided as variable names in your datasets**
   - Dates of Study Conduct
   - Date the first subject was randomized
   - Date the last subject was randomized
   - Date of the last subject’s last visit
   - Date of database lock
   - Date the study was unblended

10. **Silent myocardial infarction**: Please be clear in your submission on how silent MIs were diagnosed i.e., was this endpoint based on investigator review? on a local (or central) ECG machine’s interpretation only? Once a silent MI was detected on an ECG, was the event sent for adjudication?
11. **Communication for data handling:** For all parties involved in data handling, provide a figure showing the flow of communications between parties, in particular making note of which parties were blinded and which parties were un-blinded.

12. **Sample charts:** For all the adjudicated categories, please create flow charts as shown in the examples below. Create one chart for the semaglutide arm (combined 0.5mg and 1 mg) and another separate chart for the placebo, active control and pooled comparator arm.
   - For all figures, the N’s in the subordinate categories should add up to the parent category (i.e., for the death table the known cause + unknown cause = death total).
   - For all figures, please include reference of how the information is derived from the datasets provided. Specifically data set used, variables used and other pertinent selection criteria. Reference to a program code that may be submitted in the application is not sufficient documentation.

13. **Concomitant meds:** please fill in the following shell table and provide with your NDA submission.

<table>
<thead>
<tr>
<th></th>
<th>Sema 0.5 N=</th>
<th>Sema 1 N=</th>
<th>Placebo N=</th>
<th>Active comparator N=</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihypertensives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ACE inhibitors/ARBs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Beta-blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Calcium channel blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mineralocorticoid receptor antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Renin inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Platelet aggregation inhibitors excluding heparin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Heparin group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Vitamin K antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Direct factor Xa inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Direct thrombin inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lipid lowering drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Statins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Fibrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ezetimibe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sema 0.5 N (%)</td>
<td>Sema 1 N (%)</td>
<td>Placebo N (%)</td>
<td>Active comparator N (%)</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
<td>--------------</td>
<td>---------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Niacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihyperglycemics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP-4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others specified by class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For all the adjudicated categories, please create flow charts as shown in the examples below. Create one chart for the semaglutide arm (combined 0.5mg and 1.0 mg) and another separate chart for the placebo arm.

For all figures, the N’s in the subordinate categories should add up to the parent category (i.e., for the death table the known cause + unknown cause= death total).

For all figures, please include reference of how the information is derived from the datasets provided. Specifically data set used, variables used and other pertinent selection criteria.
Sample name: Figure X- death SEMAGLUTIDE 0.5 +1.0 mg

- **All-cause mortality total**
  - **Known cause of death**
    - **Non-cardiovascular death**
      - **Pulmonary causes**
      - **Renal causes**
        - N (%)
      - **GI causes**
      - **Hepato-biliary causes**
      - **Etc.**
  - **Cardiovascular death**
    - **Sudden cardiac death**
    - **Acute MI**
      - N (%)
    - **Heart Failure**
    - **Stroke**
    - **Other CV causes (specify what are these)**
    - **Etc.**
Sample name: Figure X- AMI SEMAGLUTIDE 0.5 +1.0 mg

Acute MI
N (%)

Non-fatal Acute MI
N (%)

Non silent MI
N (%)

Type X
N (%)

Type xx
N (%)

Etc...

Silent MI
N=

Acute MI resulting in death
(should match death)

Type X
N (%)
Sample name: Figure X- adjudicated Stroke SEMAGLUTIDE 0.5 +1.0 mg

Stroke N (%)

Non-fatal Stroke N (%)

Hemorrhagic stroke N (%)

Ischemic stroke N=

Undetermined stroke N=

Stroke resulting in death (should match death number for category) N (%)

Type X N (%)

Reference ID: 3980435
Sample name: Figure X- adjudicated heart failure SEMAGLU TIDE 0.5 +1.0 mg

Heart failure
N (%)

Hospitalization for HF
N (%)

Non-fatal HF
N(%)=

Category x
N(%)=

Fatal HF
N(%)=

Category x
N(%)=

HF without hospitalization
N (%)

Non-fatal HF
N(%)=

Category x
N(%)=

Fatal HF
N(%)=

Category x
N(%)=
Sample name: Figure X- adjudicated neoplasms for SEMAGLUTIDE 0.5 +1.0 mg

Neoplasms
N (%)

non-fatal neoplasms
N (%)

Category x
N (%)

Category x
N (%)

Category x
N (%)

fatal neoplasms
N (%)

Category x
N (%)

Category x
N (%)

Category x
N (%)
Hello Stephanie,

Please see the attached clinical pharmacology information request pertaining to NDA 209637 semaglutide injection. A response is needed by **August 3, 2017**. Let me know if there are any questions, and please acknowledge receipt of this email.

Sincerely

Pete

**Peter Franks, M.S.**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
For method validation report number VCA11773, provide a summary of the analytical method used to quantify semaglutide in human urine using stable labelled internal standard.

For Studies NN9535-3818, NN9535-3817, NN9535-3819, NN9535-3685, NN9535-1821 a summary of the bioanalytical results for atorvastatin, ortho-hydroxy-atorvastatin, para-hydroxy-atorvastatin, digoxin, metformin, R-warfarin, S-warfarin, ethinylestradiol, levonorgestrel, and paracetamol has not been provided in the individual clinical study reports. For each analyte provide a summary of the accuracy and precision of the quality control samples that were used in the runs to quantify patient/clinical samples, as shown below:

<table>
<thead>
<tr>
<th>QC sample</th>
<th>Concentration (units)</th>
<th>N</th>
<th>Accuracy</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low QC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid QC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High QC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilution QC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In addition provide a summary of the incurred sample reanalysis that was conducted for each of the analytes listed above.

For study NN9535-3819, clarify whether stability assessments (short-term, long-term, freeze-thaw) was conducted for levonorgestrel. Specify the location or submit the relevant information. If such stability assessments were not conducted provide adequate justification.

For study NN9535-3616 we note that the classification of subjects into renal function groups (Table 9-1) is based on the previous Guidance for Industry. We recommend that you use the current Guidance for Industry: Pharmacokinetics in patients with impaired renal function – study design, data analysis, and impact on dosing and labeling (March 2010) to re-classify subjects into renal function groups. The primary and secondary endpoints of the study should be re-analyzed based on the new classification of subjects. Submit this information to the Agency. Additionally, for each subject provide the estimated creatinine clearance (mL/min) and renal function/impairment category.

Please submit your responses by COB 3rd August, 2017.
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/s/

PETER D FRANKS
07/28/2017
Hi Pete,

We did not have a Steering Committee overseeing any of the phase 3 trial, including the cardiovascular outcomes trial.

Do you need me to submit a formal response via the Gateway or does this e-mail suffice?

Thanks,
Stephanie

---

Hello Stephanie,

Please see the information request below and let me know if you have any questions. A response is appreciated by August 3, 2017, but let me know if the team needs more time for this. Please confirm receipt of this email.

Please indicate whether a Steering Committee was overseeing the semaglutide program, and provide the location of the Steering Committee meeting minutes within the semaglutide application. If they were not previously submitted, please provide the Steering Committee meeting minutes for all phase 3 studies, including the cardiovascular outcomes trial.

Sincerely,

Pete

---

**Peter Franks, M.S.**  
*Regulatory Project Manager*  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
U.S. Food and Drug Administration  
Tel: 240-402-4197  
Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
08/03/2017
The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA# 209637
Drug Name: Semaglutide (Ozempic)
Sponsor: Novo Nordisk

Background
Semaglutide is a novel glucagon-like peptide-1 (GLP-1) analogue for once-weekly subcutaneous administration in patients with type 2 diabetes.

Mouse Carcinogenicity Study
Male and female Crl:CD1(ICR) mice were administered semaglutide via subcutaneous injection at 0.3, 1, 3 mg/kg/day and 0.1, 0.3, 1 mg/kg/day, respectively, for up to 104 weeks. One vehicle control group per sex (1.42 mg/mL disodium phosphate, dehydrate, 14.0 mg/mL propylene glycol and 5.50 mg/mL phenol in water for injection) was included. The doses were in accordance with ECAC recommendations; however, a water injected control group, which was also recommended by ECAC, was not implemented. A statistically significant increase in the incidence of thyroid C-cell adenomas and combined C-cell adenomas and carcinomas was observed in all treated male (pairwise comparison; all p<0.0001) and female (trend and pairwise tests; all p<0.0001) groups.
Rat Carcinogenicity Study
Male and female Sprague Dawley rats were administered 0.0025, 0.01, 0.025, and 0.1 mg/kg/day semaglutide via subcutaneous injection for up to 104 weeks. One vehicle control group per sex (1.42 mg/mL disodium phosphate, dehydrate, 14.0 mg/mL propylene glycol and 5.50 mg/mL phenol in water for injection) was included. The doses were not concurred with by the ECAC because the Committee had insufficient data upon which to base dose recommendations. In the 3-month study, there no no-effect level for the excessive decrease in body weight gain at the lowest dose tested. Lower doses were used in the 2-year study; however, ECAC was not re-consulted before study initiation. A water injected control group was also recommended by ECAC, but was not implemented.

A statistically significant dose related increase in the incidence of thyroid C-cell adenomas and combined C-cell adenomas and carcinomas was observed in males and females at \( \geq 0.01 \text{mg/kg/day} \) (trend and pairwise tests; \( p < 0.0001 \) all). A statistically significant dose related increase in the incidence of C-cell carcinomas was observed in males at \( \geq 0.025 \text{mg/kg/day} \) (trend and pairwise tests).
Executive CAC Conclusions

**Rat**
- The Committee noted the lack of prior protocol and dose concurrence by CDER.
- The Committee noted that a water control dose group was not used as previously recommended.
- The Committee concurred that thyroid C-cell adenomas, thyroid C-cell carcinomas, and the combined incidence of thyroid C-Cell adenomas and carcinomas were drug related in male rats and thyroid C-cell adenomas and the combined incidence of thyroid C-Cell adenomas and carcinomas in female rats were drug related. The combined incidences were statistically significant at doses of $\geq 0.01\text{ mg/kg/day}$ in both males and females.

**Mouse**
- The Committee concurred that the study was adequate, noting prior approval of the protocol.
- The Committee noted that a water control dose group was not used as previously recommended.
The Committee concurred that the thyroid C-cell adenomas and the combined incidence of thyroid C-Cell adenomas and carcinomas were drug related at all doses in males and females.

Karen Davis Bruno, PhD
Chair, Executive CAC
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/s/
---------------------
KAREN L DAVIS BRUNO
07/27/2017
Hello Stephanie,

Please see the information request below and let me know if you have any questions. A response is appreciated by August 3, 2017, but let me know if the team needs more time for this. Please confirm receipt of this email.

Please indicate whether a Steering Committee was overseeing the semaglutide program, and provide the location of the Steering Committee meeting minutes within the semaglutide application. If they were not previously submitted, please provide the Steering Committee meeting minutes for all phase 3 studies, including the cardiovascular outcomes trial.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
07/26/2017
Information Request – CMC only

NDA 209637

Dear Stephanie:

Please refer to your New Drug Application (NDA) dated December 5, 2016, received December 5, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for semaglutide injection.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by Friday, July 14, 2017 in order to continue our evaluation of your NDA.

1. Design Control, General (21 CFR 820.30)

Your firm has inadequately addressed the requirement for 21 CFR 820.30, design control.

You provided a listing of your firms Management Control SOPs. Additionally, you provided Design Control information in your application as well as your responses to information requests. However, several aspects of Design Controls could not be evaluated due to the lack of information. Please provide responses to the following questions:

   a. Who is the owner of the design history file and what is the location?

   b. Summarize the Procedures/SOP for Process/Design Change for a validated product.

For changes made to the device constituent part of the combination product, the impact of the design changes on the overall combination product performance should be considered and documented. All the design control activities must be documented in the Design History File (DHF) and subjected for design reviews. In addition, the location of DHF should be provided to the Agency for the facility inspection determination.

2. Management Responsibility (21 CFR 820.20)

Your firm has inadequately addressed the requirement for 21 CFR 820.20, management responsibility.

You provided a listing of your firms Management Control SOPs. However, we could not determine the Management Control responsibility for the Combination Product. Please provide
a summary of the firm’s management structure with executive responsibility who manage, perform, and assess work affecting quality of the product and related controls to ensure that the firm’s quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met as per 21 CFR 820.20.

3. Purchasing Controls (21 CFR 820.50)

Your firm has inadequately addressed the requirement for 21 CFR 820.50, purchasing controls.

You provided a listing of your firm’s Purchase Control SOPs. However, we could not evaluate aspects of the procedures for Purchasing Controls. Please provide a summary that:

a. Describes your supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers.

b. Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.

c. Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

Please explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).

4. Corrective and Preventive Action (CAPA) (21 CFR 820.100)

Your firm has inadequately addressed the requirement for 21 CFR 820.100, corrective and preventive actions.

You provided a listing of your firm’s CAPA SOPs. However, we could not evaluate the adequacy of the CAPA Procedures. Please summarize the procedure(s) for your Corrective and Preventive Action (CAPA) System that addresses:

a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;

b. Investigation of nonconformities and their causes;

c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and

d. Verification or validation of the actions taken.

Kindly acknowledge receipt.
Regards.

-Anika

Anika Lalmansingh, PhD  
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)  
Office of Pharmaceutical Quality/CDER/FDA  
10903 New Hampshire Ave, Bldg #75 Room 4631, Silver Spring, MD 20993-0002  
(240) 402-0356 | anika.lalmansingh@fda.hhs.gov
Hello Stephanie,

Please see the information request below from CDRH pertaining to NDA 209637 semaglutide injection. Please respond by July 14, 2017. Also, please confirm receipt of this email.

1. You have not included a comprehensive risk analysis in this NDA. You state that the PDS290 pen-injector for semaglutide 1.34 mg/ml utilizes some generic PDS290 components and uses similar manufacturing processes to other marketed PDS290 pen-injectors and have been analysed with regard to risks related to the design and manufacturing processes by the use of the FMECA method. You also state that the conclusion of the design and manufacturing risk management analysis for the PDS290 pen-injector for semaglutide 1.34 mg/ml is that all risks have been analysed, assessed and reduced as documented in the FMECA document; however, this document has not been provided. Please clarify if there are any differences between the FMECA performed on the PDS290 semaglutide 1.34 mg/ml pen injector and the FMECA performed on previously approved PDS290 pen injectors. If there are any differences, please provide a list of the differences and the corresponding risk analysis information.

Thanks very much,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/
PETER D FRANKS
06/27/2017
Hello Stephanie,

Please see the IR below pertaining to NDA 209637 semaglutide injection. We ask that you respond to this information request and return comments as soon as possible, but no later than close of business Wednesday, June 28, 2017. Let me know if you have any questions. Please confirm receipt of this email.

We refer to your Human Factors Engineering and Usability Evaluation (HFE/UE) Report and Instructions for Use (IFU) for Ozempic (semaglutide) PDS290 pen-injector under NDA 209637, submitted on December 05, 2016. We also refer to your Amendment proposing to modify the flexible-dose pen-injector submitted on June 7, 2017. Please provide responses to the following requests:

1. In the HFE/UE Report, you indicate that evaluation of the PDS290 pen-injector portfolio formative results informed the device user interface design for the PDS290 semaglutide pen-injector and it was determined that the IFU/Quick Guide design of the device user interface should be modified for the PDS290 semaglutide pen-injector to address specific known use problems. You also specify that based on the formative testing results for the PDS290 semaglutide pen-injector, design modifications focused on the product color and carton design, which included a Quick Guide that was aligned with the IFU. Please address the following:

   a. the number of formative testing to date and date of each test

   b. a summary of each formative testing results

   c. list and describe user interface modifications as a result of your formative testing results, highlighting where you determined that a Quick Guide is necessary and the rationale for why you believe the use of the Quick Guide would address the results of which formative testing

   d. any human factors validation data you have to support the use of the Quick Guide

Understanding the formative testing results and user interface modifications that informed your rationale for the use of a Quick Guide will help us proceed with our review.

2. The proposed IFU includes the following statement: “(b) (4) [Please submit]” Please submit
the following information for our review:

3. Your Amendment proposes to modify the flexible-dose pen-injector by removing the 1 mg dose so it only delivers 0.25 mg and 0.5 mg doses. Please provide three samples of the intend-to-market products (fixed-dose pen-injector and flexible-dose pen-injector) with complete packaging (e.g., carton, pen-injector, and pen needles).

Thanks very much,

Pete

Peter Franks, M.S.
Regulatory Project Manager
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Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
06/22/2017
Hi Arati,

I confirm receipt, thanks.

Stephanie

---

From: Kamath, Arati [mailto:Arati.Kamath@fda.hhs.gov]
Sent: Wednesday, June 14, 2017 9:08 AM
To: SDEC (Stephanie DeChiaro)
Cc: Franks, Peter
Subject: NDA 209637 semaglutide injection: Statistics Information Request June 14, 2017

Good Morning Stephanie,

We have an additional information request in response to your recent submission for NDA 209637, on June 8, 2017.

Please submit the ADAM dataset advs for Trial 3744 (used in the analysis for body weight in 101_in_trial_mkdata_bw_3744_4windows.txt) or point out where it can be found.

Please confirm receipt of this email and provide a response by June 20, 2017.

Regards,

Arati

Arati B. Kamath, Ph.D.
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
ODE II/OND/Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 301-796-3159
Fax: 301-796-9712
Arati.Kamath@fda.hhs.gov
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/s/

ARATI B KAMATH
06/14/2017
Hello Stephanie,

In response to the recent submission received on June 7, 2017, pertaining to the proposed device modification for NDA 209637 semaglutide injection, please see the CDRH information request below. A response is needed by **June 12, 2017**. Please confirm receipt of this email.

1. Please provide a more detailed description of the proposed modification.
   
   a. Please include the mechanism of the dose stop and technical drawings.
   
   b. Please clarify if the dose stop is right at .5 mg.

2. Please clarify how you plan to verify that the dose stop works after shipping, dropping, etc.

3. Please provide a specification for the force at which the user can overcome the dose stop and a justification for the acceptance criteria.

Sincerely,

Pete

---

**Peter Franks, M.S.**  
*Regulatory Project Manager*  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
U.S. Food and Drug Administration  
Tel: 240-402-4197  
[Peter.Franks@fda.hhs.gov](mailto:Peter.Franks@fda.hhs.gov)
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/s/

PETER D FRANKS
06/09/2017
NDA 209637

MID-CYCLE COMMUNICATION

Novo Nordisk Inc.
Attention: Stephanie DeChiaro
Director Regulatory Affairs
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Ms. DeChiaro:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for semaglutide injection.

We also refer to the teleconference between representatives of your firm and the FDA on June 1, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Peter Franks, Regulatory Project Manager, at (240) 402-4197.

Sincerely,

William Chong, M.D.
Clinical Team Lead
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication
Applicant’s slides presented at teleconference
Meeting Date and Time: June 1, 2017

Application Number: NDA 209637
Product Name: semaglutide injection
Indication: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Applicant Name: Novo Nordisk Inc.

Meeting Chair: William Chong, M.D.
Meeting Recorder: Peter Franks, M.S.

FDA ATTENDEES
Division of Metabolism and Endocrinology Products
James P. Smith, MD, MS, Deputy Director
William Chong, MD, Clinical Team Lead
Andreea Lungu, MD, Clinical Reviewer
Eugenio Andraca-Carrera, PhD, Statistical Team Lead
Ya-Hui (Catherine) Hsueh, PhD, Mathematical Statistician
Susan Rimmel, PharmD, Safety Evaluator
Sarah Mollo, PhD, Immunologist
Till Olickal, PhD, PharmD, Risk Management Analyst
Julie Van der Waag, MPH, Chief, Project Management Staff
Peter Franks, MS, Regulatory Project Manager
Elizabeth Godwin, MSHS, CCRP, Regulatory Project Manager

APPLICANT ATTENDEES
Anders Hvelplund, Senior Director, Medical and Science
Anne Phillips, Senior Vice President, Clinical, Medical and Regulatory
David Truloff, Director, Safety Surveillance GLP-1 & Obesity
Henning Pontoppidan Föh, Principal Programmer, Biostatistics
Henrik Kim Nielsen, Corporate Vice President, Regulatory
Katarina Jelic Maiboe, Director, Regulatory
Lars Holm Damgaard, Senior Statistical Director, Biostatistics
Lene Melchiorsen, Project Vice President, Semaglutide
Mads Frederik Rasmussen, Corporate Vice President, Medical and Science
Marie Lindegaard, Vice President, Medical and Science
Peter Kristensen, Senior Vice President, Global Development
Robert Clark, Vice President, US Regulatory

Reference ID: 4114878
1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical: The imbalance in events of retinopathy not favoring semaglutide remains a concern. We have not identified any other major safety issues at this time; however, the review is ongoing.

CMC: There are no significant issues to discuss at this time. An information request was sent on May 24, 2017, and responses are still pending.

Efficacy Statistics: The review is ongoing. No significant review issues have been identified at this time. An information request was sent on May 25, 2017, and responses are pending.

Safety Statistics: The review is ongoing. The results of the primary MACE analysis and the analyses of other cardiovascular endpoints have been verified. The review of other safety endpoints such as retinopathy is ongoing. An information request was sent on May 25, 2017, and responses are pending.

Clinical Pharmacology: An information request was sent on May 19, 2017 and a response was received on May 26, 2017. There are no other issues to discuss at this time.

Nonclinical: No significant issues have been identified to date.

CDRH: The review is ongoing. Two IRs concerning the device constituent were sent on May 16, 2017: IR (1) Requested clarification and information on dose accuracy testing performed in stability studies; IR (2) Requested clarification of on the specifications included in 3.2.P.5. The IR response was received on 5/30/2016 and is currently under review.

DMEPA: The review is ongoing. There are no significant issues to discuss at this time.
OSI site inspection update: There are no significant issues to discuss at this time.

OBP: An information request was sent on May 26, 2017, and a response was pending at the time of the teleconference. There are no other significant issues to discuss at this time.

3.0 INFORMATION REQUESTS

Information requests have been sent from the project manager to the regulatory contact person at Novo Nordisk as they have been requested by the reviewers throughout the review to date. The following Information Requests had been communicated by the project manager but were pending a response to FDA at the time of the mid cycle meeting. Responses that were received since the meeting are noted below.

<table>
<thead>
<tr>
<th>Date IR/Hold Comments Sent</th>
<th>Discipline Sending Comments</th>
<th>Date Response Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/24/2017</td>
<td>CMC</td>
<td>6/23/2017</td>
</tr>
<tr>
<td>5/26/2017</td>
<td>Office of Biological Products</td>
<td>6/5/2017</td>
</tr>
</tbody>
</table>

The response to this IR was received on June 8, 2017

The response to this IR was received on June 8, 2017

The response to this IR was received on June 2, 2017

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Retinopathy: We remain concerned regarding the findings of retinopathy with semaglutide. We would like clarification on what patient-level self-monitored glucose data that you have available to explore the impact of changes in glucose on retinopathy early in the course of the study (i.e., before an effect on HbA1C was apparent).

Meeting discussion: The applicant provided slides describing the available self-monitored plasma glucose (SMPG) data as well as presenting additional analyses of sub-groups such as subjects using insulin and with retinopathy at baseline. See below for the “Discussion of the Applicant’s Slides”.

There are no updates to Risk Management at this time.

5.0 ADVISORY COMMITTEE MEETING

The Advisory Committee Meeting is tentatively scheduled for October 18, 2017. The location has not been determined.
6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late Cycle Meeting is tentatively scheduled as a face to face meeting for August 30, 2017, but could be moved to a later date as Advisory Committee planning becomes solidified. Initial labeling comments are scheduled to be sent to the applicant by August 12, 2017, and the PDUFA goal date is December 5, 2017.

7.0 DISCUSSION OF APPLICANT SLIDES

Meeting Discussion: The applicant presented 7 slides that were sent to FDA on June 1, 2017.

The applicant confirmed that only fasting values were collected for the SMPG data set, and no other data points were obtained.

The applicant stated that they will submit the additional analysis from SUSTAIN 6 (from slide 6) that shows differences in baseline retinopathy with and without concomitant insulin use.

FDA recommended that if the analysis is submitted, that it should include a thorough description of the subgroups, since the subjects who use insulin are likely to differ from those who do not use insulin, and those differences may modify the risk of retinopathy.

The applicant acknowledged that the increased risk of retinopathy observed in SUSTAIN 6 was unexpected to them, and they are taking it very seriously by both attempting to better understand the risk as well as considering how to best design a trial to evaluate it further after approval, if semaglutide is approved. They also proposed to submit a revised REMS in a few weeks that would include information regarding diabetic retinopathy. Since diabetic retinopathy is still being assessed and the review is still ongoing, FDA stated that it was premature to submit a revised REMS; discussion of any REMS would take place at a later date.

The applicant proposed sending in an amendment pertaining to the PDS290 pen-injector, which includes modifying the 0.25/0.5/1 mg pen injector so it can only deliver 0.25/0.5 mg, as well as providing dose accuracy data to support this change. The modification was communicated to FDA on June 1, 2017, and the applicant was informed that the FDA would need further internal discussion and consideration of this proposal prior to commenting.

The FDA stated that if the applicant wanted feedback on whether this additional data could impact the ability to meet the current PDUFA goal date that a proposal outlining the contents of the proposed amendment should be submitted such that FDA could review the proposed new data and consider whether this could impact the review timeline. While a preliminary assessment of the impact to the review timeline could be communicated, a final determination regarding a modification of review timelines would not be made until after receipt of the amendment, if one were to be submitted.
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/s/

WILLIAM H CHONG
06/21/2017
Hello Stephanie,

Please see the information request below from efficacy statistics. A response is needed by June 8, 2017. Let me know if there are any questions, and please acknowledge receipt of this email.

1. For the 5 key efficacy trials, it appeared that the sum of the number of subjects with missing HbA1 value at endpoint visit and the number of retrieved dropouts (ISE Tables 6.9.8-6.9.12) was more than the number of subjects who had premature treatment discontinuation (CSR subject disposition tables). Please explain the difference.

For instance, among the exposed subjects in trial 3623:

<table>
<thead>
<tr>
<th></th>
<th>Sema 0.5mg</th>
<th>Sema 1.0mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized and treated</td>
<td>128</td>
<td>130</td>
<td>129</td>
</tr>
<tr>
<td>Premature treatment discontinuation, n(%)</td>
<td>17 (13.3)</td>
<td>16 (12.3)</td>
<td>14 (10.9)</td>
</tr>
<tr>
<td>Missed HbA1c value at endpoint visit, n(%)</td>
<td>9 (7.0)</td>
<td>9 (6.9)</td>
<td>13 (10.1)</td>
</tr>
<tr>
<td>Retrieved dropouts, n(%)</td>
<td>11 (8.6)</td>
<td>12 (9.2)</td>
<td>6 (4.7)</td>
</tr>
</tbody>
</table>

2. We noticed you have submitted the results for in-trial analysis using multiple imputation based on retrieved dropouts for the CVOT trial 3744 in Tables 6.9.1 and 6.9.5 of ISE but we could not find the corresponding analysis programs. Please provide the programs or point out where the files can be found if you have submitted them already. Please use the same format as the In_Trials_MI_bodyweight and In_Trial_MI_HbA1c analysis programs of the other phase 3 trials.

Please also provide the results and corresponding programs for retrieved drop-out analysis of HbA1c endpoint at Week 30 for the two subgroups: subjects on premix insulin at baseline and subjects on SU monotherapy at baseline.

Sincerely,

Pete
Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION
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/s/

PETER D FRANKS
05/26/2017
Hello Stephanie,

Please see the information request below and let me know if there are any questions. The team would like this response provided by June 5, 2017. Please acknowledge receipt of this email.

The clinical study report for your pivotal trials shows no values for ADA testing for several clinical samples. The list states that several samples were “not collected”, however the samples for the same subjects and same time points have results for the confirmatory assay. Please explain this discrepancy and correct any errors as needed. If samples were not collected please specify the cause. Please provide this information by June 5.

Thank you,
Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov

Reference ID: 4103918
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/s/

PETER D FRANKS
05/26/2017
Hello Stephanie,

Please see the information request below pertaining to NDA 209637 semaglutide injection. The safety statistics team needs the response by June 8, 2017. Let me know if there are any questions. Please confirm receipt of this email.

1. Provide the executable SAS program with adequate documentation to reproduce the analysis results (counts of events and denominators) for the post hoc statistical subgroup analyses in Figure 11-31, page 285, from the Report Body.

2. Provide the executable SAS program and individual subject identifiers to reproduce the analysis results in Figure 11-16 “Reasons for eye examination of first EAC-confirmed events of diabetic retinopathy complications” in the Report Body.

Thank you very much.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
05/26/2017
Information Request – CMC only

NDA 209637

Dear Stephanie:

Please refer to your New Drug Application (NDA) dated December 5, 2016, received December 5, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for semaglutide injection.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by **Friday, June 23, 2017** in order to continue our evaluation of your NDA.

1. We acknowledge that you have provided master batch record in English. Also provide your executed batch records in English translation.

2. Provide a summary table for the yields and reconciliation for the three submission batches, and compare with the proposed yield for intended commercial batch.

3. Provide a list of major equipment used in manufacturing process. Further, manufacturing equipment compatibility study results should be submitted and evaluated to ensure that the formulation contacting components (for example, the inner surface of vessels, tubing, filters, diaphragms of pumps) is not reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product. The level of investigation (including CFR citation for direct food contact, in vitro and in vivo biological reactivity tests, and extractable profile and leachable studies) should be commensurate with the risks associated with the dosage form, composition, drug loading, and manufacturing conditions. Summary of those studies, whenever appropriate, should be documented and discussed.

4. Drug Master File (DMF) is being reviewed and the DMF holder has been notified of deficiencies. We will work with the DMF holder to resolve any issues if the DMF holder responds in a timely manner. Please be aware that the Quality review of the NDA cannot be fully completed until all DMF issues are adequately resolved. Please acknowledge this in your response.

Kindly acknowledge receipt.

Regards.

-Anika
Anika Lalmansingh, PhD  
Regulatory Business Process Manager  

Center for Drug Evaluations and Research (CDER)  
Office of Pharmaceutical Quality (OPQ)  
U.S. Food and Drug Administration  
Tel: 240-402-0356  
anika.lalmansingh@fda.hhs.gov  

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Hello Stephanie,

Please see the attached clinical pharmacology information request pertaining to NDA 209637 semaglutide injection. A response is needed by May 26, 2017. Let me know if there are any questions, and please acknowledge receipt of this email.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov

Reference ID: 4100777
NDA 209637 – Semaglutide injection

- Carry-over assessment for semaglutide (NNC-0113-000-0217) and internal standard (unextracted samples ÷ extracted samples) ×100, rather than [extracted samples ÷ unextracted samples] ×100.

- In method validation report number: VAA91659, provide clarification as to why the %recovery for the internal standard was estimated using the equation [unextracted samples ÷ extracted samples] ×100, rather than [extracted samples ÷ unextracted samples] ×100.

- In method validation report number: AA95860, the %recovery for semaglutide in the extracted samples was >100% which you attribute to the non-specific binding of semaglutide to tube surfaces during preparation of the unextracted samples. Provide an explanation as to why such observations were evident in this method validation report but not in the method validation report number: VAA91659.

- Method validation report number: VCA11388 reports the validation assessment conducted for the LC-MS/MS method for semaglutide using a stable labelled internal standard. Specify whether recovery assessment for semaglutide and internal standard and matrix effect for internal standard was conducted. Specify the location of this information or submit the relevant documents.

- Based on the reported results for short-term solution stability for the internal standard in method validation report number: AA95860, provide an explanation as to why you concluded that internal standard solutions freshly prepared can be used between 1 hour and 5 hours after preparation if maintained at room temperature.

- Specify whether the recovery of semaglutide and internal standard in human urine matrix was assessed. Specify the location of this information or submit the relevant documents.

- Provide clarification as to whether the acceptance criteria of “at least two-thirds of the QC samples and at least 50% at each concentration level were within ±15% of their nominal concentration” was assessed in the precision & accuracy runs (P&A) and non-P&A runs for all the bioanalytical method validation runs for NDA 209637.

- Specify the location of the validation reports for quantification of atorvastatin, digoxin, and paracetamol or submit the relevant documents. Specify whether a summary of the analytical
methods for warfarin, metformin, atorvastatin, digoxin, ethinylestradiol/levonorgestrel, and paracetamol was submitted in Section 2.7.1, if not submit the relevant document.

- In Study NN9535-3818 you report that following administration of atorvastatin a majority of subjects had atorvastatin concentrations below the LLOQ at 72 hours post-dose. During data analysis, specify how concentrations below LLOQ were handled and the accuracy to which the PK endpoint AUC<sub>0-72hr</sub> was estimated.

Please response by COB 26<sup>th</sup> May, 2017.
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/s/
PETER D FRANKS
05/19/2017
Hello Stephanie,

Please see the CDRH information request below pertaining to NDA 209637 semaglutide injection. Let me know if there are any follow up questions. Please provide a response by May 29, 2017. Please acknowledge receipt of this email.

1. On April 21, 2017, the Agency asked for clarification for why [ ] increments was chosen for the assessment of dose accuracy post stability studies. Please provide the following clarifications for your response.

   a. Table 1 "Supplementary PDS290 pen-injector comparison information with regard to the device used for testing of dose accuracy in the stability study" states that the dose accuracy testing at [ ] % is completed for [ ] increments (corresponding to [ ] mg) showing as '5.0 mg' (see footnote 1) on scale drum'. It is unclear how [ ] increments equals [ ] mgs (or [ ] mgs is a typo) as the submission states that [ ] increment = [ ] ml drug product and the concentration of the drug is 1.34 mg/mL.

You state that the dose accuracy testing stability studies documented in 3.2.P.8.3 Primary Stability Data performed on the PDS290 pen-injector for semaglutide used in the phase 3a clinical trial programme (SUSTAIN 1-5) and (SUSTAIN 6) demonstrate that the PDS290 pen-injector for semaglutide 1.34 mg/ml meets the shelf life specifications for the dose accuracy. Additionally, you state that the dose accuracy testing in the stability studies for the lowest and highest labelled doses are considered unnecessary and the dose accuracy test at dose setting at midpoint of [ ] increments is considered sufficient. This is based on the data leveraged from the PDS290 pen-injector for insulin (FlexTouch) as the dose accuracy for the PDS290 pen-injector for insulin (FlexTouch®) has been tested at [ ] increments, which are representative of the increments used in the semaglutide pen injector (i.e. [ ] increments). You reference supplement 61 of NDA 020986 for the FlexTouch. This appears to be a labeling supplement and does not contain the stability data.

   i. Please clarify the concentration of the Semaglutide used in the stability studies and the concentration of the Semaglutide used in the clinical studies.

   ii. Footnote 1 could not be located in the response document. Please update the information provided to include footnote 1.

   iii. To leverage data from the FlexTouch pen for stability studies, please provide a
iv. Please provide the location of the stability testing for the FlexTouch combination product that you are leveraging as part of your assessment of the dose accuracy/stability studies.

b. In response to Question 5, you included the following information on the SUSTAIN 6 clinical trial:

**PDS290 pen-injector for semaglutide used in the phase 3a clinical trial programme**

(SUSTAIN 6; 3297 participants for two years), with an imprint on the scale drum of [ ] mg with imprints every [ ] mg

The stability data provided in Appendix C, lists the dose accuracy in around [ ] mg. Footnote 2 includes the following information:

*The dose settings appearing on the PDS290 pen-injector for semaglutide used in the phase 3a clinical trial programme (SUSTAIN 6) do not correspond to the actual number of milligram of active semaglutide 1.34 mg/ml solution for injection. In clinical trial SUSTAIN 6, a conversion table is used to dial the number of milligrams on the scale drum, which corresponds to the prescribed number of milligrams of active semaglutide 1.34 mg/ml solution for injection.*

It is unclear how this relates to the drug product as [ ] increment = [ ] ml drug product and the concentration of the drug is 1.34 mg/mL.

i. Please clarify the concentration of Semaglutide in the PDS290 pen-injector for Semaglutide used in the phase 3a clinical trial programme (SUSTAIN 6).

ii. Please provide a rationale for why the dose accuracy testing using the [ ] mg pen injector is applicable for the to-be marketed combination product (1.34 mg/mL, 1.5 mL cartridge).

2. On April 21, 2017, the Agency requested that you include a dose accuracy specification for the lowest dose (0.25 mg) in your release specifications. The release specifications are included below:

<table>
<thead>
<tr>
<th>Dose accuracy</th>
<th>Weighing A332601a</th>
<th>Complies</th>
</tr>
</thead>
</table>

Reference ID: 4100653
5: Complies means that the specification limit of (b)(4)% at a dose of 0.5 mg semaglutide (corresponding to solution for injection) for the PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg), item no. 5-9538-xx is fulfilled using ISO 3951-1:2005 or ISO 3951-2:2006

6: Complies means that the specification limit of (b)(4)% at a dose of 1.0 mg semaglutide (corresponding to solution for injection) for the PDS290 pen-injector for semaglutide 1.34 mg/ml (1.0 mg), item no. 5-9506-xx is fulfilled using ISO 3951-1:2005 or ISO 3951-2:2006

Please clarify if (b)(4) mg is a typo and is meant to state (b)(4) ul. If so, please update your specifications document to include the correct units. If not, please clarify how 0.5 mg and 1.0 mg of Semaglutide corresponds to (b)(4) mgs of solution for injection, respectively.

Thank you,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION
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/s/

PETER D FRANKS
05/19/2017
Hello Stephanie,

Please see the CDRH information request below pertaining to NDA 209637 semaglutide injection. Let me know if you have any questions. Please provide a response by April 27, 2017. Also, please acknowledge receipt of this email.

1. In the document "Test Report According to ISO 11608-1 - Needle Based Injection Systems for Medical Use" (novoDOCS ID 002987428), you have included dose accuracy testing for the last dose. Table 8 shows the test results for the minimum dose, (0.25 mg). The pen-injector is able to dose . In addition to the lowest dose, please provide the dose accuracy testing for the last dose for the highest dose (1.0 mg).

2. The Semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg) Pen-injector is labeled for administration of three doses, 0.25 mg/0.5 mg/1.0 mg. However, the dose dial includes unlabeled increments in between the labeled doses. The user/patient is able to select and administer any of the unlabeled dose increments on the dose dial. Please provide a risk analysis of incorrect dosing based on the user/patient setting the dose at one of the unlabeled increments (therefore, over or under dosing). Please include in the risk analysis how the risk(s) to the patient if an unlabeled dose is selected, have been mitigated. For example, a human factors validation study including a critical task for users to select and administer the correct dose in which the user/patient has to select from multiple doses with increments in between doses unlabeled.

3. The injection time specification for the pen-injector is: seconds. The performance testing results for this specification ranged from seconds, depending on the gauge and length of needle; however, if the maximum injection time specification is seconds, that injection time should be validated for the user population. Please provide validation data that the patient is able to understand that the injection is completed based on audible and visual feedback cues. Additionally, please provide validation that that the patient population is capable of holding the pen injector for seconds, if necessary. Alternatively, please tighten the injection time specification to be closer to the actual verification testing results.

4. Please provide a specification for the residual medication in the pen after last dose or provide a rationale for why a specification for the residual volume is not necessary.

5. The shelf-life of the combination product is 36 months. Appendix E of the document "Primary Stability Data for Semaglutide 1.34 mg/ml Solution for Injection Up to 36 Months at 5°C, 6 Months at 25°C" includes a summary of dose accuracy testing at % for the increment.

Reference ID: 4092133
dose (2 batches) and increment dose (1 batch up to 24 months). It is unclear why the increment dose is used, as that is not a labeled dose for this combination product. It is also unclear how the testing for increments was performed given the scale drum is not labeled for a dose amount that corresponds to increments.

a. Please clarify why increments was chosen and how the testing was performed.

b. You have not included dose accuracy testing for the lowest (increments) and highest (increments) dose. Please provide dose accuracy testing in your stability studies for the lowest and highest labeled doses.

c. The reviewer is unable to locate the test protocols and test reports for the dose accuracy testing post stability studies. Please provide the location or the protocols and test reports for the verification testing of the dose accuracy testing post stability studies.

d. There are two pens within the NDA, a pen labeled with 1mg dose only and a pen with options for 0.25 mg, 0.5 mg, and 1 mg doses. Please clarify which pen the stability studies were performed on and provide a rationale for why the testing is applicable for both pens.

e. Please clarify if the shelf-life of the pen-injector, prior to being incorporated into the combination product has been addressed in your stability studies. For example, if the pen-injector has a shelf-life of X number of years and the combination product has a shelf-life of three years, please clarify if you have provided testing demonstrating that the performance of the device remains acceptable considering the X + 3 years total shelf life/aging for the pen-injector component.

6. You have included a dose accuracy specification within your release specification document (3.2.P.5.1) that states that the dose accuracy requirement "complies". Please see below:

<table>
<thead>
<tr>
<th>Dose accuracy</th>
<th>Weighing A332601a</th>
<th>Complies³,⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>5: specification limit % at a dose of 0.5 mg semaglutide for the PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg), item no. 5-9558-xx is fulfilled using ISO 3951-1:2005 or ISO 3951-2:2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6: Complies means that the specification limit % at a dose of 1.0 mg semaglutide for the PDS290 pen-injector for semaglutide 1.34 mg/ml (1.0 mg), item no. 5-9506-xx is fulfilled using ISO 3951-1:2005 or ISO 3951-2:2006</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. You can include that the device should conform to a standard in the release specifications; however, the specification acceptance criteria should state the actual dose accuracy specification within the release specifications (i.e. % for the doses: or the range if acceptable doses: )

Reference ID: 4092133
b. You have only included only a dose accuracy specification for the middle (0.5 mg) and highest dose (1.0 mg). The Agency recommends that you bracket the range of possible doses in your release specifications. Please include a dose accuracy specification for the lowest dose (0.25 mg) in the release specifications (3.2.P.5.1) in addition to the specifications currently included.

7. You have labeled the device for use with NovoFine needles. Please still include a specification for the length and gauge of the needles that should be used with your combination product within your essential performance and safety requirements document.

8. You have provided a Product Risk Management Summary for PDS290 Pen-injector for Semaglutide 1.34 mg/ml (novoDOCS ID: 003159739). The reviewer is unable to locate a comprehensive risk analysis for the device constituent of the combination product. The risk analysis should characterize and assess the potential risks posed to the user during correct normal use, probable misuse, and in situations where there is a potential device system failure that prevents the device from achieving its intended use. Specifically, the risk analysis should clearly describe the potential hazards that are apparent to your device, describe the safety mitigations you have implemented to address the identified hazards, explain why these mitigations are acceptable, and provide evidence that demonstrates the effectiveness of those mitigations. Furthermore, the risk analysis should include a scientific rationale and clinical justification regarding the acceptability of any residual risks posed within the final finished device system(s). Please provide the location of the risk analysis or provide the risk analysis document(s) that contains the above information.

Thanks,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
05/02/2017
Hello Stephanie,

Please see the information request below from the stats team for NDA 209637 (semaglutide injection). Please provide a response by Monday, May 1, 2017. Let me know if there are any questions. Please confirm receipt of this email.

1. Record deletion because of “EoTpd takes precedence” should not be applied in the in-trial MMRM analysis or the retrieved dropout analysis, especially if such replacement takes place at the endpoint visit. Please clarify what you did in these analyses. We are most concerned about the retrieved dropout analysis.

2. Please elaborate on the following reasons for record deletion (ADELREAS) or point out where this information can be found:
   - Not done
   - Retest Rule 1
   - Measurement after first exposure time

3. It stated in 1.5.1 of the summary of clinical efficacy that screening value carried forward was used for missing baseline values in the MMRM analyses. Please confirm whether the same imputation procedure was used for the retrieved dropout analysis.

Thanks very much,

Pete

**Peter Franks, M.S.**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
05/02/2017
Hello Stephanie,

Please see the comment below from the nonclinical review team pertaining to NDA 209637 (semaglutide injection). Please provide a response by May 4, 2017. Let me know if there are any questions, and please confirm receipt of this email.

- In support of your proposed limits on impurities, provide impurity data in a tabular format for all nonclinical and clinical batches.

Thanks very much,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fdahhs.gov
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/s/

PETER D FRANKS
05/02/2017
Hello Stephanie,

See the information request below for NDA 209637 (semaglutide injection). Please respond by April 21, 2017. Let me know if there are any questions. Also, please confirm receipt of this email.

In review of the semaglutide NDA, we are unable to locate the adjudication packets for the adjudicated events in SUSTAIN-6. Please provide details on the location of the adjudication packets in the NDA. If these have not been submitted, we request that you submit the adjudication packets for our review. These should be organized by event and by adjudication outcome (i.e., positively adjudicated vs. not confirmed). For ease of review, we would request that a table listing all events referred for adjudication with hyperlinks to the associated adjudication packages be included.

Thanks very much,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov

Reference ID: 4081478
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/s/

PETER D FRANKS
04/07/2017

Reference ID: 4081478
Hello Stephanie,

Please see the information request below pertaining to NDA 209637 (semaglutide injection). Let me know if you have any questions. Please confirm receipt of this email as well.

We refer to your NDA 209637 submission for semaglutide injection dated December 5, 2016. Please provide responses to the following requests:

1. We note in your submission you propose two strength variations of Ozempic (e.g., a pen-injector that doses 1 mg only and a pen-injector that doses 0.25 mg, 0.5 mg, or 1 mg). Because one of the pens covers the three available doses, please submit your rationale for why the pen-injector that offers only 1 mg doses is needed.

2. Provide five samples of the intend-to-market complete packaging (e.g., carton and pen-injector) for both strengths that include pen needles.

We request that you respond to this information request and return comments as soon as possible, but no later than close of business Friday, April 14, 2017.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
04/07/2017
MEMORANDUM OF TELECONFERENCE

Teleconference Date: April 6, 2017

Application Number: NDA 209637
Product Name: semaglutide injection
Sponsor/Applicant Name: Novo Nordisk

Subject: Advisory Committee Status

FDA Participants:
Jean-Marc Guettier, Director, DMEP
Andreea Lungu, Clinical Reviewer, DMEP
Peter Franks, Regulatory Project Manager, DMEP

Sponsor/Applicant Participants:
Lene Melchiorsen, Project Vice President, Semaglutide
Katarina Jelic Maiboe, Director, Regulatory
Robert Clark, Vice President, Regulatory
Stephanie DeChiaro, Director, Regulatory

1.0 BACKGROUND:

An ad hoc internal team meeting occurred on April 3, 2017, to discuss retinopathies associated with semaglutide injection. There is evidence for an increased risk for retinopathy with this drug, and given that antidiabetic agents are intended to reduce the risk of microvascular complications, we believe that a public discussion would be necessary prior to taking an action. Participants at the meeting, including DMEP Director, DMEP Division Director, CDTL, and ODE signatory for the application agreed that an advisory committee meeting will be needed prior to action.

2.0 DISCUSSION:

The purpose of the call was to inform the applicant of the decision to have an advisory committee meeting for this application. The main focus of the advisory committee meeting will be to assess the benefit/risk of the product.

3.0 ACTION ITEMS:

DMEP: Convey any additional information pertaining to the topics for the advisory committee meeting at the mid-cycle communication teleconference meeting in June.
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/s/

PETER D FRANKS
05/02/2017
NDA 209637

INFORMATION REQUEST

Novo Nordisk Inc.
Attention: Stephanie DeChiaro
Director Regulatory Affairs
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Ms. DeChiaro:

Please refer to your New Drug Application (NDA) dated December 5, 2016, received December 5, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for semaglutide injection.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response within thirty (30) U.S. business days in order to continue our evaluation of your NDA.

1. Provide a description of [Redacted]

2. Provide representative Certificates of Analysis for [Redacted]

3. Provide a representative mass spectrometry spectrum used to support the structure elucidation of semaglutide drug substance.

4. Provide a description of the product related impurities classified within the Hydrophobic Impurities 2 grouping of impurities. Also include details of how these impurities are formed [Redacted]

5. Provide information regarding potential genotoxic/carcinogenic impurities that might arise from [Redacted], and known/potential impurities of the semaglutide drug substance manufacturing process.
6. Specific Bioactivity should be included as a test in the release specifications for all batches of semaglutide drug substance and not “

7. Provide a tabular summary of the results from a) elevated temperature, and b) light exposure studies conducted on the semaglutide drug substance as part of the Forced Degradation Study of Semaglutide. Data should include values for Content, Related Impurities (Hydrophilic impurities, Hydrophobic impurities 1, Hydrophobic impurities 2, Sum of impurities, High molecular weight proteins (HMWP)) and Specific Bioactivity at both the start and conclusion of each study.

8. Include an annual testing of Microbial Limit Test as part of the Post-approval Stability Commitment for Semaglutide Drug Substance.

9. DMF # has been reviewed and found inadequate.

10. Address the following issues concerning the intended commercial manufacturing process for the subject drug product:
    a. Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls indicates that
    b. It is noted that the Agency requests that bioburden sampling be performed
    c. Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls indicates that
    d. Section 3.2.A.1 Facility for Formulation, Filling and Inspection of Injectable Identify the filling room(s) and filling line(s) for commercial production of the subject drug product.
    e. Provide a commitment that the subject drug product and that if a decision is made , prior approval will be sought from the Agency.

11. Regarding commercial production of the subject drug product, address the following issues:
a. Identify the equipment that will be used to (i.e. equipment manufacturer, make/model, and equipment ID).

b. Identify the equipment that will be used to (i.e. equipment manufacturer, make/model, and equipment ID). Alternatively, provide a letter of authorization to access a drug master file with the submission dates and location of the relevant validation information for the subject drug product container-closure system specified.

c. Identify the filling machine(s) (i.e. manufacturer, make/model, and equipment ID).

12. Regarding the validation of the , address the following issues:
   a. Section 3.2.P.3.4 Controls of Critical Steps and Intermediates indicates that the and update Section 3.2.P.3.4 of the submission accordingly.
   b. Section 3.2.P.3.4 Controls of Critical Steps and Intermediates indicates that the and update Section 3.2.P.3.4 of the submission accordingly.
   c. Provide data supporting the product-specific bubble point acceptance criteria for post-use integrity testing.
   d. Describe the viability studies reported in validation project nos. 8-28-8110-01 / Phase I for Semaglutide

13. Regarding the commercial manufacturing process for the subject drug product, address the following issues:
   a.

   b.
14. Provide data supporting the suitability of the sterility test method for the subject drug product.

If you have any questions, please contact Anika Lalmansingh, Regulatory Business Process Manager at (240) 402-0356.

Sincerely,

Suong Tran, PhD
Application Technical Lead
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Hello Stephanie,

We refer to NDA 209637 (semaglutide injection) and your submission dated December 5, 2016 (sequence number 001) regarding NN9535-3744 – A Long-Term, Randomised, Double-Blind, Placebo-Controlled, Multinational, Multi-Centre Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide with Type 2 Diabetes. We have the following information request:

Provide the analysis dataset(s) and executable SAS program(s) with adequate documentation to duplicate the analysis results for the post hoc mediator analysis (pages 290-292 from the Report Body).

Please confirm receipt and provide the response by April 11, 2017.

Sincerely,

Pete

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

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/s/

PETER D FRANKS
03/28/2017
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NDA  209637

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Novo Nordisk Inc.
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Attention: Stephanie DeChiaro
Director, Regulatory Affairs

Dear Ms. DeChiaro:

Please refer to your New Drug Application (NDA) dated December 5, 2016, received December 5, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Semaglutide Injection, 1.34 mg/mL.

We also refer to your December 6, 2016, correspondence, received December 6, 2016, requesting review of your proposed proprietary name, Ozempic.

We have completed our review of the proposed proprietary name, Ozempic 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:

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 Martin White, Regulatory Project Manager, in the Office of New Drugs at (240) 402-6018.

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
02/27/2017
Hello Stephanie,
Please see the statement below, and let me know if you have any additional questions.

Withdraw

Thanks,
Pete

---

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov

---

Hi Peter,
The team was hoping you could help us with some clarification on the comment we received on the CMC comparability protocol. The letter states “proposed to be submitted as a

In addition, we have filed similar in other NDAs and it has been accepted by the Agency.

Reference ID: 4065068
Would you be able to ask the reviewer for some clarification?

Thanks,
Stephanie

From: Franks, Peter [mailto:Peter.Franks@fda.hhs.gov]
Sent: Thursday, February 16, 2017 3:34 PM
To: SDEC (Stephanie DeChiaro)
Cc: White, Martin
Subject: NDA 209637 (semaglutide injection): 74-day Filing Review Communication

Hi Stephanie,

With reference to your above-mentioned NDA, I am sending you an electronic copy of the 74-day Filing Review Communication Letter (see attached). The hard copy will be sent to you via US Postal Service. I look forward to working with you in the future on this NDA.

Please acknowledge receipt of this email.

Regards,

Peter

Peter Franks, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-4197
Peter.Franks@fda.hhs.gov
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/s/

PETER D FRANKS
03/06/2017
NDA 209637

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Novo Nordisk Inc.
Attention: Stephanie DeChiaro
Director Regulatory Affairs
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Ms. DeChiaro:

Please refer to your New Drug Application (NDA) dated December 5, 2016, received December 5, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for semaglutide injection.

We also refer to your amendments dated December 6, 2016, and January 18 and 25, 2017.

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 December 5, 2017. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.)

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 August 12, 2017.

In addition, the planned date for our internal mid-cycle review meeting is May 11, 2017. A final decision regarding whether we will hold an advisory committee meeting to discuss this application has not been made at this time, but we have scheduled our review timelines to allow for this possibility. We will notify you once a decision has been made.
During our filing review of your application, we identified the following potential review issues:

**Clinical**

A. 

B. We have concerns with regard to the reported increased incidence of retinopathy with semaglutide in your development program. These data will be reviewed carefully and it may be given special consideration in our risk-benefit assessment for semaglutide.

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.

We request that you submit the following information:

**Chemistry, Manufacturing, and Controls**

1. Submit a request to withdraw

**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.

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.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

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 prescribing information (PI), Medication Guide, and Instructions for Use. 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 PI, Medication Guide, and Instructions for Use 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.
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 requests for:

- a partial waiver of pediatric studies for patients below 10 years of age with T2DM, and
- a partial deferral of pediatric studies for patients from the ages of 10 to 18 with T2DM.

Once we have reviewed your requests, we will notify you if the requests are denied.

If you have any questions, call Peter Franks, Regulatory Project Manager, at (240) 402-4197.

Sincerely,

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

{See appended electronic signature page}
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/s/

JAMES P SMITH
02/15/2017
for Jean-Marc Guettier
NDA 209637

Novo Nordisk Inc.
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Attention: Stephanie DeChiaro
Director Regulatory Affairs

Dear Ms. DeChiaro:

Please refer to your New Drug Application (NDA) dated December 5, 2016, received December 5, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Semaglutide Injection, 1.34 mg/mL.

We acknowledge receipt of your December 6, 2016, correspondence, received December 6, 2016, requesting a review of your proposed proprietary name, Ozempic.

The user fee goal date is March 6, 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 Martin White, Regulatory Project Manager, in the Office of New Drugs at (240) 402-6018.

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
02/10/2017
From: White, Martin
To: "SDEC (Stephanie DeChiaro)"
Cc: Franks, Peter
Subject: RE: NDA 209637_semaglutide injection_QT/IRT Information Request_2-07-2017
Date: Wednesday, February 08, 2017 4:58:00 PM

Stephanie,

According to the reviewers, what is meant by “analyte (name)” is any substances that were measured, including parent drugs and/or their active metabolites.

Thanks
Martin

From: SDEC (Stephanie DeChiaro) [mailto:sdec@novonordisk.com]
Sent: Wednesday, February 08, 2017 7:57 AM
To: White, Martin
Cc: Franks, Peter
Subject: RE: NDA 209637_semaglutide injection_QT/IRT Information Request_2-07-2017

Hi Martin,

Would it be possible to ask the review for clarification on #1 and what is meant by “analyte (name)”? We believe what is meant by “analyte (name)” is ‘semaglutide’, ‘moxofloxacin’ and ‘placebo’, but then we were unsure how this would differ from ‘treat (treatment for the visit)’.

Thank you for your help.

Stephanie

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Tuesday, February 07, 2017 4:14 PM
To: SDEC (Stephanie DeChiaro)
Cc: Franks, Peter
Subject: NDA 209637_semaglutide injection_QT/IRT Information Request_2-07-2017

Stephanie,

With reference to your above-mentioned NDA submitted on December 5, 2016, we have the following information request:

1. Please update and resubmit the analysis datasets for Study NN9535-3652:
   • Add height and weight to the subj.xpt
   • Add visit, visitdy (visit day, protocol day), egdy (study day), treat (treatment for the visit) to ecg.xpt and ecgaggr.xpt, also provided a SAS XPT dataset for correction factors of QTcI and QTcL for each subject.
   • Add visit, visitdy, pcdy (study day), treat (treatment for the visit), analyte (name), conc_u (concentration unit) to pkinput.xpt.
2. Please confirm whether the following baseline definition is correct:
   - Time-matched baseline is used.
   - Time 0, 12, 18, 24, 25, 26, 27, 30, 36, 42, and 48 of day 1-3 (baseline days) are used to correct corresponding time-points for drug/placebo at Visit 5, 7 and 11.
   - Time 24, 25, 26, 27, 30, 36, 42, and 48 of day 2-3 (baseline days) are used to correct 0, 1, 2, 3, 6, 12, 18, 24 for moxifloxacin/placebo at Visit 2 and 11.

Please confirm receipt and provide your response on February 21, 2017.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov
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/s/

MARTIN L WHITE
02/09/2017

Reference ID: 4054334
I confirm receipt and will work with the team on the response.

Thanks,
Stephanie

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Tuesday, February 07, 2017 4:14 PM
To: SDEC (Stephanie DeChiaro)
Cc: Franks, Peter
Subject: NDA 209637_semaglutide injection_QT/IRT Information Request_2-07-2017

Stephanie,

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   - Time 24, 25, 26, 27, 30, 36, 42, and 48 of day 2-3 (baseline days) are used to correct 0, 1, 2, 3, 6, 12, 18, 24 for moxifloxacin/placebo at Visit 2 and 11.

Please confirm receipt and provide your response on February 21, 2017.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389

Reference ID: 4052872
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov
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/s/

MARTIN L WHITE
02/07/2017
Hi Martin,

I confirm receipt and will work with the team on the response.

KR,
Stephanie

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Monday, January 30, 2017 3:44 PM
To: SDEC (Stephanie DeChiaro)
Cc: Franks, Peter
Subject: NDA 209637_semaglutide injection_Statistical Information Request_1-30-2017

Stephanie,

With reference to your above-mentioned NDA submitted on December 5, 2016, we have the following information request:

1. To justify the assumption that the volume of placebo is not impactful, please compare each semaglutide dose to its matching placebo dose using in trial MMRM for the primary endpoint in the placebo-controlled and sitagliptin-controlled studies (3623, 3626, 3627) where the control arms were pooled in analyses.

2. We acknowledge the additional imputation analyses based on retrieved dropouts you did according to FDA’s request at the pre-NDA meeting. Please conduct exploratory analyses to investigate whether the time of discontinuing treatment is impactful for the change in HbA1c from baseline.

   For Study 3623 where imputation based on retrieved dropouts cannot be performed, we suggest the following approach: impute missing endpoint HbA1c measurements in the placebo arm based on the missing at random assumption. Impute missing endpoint HbA1c measurements in the semaglutide arms based on the baseline HbA1c and the imputation model for placebo plus an error. In the placebo-controlled study, the imputation should consider a washout of any semaglutide effect for those subjects known or believed to have discontinued protocol therapy who did not have HbA1c measurement at the endpoint. Intermediate measurements in the semaglutide arms should not be included in the imputation model.

3. In regards to how you address missing data in the CVOT Study 3744, we refer you to the FDA statistical presentation at the June 28th 2016 Advisory Committee for Empagliflozin. The presentation describes how FDA used follow-up data from retrieved drop-outs to model the missing follow-up. Please provide an additional analysis based on that with clearly annotated
SAS code.

4. We notice that you did some data reallocation (reallocating measurements at unscheduled visits to scheduled visits). For each key efficacy trial, please provide a list of subjects who had data reallocation to the end-of-study visit for HbA1c and the details about the reallocation procedure.

Please confirm receipt and provide your response by **February 22, 2107**.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov
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/s/

MARTIN L WHITE
01/30/2017
Hi Martin,

I confirm receipt and will work with the team on the response.

Thanks,
Stephanie

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Stephanie,

With reference to your above-mentioned NDA submitted on December 5, 2016, we have the following information request:

- We were unable to locate the electronic datasets for the pharmacokinetic (PK) concentrations, PK parameters, pharmacodynamic (PD) concentrations, and PD parameters (if applicable) for the clinical pharmacology studies (Phase 1 studies), Study NN9535-1821 (Phase 2 study), and the Phase 3 studies for which PK and/or PD assessments were conducted. Please specify the location of this information in the electronic datasets (SAS transport files) submitted with the original NDA or submit the relevant data.

Please confirm receipt and provide your response by **noon on January 26, 2017**.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov
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/s/

MARTIN L WHITE
01/24/2017
Information Request – CMC only

NDA 209637

Dear Ms. DeChiaro,

Please refer to your New Drug Application (NDA) dated December 5, 2016, received December 5, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for semaglutide injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information requests. We request a prompt written response by **Thursday, February 2, 2017** in order to continue our evaluation of your NDA:

1. Submit an update to your submission and Form FDA 356h to reflect all registered (FEI) numbers and related Establishment DUNS numbers for the following site:

   Novo Nordisk A/S, Brennum Park,
   Hillerod, Denmark, 3400.

Kindly acknowledge receipt of this email.

Regards.

-Anika

Anika Lalmasingh, PhD
Regulatory Business Process Manager

Center for Drug Evaluations and Research (CDER)
Office of Pharmaceutical Quality (OPQ)
U.S. Food and Drug Administration
Tel: 240-402-0356
anika.lalmasingh@fda.hhs.gov
Hi,

We refer to your NDA 209637 submission for Ozempic (semaglutide) dated December 5, 2016. In the submission you reference the Type C meeting written responses on November 13, 2015, regarding the human factors/usability validation test protocol. However, your NDA submission did not include the information we requested. Specifically, the human factors validation study report, or a use-related risk analysis along with the justification for why additional human factors studies are not needed. We also requested that you conduct a differentiation testing regardless of the determination to conduct the usability portion of your human factors validation study. In order to proceed with our review, please submit by close of business Friday, January 20, 2017, the following items:

1. The human factors validation study report, or the use-related risk analysis and your justification for why additional human factors studies are not needed.
2. The differentiation testing report.
3. Five samples of each strength of the pen-injector.

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/

PETER D FRANKS
10/25/2017
NDA 209637

Novo Nordisk Inc.
Attention: Stephanie DeChiaro
Director Regulatory Affairs
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Ms. DeChiaro:

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: semaglutide injection

Date of Application: December 5, 2016

Date of Receipt: December 5, 2016

Our Reference Number: NDA 209637

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 3, 2017, 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, call me at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

Martin White, M.S.  
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/

MARTIN L WHITE
12/08/2016
IND 079754

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 for GLP-1 Analogue (NNC 0113-0217).

We also refer to the meeting between representatives of your firm and the FDA on June 9, 2010. The meeting was a milestone meeting marking the End of Phase 2 development.

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 John Bishai, Regulatory Project Manager, at (301) 796-1311.

Sincerely,

{See appended electronic signature page}

John Bishai, Ph.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosure

Meeting Minutes Attached
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: June 9, 2010
Meeting Location: White Oak Building 22

Application Number: IND 79,754
Product Name: Semaglutide
Indication: Treatment of type II diabetes
Sponsor/Applicant Name: Novo Nordisk

Meeting Chair: Mary Parks, M.D.
Meeting Recorder: John Bishai, Ph.D

FDA ATTENDEES
Mary H. Parks, M.D.  Director, DMEP
Ilan Irony, M.D.   Clinical Diabetes Team Leader, DMEP
Valerie Pratt, M.D.   Clinical Reviewer, DMEP
John Bishai, Ph.D.  Regulatory Health Project Manager, DMEP
Karen Davis Bruno, Ph.D,  Supervisor, Pharmacology/Toxicology, DMEP
Sally Choe, Ph.D.    Clinical Pharmacology Team Leader, DCP
Tim Hummer, Ph.D.  Pharmacology/Toxicology Reviewer, DMEP
Manoj Khurana, Ph.D  Clinical Pharmacology Reviewer, DCP2
Suong Tran, Ph.D.  Product Assessment Lead, ONDQA
Joseph Leginus, Ph.D.  Chemistry Reviewer, ONDQA
Todd Sahlroot, Ph.D.  Deputy Division Director and Biometrics Team Leader
Wei Liu, Ph.D.  Statistical Reviewer, Division of Biometrics

SPONSOR ATTENDEES
Ole Kim Eskerod  VP, Medical & Science
Anne Flint   Specialist, Clinical Pharmacology
Vibeke Hatorp  Director, Regulatory Affairs
Christine Bjorn Jensen  Director, Medical
Peter Kristensen  Sr. Vice President, Global Development
Henrik Kim Nielsen  Corporate VP, Regulatory Affairs
Ulf Linderoth Norlin  Sr. Project Manager, Preclinical
Niels C. Nyborg  Project Director, Preclinical
Niklas Ohrner  Corporate Project VP, Global Development
<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
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<tbody>
<tr>
<td>Gabriela Martinez Ravn</td>
<td>International Project Statistician, Biostatistics</td>
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<tr>
<td>Zaki Salanti</td>
<td>Specialist, Toxicology</td>
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<tr>
<td>Dorte Waaben</td>
<td>Project Director, CMC Project Planning and Management</td>
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<tr>
<td>Lois Kotkoskie</td>
<td>Senior Director Regulatory Affairs</td>
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<tr>
<td>Mary Ann McElligott</td>
<td>Associate VP Regulatory Affairs</td>
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<tr>
<td>Mads Frederik Rasmussen</td>
<td>Executive Director, Clinical Development</td>
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<tr>
<td>Elizabeth L. Tan</td>
<td>Director Regulatory Affairs</td>
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DISCUSSION

Chemistry

**Question 1:** Does the Agency agree that the comparability data package qualifies the improved drug substance process for phase 3a clinical trials and marketing authorization approval?

**Agency Response:** We agree that the analytical and physico-chemical data provided support the conclusion that batches of semaglutide drug substance to be used for phase 3a clinical studies (batches are comparable with semaglutide drug substance batches used for phase 1 and 2). Any conclusions concerning the appropriateness of marketing authorization approval for semaglutide drug substance batches will be made during the NDA review cycle.

**Sponsor’s Response:** Agreed

**Question 2:** Does the Agency agree with Novo Nordisk’s designation of starting materials (substances) for manufacture of drug substance for phase 3a clinical trials and marketing authorization?

**Agency Response:** The designation of the starting materials for the drug substance is acceptable provided that:

i) If the are purchased, the manufacturer’s name and address should be provided. Test results, including optical rotation, melting point, chemical and chiral purity and chromatographic behavior (e.g., HPLC) should be provided in a Certificate of Analysis (CoA) by the manufacturer who has demonstrated the capability of supplying materials of consistent quality. If the qualified vendor provides a CoA, the sponsor should run a confirmatory identity test, at a minimum, upon receipt.

ii) If the are synthesized by the sponsor, a detailed description of their syntheses and complete characterization should be provided. At a minimum, their chemical structures should be characterized by NMR (H and C), IR spectroscopy, mass spectrometry and optical rotation. Purity should be ensured by monitoring by, for example, HPLC.
However, we do not agree with your proposal to designate 
starting material for semaglutide drug substance. As a 
A starting material should be separated from the final intermediate by 
several reaction steps that result in isolated and purified intermediates. This provides 
some assurance that levels of potential new impurities in future sources of the starting 
material(s) would be reduced and/or eliminated in the drug substance. The identification 
of starting material(s) 3 or more synthetic steps removed from the formation of the drug 
substance provides regulatory oversight over the extended synthesis.

Compounds are more appropriate starting materials 
since these fulfill a number of the criteria for starting materials, including a) significant 
contributions to the chemical structure of the active moiety of the drug substance, and b) 
more than 3 reaction/purification steps removed from the drug substance.

Sponsor’s Response: Agreed

Nonclinical

Question 3a: Does the Agency consider the reproduction toxicology data available to date 
adequate to allow inclusion of women of childbearing potential in future clinical trials, 
including phase 3 trials, provided that they are confirmed not pregnant and are required to 
use an effective contraceptive method?

Agency Response: Yes, provided women of child-bearing potential use two forms of 
birth control. The informed consent document should be updated to include current 
nonclinical information. A plan to follow potential unintended pregnancies should be 
clearly stated in the study protocol.

Sponsor’s Response: The sponsor questioned the need for two forms of birth control and 
inquired about the Division’s primary concern. After further discussion, the sponsor 
agreed to utilize two forms of birth control, one physical barrier and one systemic 
contraceptive.

Agency Response: It was explained that the request for two forms of birth control stems 
from the following concerns: 1) there is currently insufficient evidence to conclude that 
the teratogenicity observed in rats is not relevant to humans; 2) some malformations were 
observed in the embryo-fetal developmental toxicology study in monkeys and because 
historical control databases are generally small for developmental toxicology studies in 
monkeys, a relationship to test article cannot be discounted at this time; 3) there is 
currently no available data regarding the potential of semaglutide affecting the efficacy of 
oral contraceptives. As more data become available, contraception requirements could be 
reduced.
**Question 3b: Does the Agency consider the proposed non-clinical program (mode-of-action studies and embryo-fetal development studies in cynomolgus monkeys) adequate to further explain the observations made in the rat embryo-fetal development studies?**

**Agency Response:** The sponsor's proposed approach appears reasonable at this time. A determination on whether the mechanistic data explain the abnormal fetal developmental observations in rats and the relevance to humans will ultimately depend on the data from the proposed studies. Depending on the study findings, additional studies could be warranted.

*Sponsor’s Response:* The sponsor clarified that the initiation of dosing for the ongoing Segment III monkey study is the same gestation day (GD16) that was used for the Segment II study; therefore, additional data will become available to further evaluate the potential drug-relationship to skin reddening, as well as to the malformations occurring at a low incidence, that were observed in the Segment II monkey study.

**Clinical Pharmacology**

**Question 4: Does the Agency agree that the proposed clinical pharmacology program is adequate to support the proposed indication?**

**Agency Response:** Your proposed clinical pharmacology program appears reasonable. However, we have the following specific comments:

1. The renal impairment study. We recommend following the full design as in Agency’s experience with GLP-1 receptor agonists, data from severe renal impairment/ESRD may not necessarily be predictive of expected pharmacokinetic profile in mild or moderate renal impairment patients.

2. *Your proposed plan for DDI studies, which typically involve over 20 weeks of continuous exposure to semaglutide. We recommend you consider conducting these evaluations in Type 2 DM subjects who are newly diagnosed and are maintained on diet and exercise to minimize confounding with the co-administered drugs.*

*Sponsor’s Response:* Agreed
**Question 5:** Does the Agency agree with the maximum dose and study design for the proposed thorough QTc study (Trial NN9535-3652)?

**Agency Response:** Please submit your QTc protocol for review by the QT Interdisciplinary Review Team. Please include an evaluation of the effects on heart rate and the PR interval.

**Sponsor’s Response:** Agreed

**Question 6:** The planned human metabolism study aims to determine the metabolite profiles in order to compare it with the profiles obtained in the preclinical toxicity species. Does the Agency consider the proposed study design and measurements planned for the ADME study adequate to provide sufficient documentation for marketing approval?

**Agency Response:** Your plan seems reasonable. However, please clarify the rationale behind choice of $^3$H over $^{14}$C label.

Meeting Discussion: Novo Nordisk explained that based on their non-clinical experience, they are comfortable in characterizing the metabolic profile of semaglutide using the $^3$H label. Agency mentioned that the concern over using $^3$H label is that it can easily be exchanged with body water and pose difficulties in interpreting the data from ADME studies.

**Question 7:** Does the Agency agree that the proposed population pharmacokinetics analysis plan, involving 100% of available data from all subjects in two out of six Phase 3a studies, is sufficient for investigating the effects of pre-specified covariates (body weight, dose, sex, race, injection site, time after first dose, age and ethnicity) on pharmacokinetics of semaglutide?

**Agency Response:** Yes, we agree that conceptually you should be able to conduct a covariate analysis from the planned Phase 3 trials. However, we are unable to comment on the sufficiency of expected data for investigating the effects of covariates as this will truly be determined by the distribution of these covariates in your final data set.

Also, it is not clear what injection sites will be used in the Phase 3 trial, and if they will be fixed for a given subject to allow for use of injection site as categorical covariate.

We recommend that you collect the semaglutide exposure data, if possible, in all the Phase 3 trials including the CV safety trial for a comprehensive evaluation of exposure-response relationship for efficacy and safety, and effect of covariates.

Overall, your proposed population pharmacokinetics analysis plan appears reasonable. However, we encourage you to submit the detailed analysis plan for Agency’s review. This plan should also outline the proposed sample collection plan, NONMEM dataset definition table and the contents to be submitted for regulatory review. You can further refer to the following general pharmacometric data and models submission guidelines:

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in
a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Please refer to the following link for more details:
(http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm167032.htm)

Clinical

**Question 8** Assuming that the data are supportive:

**Question 8a:** Does the Agency agree that the proposed phase 3a development program for semaglutide is adequate to support the following indication? Does it have any additional comments to the program?

**TRADE NAME (semaglutide) is a GLP-1 agonist indicated to improve glycemic control in patients with type 2 diabetes mellitus as an adjunct to diet and exercise.**

**Agency Response:** No, we have the following comments on the proposed phase 3a development program:

- **Semaglutide**, if approved, will be indicated for use in adults with type 2 diabetes, and will not be recommended as first line therapy (similar to liraglutide).
  - **Sponsor’s Response:** Agreed.

- You propose a hepatic steatosis substudy in studies 1 and 2 (3623 and 3624). Please also include a hepatic steatosis substudy in trial 5 (3627).
  - **Meeting Discussion:** The agency clarified that the recommendation to include a hepatic steatosis substudy in trial 5 (3627) was not related to a safety concern. It is a suggestion, not a requirement. The agency pointed
out that, if the sponsor intends to add its findings to the semaglutide label, the comparison of liver effects to other drug products, if deemed clinically relevant, becomes a review issue.

- You include an assessment of patient-reported outcomes in phase 3 studies. Please clarify the purpose of this assessment. Please be aware that if you intend to label the results of these assessments, these patient-reported outcomes must be submitted for review by our Study Endpoints and Labeling Development (SEALD) Team.
  
  ○ Sponsor’s Response: The sponsor does not intend on labeling patient reported outcomes.

- Regarding CV study 6 (3744):
  
  ○ In defining the primary endpoint, you use terms such as endpoints. These terms are not clear for the purposes of an adequate review of study design, study power and statistical analyses. The assessment of the upper bound of the 95% CI of the hazard ratio will be based on the major adverse CV endpoints of CV death, nonfatal MI, and nonfatal stroke. The agency considers other CV events as secondary endpoints.
    
    ○ Sponsor’s Response: The sponsor will replace the word ”primary” with “primary” and with “secondary”. This was acceptable.

  ○ Sponsor’s Response: Agreed.

Question 8b: Does the Agency agree that the proposed dose levels of background medication in add-on clinical trials, i.e. of metformin, sulfonylureas and thiazolidinediones are appropriate to reflect the target population and support the use of semaglutide in this patient population?

Agency Response: You propose, in study 1 (3623), that a fraction of patients (maximum 40%) may be treated with half-doses of metformin or a SU. Please ensure that the washout from metformin and SU is sufficient to establish a baseline for appropriate pooling with truly drug-naïve subjects’ data. We recommend stratification of the randomization scheme based on presence or absence of background therapy at screening.

Sponsor’s Response: The sponsor agreed.
Question 8c: Does the Agency agree with the choice and selected dose levels of comparators in the proposed development program for semaglutide?

Agency Response:

- Please clarify [REDACTED] in study 2 (3624).

  Meeting Discussion: [REDACTED]

  The agency and stated that labeling would be a review issue.

- Please be aware that the efficacy of semaglutide compared to glargine in Study 3 (3625) will a review issue, based on adequate titration of glargine.

  Sponsor’s Response: Agreed.

Question 8d: Does the Agency agree to the proposed rescue criteria for the phase 3a trials?

Agency Response:

- The proposed rescue criteria are acceptable. However, we caution you [REDACTED] and affect the interpretability of the efficacy results. Please consider using a “FPG only” criterion until week 16, and perhaps a combination of FPG and/or HbA1c beyond that timepoint.

  Meeting Discussion: The sponsor proposed FPG >240 mg/dl from week 6 – 16 [REDACTED] and FPG >200 mg/dl or HbA1c >8% from week 16 [REDACTED] to 56. The agency agreed. The sponsor plans a sensitivity analysis on all data.

- You propose that the rescue medication will be at the discretion of the investigator [REDACTED]. Consider standardizing rescue therapy within phase 3 trials to avoid confounding the safety results.

  Meeting Discussion: The sponsor considered standardizing rescue therapy but felt with this global development program it was not feasible. Instead, it proposed rescue therapy using a class of antidiabetic medications. The agency agreed.
The agency inquired... The sponsor replied, it was unsure how it could use that data. The agency replied, it would better reflect clinical practice. The sponsor replied, it will consider... of semaglutide.

Question 8e: Can the Agency confirm the acceptability of the inclusion/exclusion criteria for the proposed phase 3a trials NN9535-Trials 3623,-3624, -3625, -3626, -3627, and 3744 to ensure that enrolled subjects are representative of the target population (type 2 diabetes), including from a CV risk perspective?

**Agency Response:** Please clarify your plan to evaluate the use of semaglutide in renally impaired diabetic subjects. Patients with renal function impairment constitute a significant proportion of the target population for semaglutide and the relative efficacy and safety of semaglutide need to be assessed in these patients.

Meeting discussion: The sponsor does not plan to exclude renally impaired subjects. It will do its best to enroll these subjects and analyze them in a pooled analysis for efficacy and safety. The agency agreed but said there should be a meaningful number of renally impaired subjects (e.g. 100 exposed to drug). The sponsor agreed.

Question 9a: Does the Agency agree that the proposed number of exposed subjects and the duration of exposure in the proposed phase 3a program at the time of NDA filing are sufficient to support marketing authorization approval?

**Agency Response:** Yes, the duration of exposure in the proposed phase 3a program at the time of NDA filing may be sufficient, pending new safety issues becoming apparent in the Phase 3 program.

**Sponsor’s Response:** Agreed.

Question 9b: Does the Agency agree that the requirement for 18 month safety exposure data at the time of NDA submission, as stated in the February 2008 guidance for developing drugs for diabetes mellitus, can be sufficiently covered by the patient population in the cardiovascular safety trial NN9535-3744 alone?

**Agency Response:** Yes, the 18 month safety exposure data at the time of NDA submission can be covered by CV safety trial 3744 alone. However, we recommend that you evaluate the effects of prolonged semaglutide exposure in the general diabetic population, in addition to those with high CV risk, should the safety data in CV study 3744 not be favorable.

Meeting Discussion: The sponsor thanked the agency for agreeing and pointed out that controlled extension studies are planned in the DM trials. The agency agreed. The sponsor stated approximately 30% of subjects are at increased risk in the DM trials, so a mixed population would be studied if the trials are extended.
Question 10a: Does the Agency agree to the selection of the two maintenance doses for the proposed phase 3a program?

Agency Response: Yes, we agree to the selection of the two maintenance doses for the proposed phase 3a program.

Sponsor’s Response: Agreed.

Question 10b: Does the Agency agree to the proposed dosing regimen of a titration dose (0.25 mg) and two maintenance doses (low dose of 0.5 mg, high dose of 1.0 mg)?

Agency Response: Yes, we agree to the proposed dosing regimen of a titration dose (0.25 mg) and two maintenance doses (0.5 and 1.0 mg).

Sponsor’s Response: Agreed.

Question 10c: Does the Agency agree to the proposed treatment algorithm for the semaglutide adjustable arm in Trial 2 (NN9535-3624), in which treatment response will be evaluated at 3-month intervals based on HbA1c (maintain or escalate dose), and in which the high dose may be reduced to the low dose if tolerability is considered unacceptable?

Agency Response: Yes, we agree to the proposed treatment algorithm for the open label semaglutide adjustable arm in trial 2 (3624). However, data from that treatment arm cannot be combined with data from the other semaglutide equivalent doses for the purpose of efficacy analyses. In addition, the numbers of subjects uptitrated for efficacy or downtitrated for tolerability may be insufficient to form a robust conclusion on this treatment algorithm and inform labeling.

Meeting Discussion: The sponsor confirmed that the arm is exploratory; it does not intend to use it to demonstrate efficacy...

Question 11: Does the Agency agree to the proposed safety monitoring for the phase 3a clinical program?

Agency Response: Your propose pancreatitis will be a MESI in studies 1-5 (3624-3627). Please also include neoplasms (including thyroid), acute renal failure, hypoglycemia, and immunogenicity events as MESI in these studies. Please clarify your plan for evaluating antibody formation in phase 3 trials.

Meeting Discussion: The sponsor clarified where in the meeting package the proposed safety monitoring for phase 3a was explained (e.g., page 141). The agency agreed this is acceptable but inquired about antibody monitoring in phase 3. The sponsor responded that antibody samples will be collected throughout the trials on all subjects. Samples will be run at the end of the trial. If the screening assay is positive, crossover and neutralizing antibody assays will be run. The agency responded that this is acceptable, given our understanding of semaglutide at this time.
**Question 12a: Does the Agency agree with the proposal?**

**Agency Response:** No.

- Please clarify your plan to demonstrate that the upper bound of the two-sided 95% CI for the estimated risk ratio is less than [a redacted value]. Consider increasing the duration of CV study 6 (3744) to adequately address this non-inferiority margin.

**Meeting Discussion:**

- You have currently planned [a redacted plan].

  To minimize the probability of this scenario, we suggest you conduct one or more interim analyses with a group sequential or alpha-spending function approach to control the overall type I error rate. The statistical approach should use the total number of CV events as a measure of information.

**Meeting Discussion:** See above.

**Question 12b: Does the Agency agree that the proposed non-inferiority margin versus comparators (including placebo and active comparators) of 1.8 for the upper limit of a 2-sided 95% confidence interval is sufficient for marketing authorization approval?**

**Agency Response:** Yes, the proposed non-inferiority margin versus comparators (including placebo and active comparators) of 1.8 for the upper limit of a 2-sided 95% confidence interval is sufficient for marketing authorization approval, depending also on a favorable overall benefit to risk profile.

**Sponsor’s Response:** Agreed.
Question 12c: Does the Agency agree with the proposed primary analysis comparing total semaglutide to total comparators conducted on the FAS following the intention-to-treat principle?

Agency Response: Yes, we agree with the proposed primary analysis comparing total semaglutide to total comparators conducted on the FAS following the intention-to-treat principle. Please also conduct sensitivity analyses with patients as treated, adjusted for drug exposure, etc.

Sponsor’s Response: The sponsor agreed to conduct a sensitivity analysis.

Question 13: Does the Agency agree that data collected either after discontinuation of randomized treatment or addition of rescue medication can be excluded from the primary efficacy analysis and secondary efficacy comparisons?

Agency Response: Yes, we agree that data collected either after discontinuation of randomized treatment or addition of rescue medication can be excluded from the primary efficacy analysis but included in sensitivity efficacy comparisons.

Sponsor’s Response: Agreed.

Question 14: Does the Agency agree with Novo Nordisk’s plan to seek a waiver for subjects below 10 years of age and deferral for adolescents 10-17 years until safety and efficacy of semaglutide has been thoroughly demonstrated in adults?

Agency Response: Yes, we generally agree with plan for a waiver and deferral of pediatric studies. However, a decision will not be made until after the NDA is filed. Please include your plans for pediatric studies in your NDA. Please include the following in your deferral request: reason, certification of the grounds for deferring the assessment, a description of planned or ongoing studies, evidence studies are or will be conducted, and a timeline for completion of such studies. We encourage early discussions of your plans during the Phase 3 program.

Meeting Discussion: The sponsor stated it will discuss the pediatric plan. The agency agreed.

Additional Discussion:

Agency: Will semaglutide be used in an approved device? Use needs to be reviewed by CDRH and DMEPA.

Sponsor: Phase 3 will be conducted using an approved devise. The device for market has not been decided.

Agency: In that case, a separate review will be required. Please submit your materials early to CDRH.
**Sponsor:** How early should we submit the information? With the NDA review?

**Agency:** Yes with the NDA review.

Agency: The Agency asked the sponsor if they understand the effect of semaglutide on gastric motility over the full dosing interval, for example, whether the slow-down of gastric motility is observed throughout the dosing interval at steady-state or only around Tmax.

**Sponsor:** Sponsor mentioned they do not know.

Agency: The Agency suggested that the sponsor consider conducting a study evaluating the gastric motility with paracetamol given at different times during the dosing interval (e.g. co-administration, around Tmax, and during the terminal phase). This data will provide useful information in the label with regards to spacing the administration of other co-administered drugs known to be affected by reduced GI motility, if needed.
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<td>NOVO NORDISK INC</td>
<td>NNC 011309217 Injection; NN9535 Injection</td>
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/s/

JOHN M BISHAI
08/24/2010
LATE-CYCLE COMMUNICATION DOCUMENTS
NDA 209637

Novo Nordisk Inc.
Attention: Stephanie DeChiaro
Director Regulatory Affairs
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Ms. DeChiaro:

Please refer to your New Drug Application (NDA) dated December 5, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for semaglutide injection.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 19, 2017.

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

If you have any questions, call Peter Franks, Regulatory Project Manager at (240) 402-4197.

Sincerely,

{See appended electronic signature page}

William Chong, M.D.
Clinical Team Leader
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes
Applicant Slides
MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 19, 2017
Meeting Location: FDA White Oak, Building 22, Room 1421

Application Number: NDA 209637
Product Name: semaglutide injection
Applicant Name: Novo Nordisk Inc.

Meeting Chair: William Chong
Meeting Recorder: Peter Franks

FDA ATTENDEES
Office of Drug Evaluation II
Mary Thanh Hai, MD, Deputy Director

Division of Metabolism and Endocrinology Products
James P. Smith, MD, MS, Deputy Director
William Chong, MD, Clinical Team Lead
Andreea Lungu, MD, Clinical Reviewer
Julie Van der Waag, MPH, Chief, Project Management Staff
Peter Franks, MS, Regulatory Project Manager

Office of Surveillance and Epidemiology
Till Olickal, PhD, PharmD, Risk Management Analyst, DRISK

Division of Biostatistics
Eugenio Andraca-Carrera, PhD, Statistical Team Lead
Ya-Hui (Catherine) Hsueh, PhD, Mathematical Statistician
Jiwei He, PhD, Mathematical Statistician

Office of Clinical Pharmacology
Shalini Wickramaratne Senarath Yapa, PhD, Reviewer
Justin Earp, PhD, Reviewer

Division of Transplant and Ophthalmology Products
Wiley Chambers, MD, Supervisory Medical Officer, Ophthalmology

Office of Biotechnology Products
Daniela Verthelyi, M.D., Ph.D, Team Lead, Laboratory of Immunology
Mohanraj Manangeeswaran, Ph.D, Reviewer, Laboratory of Immunology
Late-Cycle Meeting Minutes

APPLICANT ATTENDEES
Anders Hvelplund, Senior Director, Medical and Science
Anne Phillips, Senior Vice President, Clinical, Medical & Regulatory Affairs, US
David Truloff, Director, Safety Surveillance
Henrik Kim Nielsen, Corporate Vice President, Regulatory Affairs
Katarina Jelic Mailboe, Director, Regulatory Affairs
Lars Holm Damgaard, Senior Statistical Director
Lene Melchiorsen, Project Vice President
Mads Frederik Rasmussen, Corporate Project Vice President
Marie Lindegaard, Vice President, Medical and Science
Robert Clark, Vice President, Regulatory Affairs, US
Stephanie DeChiaro, Director, Regulatory Affairs, US
Stephen Langford Gough, Vice President, Senior Principal Clinical Scientist

1.0 BACKGROUND

NDA 209637 was submitted on December 5, 2016, for semaglutide injection.

Proposed indication(s): As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

PDUFA goal date: December 5, 2017

The FDA issued a Background Package in preparation for this meeting on September 12, 2017.

2.0 DISCUSSION

1. Discussion of Substantive Review Issues:

Clinical: Diabetic Retinopathy Complications

Discussion: The FDA reiterated that the increased incidence of diabetic retinopathy complications associated with semaglutide that was observed in the SUSTAIN 6 trial remains a concern. While the retinopathy endpoints and the manner in which the data were collected have limitations, the findings remain concerning and a matter that continues to be under review. This will be a topic for the upcoming Advisory Committee (AC) meeting, where the FDA will seek input from panel members to inform decision making.

Novo Nordisk acknowledged the retinopathy findings and the FDA’s concern.
Novo Nordisk asked if these proposals were aligned with the FDA’s current thinking on the retinopathy issue.

The FDA responded that it was too early to comment on specifics about a REMS, The AC input will help inform the FDA on any specific concerns that the panelists have in regards to the safety of the product. Novo Nordisk inquired whether the FDA had looked across the clinical program (i.e., outside of SUSTAIN 6), to help with the overall assessment of the retinopathy signal. The FDA stated that they had looked across the entire program and encouraged Novo Nordisk to do the same as part of their analysis and AC meeting preparation, although limitations of those analyses should be considered as well. Novo Nordisk asked if there were any other analyses that could be provided at this time to help the FDA with its assessment, and the FDA responded that they could not currently recommend any additional analyses. Novo Nordisk indicated that they have looked for other possible mechanisms besides a glucose effect, and haven’t been able to identify other mechanisms to date. The FDA acknowledged that the glucose effect could be the mechanism but whether this is definitively the mechanism remains unclear. As the FDA has not identified such a signal before in other development programs, input from the AC panel will be important in considering the significance of the findings as well as possible mechanisms.

2. Discussion of Minor Review Issues

Immunogenicity: Assay

**Discussion:** The FDA reiterated that the current assay that Novo Nordisk has developed to detect neutralizing antibodies is inadequate, and that there may be a need for a post-market commitment to develop a more sensitive assay to assess the neutralizing activity of antisemaglutide antibodies. Novo Nordisk wanted confirmation that their recent response to the IR, received on September 8, 2017, was reviewed and taken into account. The FDA responded that it was taken into account and the stance that the assay is inadequate has not changed.

3. Additional Applicant Data

**Discussion:** Novo Nordisk presented 3 slides via handouts that discussed the SUSTAIN 6 data, as well as a plan for a post-marketing study for diabetic retinopathy (see Discussion in 1, above). Additional questions for the FDA were included in these slides.

Novo Nordisk inquired on the acceptability of the August 14, 2017, device submission pertaining to the modification of the multi-dose pen injector. The FDA stated that while representatives from DMEPA and CDRH were unable to attend the late-cycle meeting, there are no current issues with the proposed device modification at this time. The FDA asked for the rationale for two different pen injectors when a single device could deliver the three proposed dose levels. Novo Nordisk stated that they believe this will offer added convenience for patients.
Novo Nordisk inquired whether the FDA believes that the data from SUSTAIN 6 are adequate to conclude cardiovascular safety, and whether a postmarketing CVOT would be required. The FDA stated that it was premature to discuss PMRs, but that the opinion of the AC panel would be considered (see discussion under 5, below).

Novo Nordisk inquired as to whether there were any questions with regards to the re-adjudication of the events from the open-label trials. The FDA noted that there were significantly fewer benign neoplasms in the second adjudication, and inquired on the possible causes of this. Novo Nordisk stated that the second adjudication process was very similar to the first, and all but 2 adjudicators were the same. Novo Nordisk also stated that the adjudication instructions were slightly more detailed with later events and that there may have been additional data reviewed in the re-adjudication. This may have altered some adjudication decisions for the neoplasm events. The FDA asked if Novo Nordisk could provide information on the differences leading to changes in adjudication determinations. Novo Nordisk agreed to provide information on reasons for changes in adjudication determination.

4. Information Requests

There are no outstanding Information Requests as of the meeting.

During the meeting, the clinical reviewer requested additional information on the re-adjudicated data (see discussion under 3, above). Additionally, the clinical reviewer requested some additional data, including summary statistics of the median change from baseline for UACR (mg/g) that is needed at this time, and data collected after discontinuation of study drug. Novo Nordisk stated that data after discontinuation was not routinely collected and therefore cannot be provided.

5. Discussion of Upcoming Advisory Committee Meeting

Discussion: FDA stated that AC panel members will be asked to provide an opinion on the evidence of efficacy, findings for cardiovascular risk/safety, and findings for diabetic retinopathy complications. AC panel members will be asked to provide individual opinions on the efficacy and safety of semaglutide.

Acknowledging Novo Nordisk’s proposal with regards to the retinopathy findings (see attached slides), the FDA advised Novo Nordisk to consider whether a discussion of [REDACTED] at the AC meeting would be beneficial, as it could have the potential to influence the panelists’ conclusions on the retinopathy data under discussion. The FDA asked for clarification whether the intention of the microvascular composite endpoints were for safety or efficacy, as review of the protocol and SAP for SUSTAIN-6 suggests that these were safety endpoint. Novo Nordisk stated that this was to be a secondary efficacy endpoint. The FDA ophthalmology consultant noted that their
division requires that results supporting retinopathy claims must be replicated; therefore, one trial would have been inadequate from his standpoint, even if conducted appropriately.

Post-meeting Comment: Following the LCM, Novo Nordisk was asked to indicate where in the SAP or protocol the microvascular endpoints (which included the retinopathy composite) were defined as efficacy endpoints. Novo Nordisk acknowledged that these were not specifically identified as efficacy endpoints but that their expectation was that a benefit on these endpoints might be seen.

With regards to the assessment for cardiovascular risk/safety, the FDA stated that they would like to ensure that the AC discussion is a productive discussion and is focused on the data for semaglutide and does not become a policy discussion on the 2008 Guidance. The FDA will communicate this to the Chair of the AC prior to the meeting to try and ensure that the meeting discussion stays on topic.

Novo Nordisk asked about the re-adjudicated data and whether this will be presented. The FDA stated that they do not intend to present any of the re-adjudicated data at the AC meeting.

6. REMS or Other Risk Management Actions

Discussion: FDA stated that it was premature to provide comment on a REMS. The review of the REMS is ongoing. Novo Nordisk acknowledged the need to be added to the MTC registry.

7. Postmarketing Requirements/Postmarketing Commitments

Discussion: FDA stated that it was premature to discuss PMRs at this time. Preliminarily, the FDA anticipates at least 2 immunogenicity-related PMCs. Both have to do with the current immunogenicity assay that Novo Nordisk has developed. Novo Nordisk will continue to work on the assay and provide the data as it becomes available. No other PMRs or PMCs were discussed at the meeting.

8. Review Plans

Discussion: Novo Nordisk inquired on the goal date of the application and whether the FDA felt that the review could be completed and action could be taken by that time. The FDA responded that it intends to take an action on the goal date, but that it is premature to comment on this until after the AC meeting.
9. **Wrap-up and Action Items**

Re-adjudicated data sets, as discussed in #3 and #4 above, will be provided to the FDA.

Additional clinical data, including summary statistics of the median change from baseline for UACR (mg/g), will be provided to the FDA.

Novo Nordisk will continue to communicate progress and associated data pertaining to their immunogenicity assay development.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.
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/s/

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WILLIAM H CHONG
10/17/2017
Dear Ms. DeChiaro:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for semaglutide injection.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 19, 2017. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Peter Franks, Regulatory Project Manager, at (240) 402-4197.

Sincerely,

James Smith, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package
LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: September 19, 2017
Meeting Location: FDA White Oak, Building 22, Room 1421

Application Number: NDA 209637
Product Name: semaglutide injection
Indication: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant Name: Novo Nordisk Inc.

FDA ATTENDEES (tentative)
Office of Drug Evaluation II
Mary Thanh Hai, MD, Deputy Director
Sara Stradley, MS, Associate Director for Regulatory Affairs

Division of Metabolism and Endocrinology Products
James P. Smith, MD, MS, Deputy Director
William Chong, MD, Clinical Team Lead
Andreea Lungu, MD, Clinical Reviewer
Elisabeth Hanan, MS, Regulatory Project Manager for Safety
Julie Van der Waag, MPH, Chief, Project Management Staff
Peter Franks, MS, Regulatory Project Manager

Office of Surveillance and Epidemiology
Elizabeth Everhart, MSN, RN, ACNP, DRISK Team Lead
Till Olickal, PhD, PharmD, Risk Management Analyst, DRISK
Hina Mehta, PharmD, DMEPA Team Lead
Susan Rimmel, PharmD, Safety Evaluator, DMEPA

Division of Biostatistics
Eugenio Andraca-Carrera, PhD, Statistical Team Lead
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Jiwei He, PhD, Mathematical Statistician

Office of Clinical Pharmacology
Manoj Khurana, PhD, Clinical Pharmacology Team Lead
Shalini Wickramaratne Senarath Yapa, PhD, Reviewer
Justin Earp, PhD, Reviewer

Center for Devices and Radiological Health
Carolyn Dorgan, PhD, Team Lead, General Hospital Devices Branch
Sarah Mollo, PhD, Reviewer, General Hospital Devices Branch
Division of Transplant and Ophthalmology Products  
Wiley Chambers, MD, Supervisory Medical Officer, Ophthalmology

Office of Biotechnology Products  
Daniela Verthelyi, M.D., Ph.D, Team Lead, Laboratory of Immunology  
Mohanraj Manangeeswaran, Ph.D, Reviewer, Laboratory of Immunology

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Henrik Kim Nielsen, Corporate Vice President, Regulatory Affairs  
Katarina Jelic Maiboe, Director, Regulatory Affairs  
Lars Holm Damgaard, Senior Statistical Director  
Lene Melchiorsen, Project Vice President  
Mads Frederik Rasmussen, Corporate Project Vice President  
Marie Lindegaard, Vice President, Medical and Science  
Robert Clark, Vice President, Regulatory Affairs, US  
Stephanie DeChiaro, Director, Regulatory Affairs, US  
Stephen Langford Gough, Vice President, Senior Principal Clinical Scientist  
Lene Garde Sommer, Vice President, Regulatory (Devices)

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.
BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Diabetic Retinopathy complications observed in SUSTAIN 6.

ADVISORY COMMITTEE MEETING

Date of AC meeting: October 18, 2017

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: To be determined

Potential questions and discussion topics for AC Meeting are still under discussion. We anticipate that the discussion and questions will focus on the benefits and risks of semaglutide, including discussion of the findings related to diabetic retinopathy in the CVOT.

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location: http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm

REMS OR OTHER RISK MANAGEMENT ACTIONS

The review of the proposed REMS is ongoing.

LCM AGENDA

1. Introductory Comments (RPM/CDTL)
   Welcome, Introductions, Objectives of the meeting

2. Discussion of Substantive Review Issues
   Each issue will be introduced by FDA and followed by a discussion.
Clinical: Diabetic Retinopathy Complications. An increased incidence of retinopathy associated with semaglutide was observed in the SUSTAIN 6 trial. Post hoc analyses conducted by the sponsor assessed the possible mediator effect of a rapid reduction in HbA1c on the risk of retinopathy. These analyses have some limitations and are generally considered hypothesis-generating. The data related to retinopathy remain under discussion by the review team.

3. Discussion of Minor Review Issues
   - Immunogenicity: Deficiencies have been identified in the assay developed to assess neutralizing activity. PMCs will be recommended to address the development of a suitable assay to assess neutralizing activity of anti-semaglutide antibodies and to assess the incidence of neutralizing antibodies in the treated population.

4. Discussion of Upcoming Advisory Committee Meeting

5. REMS or Other Risk Management Actions

The review of the proposed REMS is ongoing.

6. Postmarketing Requirements/Postmarketing Commitments

If your application is approved, you will be required under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) to complete 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. Portions of this assessment may be completed as a postmarketing requirement (PMR). In addition, if your application is approved, we anticipate that you will be required to conduct a medullary thyroid carcinoma case series registry of at least 15 years duration, consistent with ongoing PMRs for other approved GLP-1 agonist products. Note that this information should be considered preliminary and we will provide you with a more detailed list of PMRs and postmarketing commitments (PMCs) later in the review cycle.

At this time, we are anticipating postmarketing commitments to address the following issues, at minimum:

PMC 1: Novo Nordisk is required to develop a sensitive assay to assess the neutralizing activity of anti-semaglutide antibodies

PMC 2: Novo Nordisk is required to utilize the sensitive assay to assess the neutralizing activity of anti-semaglutide antibodies developed for PMC1 to assess the incidence of neutralizing antibodies in subjects treated with semaglutide. The samples can be derived
from pre-existing clinical studies, but a plan to select the samples should be agreed upon with the Agency.

The possibility of additional PMRs or PMCs remains under internal discussion as well. Some may be informed by the discussion at the AC meeting.

7. Review Plans
   • Completion of discipline reviews
   • Obtain feedback from Advisory Committee panel
   • Completion of secondary and tertiary reviews
   • Labeling discussions (as needed)

8. Wrap-up and Action Items
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES P SMITH
09/12/2017