CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203313Orig1s000
203314Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	NDA 203313
Product Name:	RYZODEG 70/30 (insulin degludec and insulin aspart injection) solution for subcutaneous injection
PMR #1 Description:	An open-label, 16-week, randomized, controlled efficacy and safety trial comparing Ryzodeg 70/30 (insulin degludec and insulin aspart injection) administered once daily with a main meal and insulin aspart for additional meals to insulin detemir, in combination with mealtime insulin aspart at each meal, in pediatric patients with type 1 diabetes mellitus ages 1 to 17 years (inclusive).
Final Report Submission:	June 2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Ryzodeg is ready for approval in adults; however, pediatric studies had been deferred until adequate safety data were available.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this PMR is to establish the safety and efficacy of Ryzodeg in pediatric patients ages 1 to 17 years (inclusive).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

  ☐ Accelerated Approval (subpart H/E)
  ☐ Animal Efficacy Rule
  ☒ Pediatric Research Equity Act
  ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

  ☐ Assess a known serious risk related to the use of the drug?
  ☐ Assess signals of serious risk related to the use of the drug?
  ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An open-label, 16-week, randomized, controlled efficacy and safety trial comparing Ryzodeg 70/30 (insulin degludec and insulin aspart injection) administered once daily with a main meal and insulin aspart for additional meals to insulin detemir, in combination with mealtime insulin aspart at each meal, in pediatric patients with type 1 diabetes mellitus ages 1 to 17 years (inclusive).

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # NDA 203313
Product Name: RYZODEG 70/30 (insulin degludec and insulin aspart injection)

PMC #2 Description: To develop and validate an assay to assess for the presence of anti-degludec antibodies that has a sensitivity consistent with FDA guidance. Your final report should include a summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay standard operating procedure (SOP).

PMC Schedule Milestones: Final Report Submission: September 2016

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☒ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The assessment of anti-degludec antibodies is appropriate for a PMC because development of anti-degludec antibodies could potentially impact efficacy rather than safety. Of note, the development of anti-insulin antibodies (AIA), which do have the potential to impact safety, have been assessed by an assay with high sensitivity (20 ng/mL). The Sponsor's AIA data do not show appreciable change from baseline upon administration of RYZODEG 70/30, and are comparable between RYZODEG 70/30 and comparator arms. Therefore, RYZODEG 70/30 administration does not appear to pose an immunogenicity safety issue that would preclude approval or necessitate a PMR.

2. Describe the particular review issue and the goal of the study.

The development of anti-degludec antibodies should be evaluated because their development may impact efficacy. However, the Sponsor's current assay for detection of anti-degludec antibodies has a very low sensitivity of 1800 ng/mL, making it impossible to accurately assess the incidence of anti-degludec antibodies. Therefore, the Sponsor will need to develop an assay with sensitivity of at least 250-500 ng/mL as recommended by FDA guidance, and submit validation of this assay to the FDA for approval.

3. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   - ☐ Dissolution testing
   - ☒ Assay
   - ☐ Sterility
   - ☐ Potency
   - ☐ Product delivery
   - ☐ Drug substance characterization
   - ☐ Intermediates characterization
   - ☐ Impurity characterization
   - ☐ Reformulation
   - ☐ Manufacturing process issues
   - ☐ Other

   Describe the agreed-upon study:

Development of an anti-degludec antibody assay that has sensitivity consistent with FDA guidance, and submission of assay validation to the FDA for approval.

4. To be completed by ONDQA/OBP Manager:

   - ☒ Does the study meet criteria for PMCs?
   - ☒ Are the objectives clear from the description of the PMC?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	NDA 203313
Product Name:	RYZODEG 70/30 (insulin degludec and insulin aspart injection)

PMC #3 Description: To assess the incidence and titers of anti-degludec antibodies in sera from patients treated with Ryzodeg 70/30 (insulin degludec and insulin aspart injection) in Ryzodeg 70/30 (insulin degludec and insulin aspart injection) clinical trials and determine whether they are associated with differences in pharmacokinetics parameters (e.g. exposure), efficacy (e.g. hemoglobin A1c, insulin dose), and safety (e.g. hypoglycemia and hypersensitivity). The clinical samples should not be tested until the results from the PMC for anti-degludec antibody assay development and validation have been submitted to and reviewed by the Agency.

PMC Schedule Milestones:		
	Final Protocol Submission:	January 2017
	Study Completion:	July 2017
	Final Report Submission:	October 2017

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☒ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The assessment of anti-degludec antibodies is appropriate for a PMC because development of anti-degludec antibodies could potentially impact efficacy rather than safety. Of note, the development of anti-insulin antibodies (AIA), which do have the potential to impact safety, have been assessed by an assay with high sensitivity (20 ng/mL). The Sponsor's AIA data do not show appreciable change from baseline upon administration of RYZODEG 70/30, and are comparable between RYZODEG 70/30 and comparator arms. Therefore, RYZODEG 70/30 administration does not appear to pose an immunogenicity safety issue that would preclude approval or necessitate a PMR.

2. Describe the particular review issue and the goal of the study.

Because the Sponsor's assay for detection of anti-degludec antibodies has a very low sensitivity of 1800 ng/mL, it is not possible to accurately assess the incidence of anti-degludec antibodies. Measurement of anti-degludec antibodies will need to be performed using an assay that has a sensitivity of at least 250-500 ng/mL consistent with FDA published guidance.
The Sponsor will need to analyze patient serum samples using the assay developed in fulfillment of PMC #2. For this purpose, the Sponsor may use frozen sera from their completed trials, and/or conduct new trials to assess immunogenicity. The Sponsor should then provide these anti-degludec antibody data to the FDA for review.

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☒ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

The Sponsor will need to use the anti-degludec antibody assay developed in fulfillment of PMC #2 to assess antibody incidence and levels in sera from patients treated in the RYZODEG 70/30 and comparator arms of RYZODEG 70/30 clinical trials, and submit these data to the FDA for review.

4. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

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

/s/

JENNIFER R PIPPINS
09/25/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 203314
Product Name: Tresiba (insulin degludec)

PMR #1 Description: An open-label, 26-week, randomized, controlled efficacy and safety trial comparing Tresiba (insulin degludec injection) with insulin detemir in pediatric patients with type 1 diabetes ages 1 to 17 years (inclusive) using insulin aspart at each meal, followed by a 26-week extension.

Final Report Submission: June 2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Tresiba is ready for approval in adults; however, pediatric studies had been deferred until adequate safety data were available.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this PMR is to establish the safety and efficacy of Tresiba in pediatric patients ages 1 to 17 years (inclusive).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An open-label, 26-week, randomized, controlled efficacy and safety trial comparing Tresiba (insulin degludec injection) with insulin detemir in pediatric patients with type 1 diabetes ages 1 to 17 years (inclusive) using insulin aspart at each meal, followed by a 26-week extension.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	NDA 203314
Product Name:	Tresiba (insulin degludec)
PMR#2 Description:	Conduct a randomized, double-blind, active-controlled trial evaluating the effect of Tresiba (insulin degludec injection) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of adjudicated MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with Tresiba to that observed in the comparator group is less than 1.3.
Trial Completion:	December 2016
Final Report Submission:	September 2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

An estimate of the cardiovascular risk derived from the pre-approval data provides sufficient evidence that insulin degludec does not unacceptably increase cardiovascular risk above the pre-approval risk margin of 1.8. A more stringent risk margin (1.3) must be demonstrated post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A signal of a serious risk of cardiovascular events was identified from a meta-analysis of data from clinical trials evaluating insulin degludec and insulin degludec/insulin aspart during a previous review cycle. Available data to date have not definitively (risk margin of 1.3) excluded the potential for this serious risk with Tresiba (insulin degludec).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

  ☐ Accelerated Approval (subpart H/E)
  ☐ Animal Efficacy Rule
  ☐ Pediatric Research Equity Act
  ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

  ☐ Assess a known serious risk related to the use of the drug?
  ☒ Assess signals of serious risk related to the use of the drug?
  ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, double-blind, active-controlled trial evaluating the effect of Tresiba (insulin degludec injection) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of adjudicated MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with Tresiba to that observed in the comparator group is less than 1.3.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☒ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☒ There is a significant question about the public health risks of an approved drug
☒ There is not enough existing information to assess these risks
☒ Information cannot be gained through a different kind of investigation
☒ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☒ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # NDA 203314
Product Name: TRESIBA (insulin degludec)

PMC #3 Description: To develop and validate an assay to assess for the presence of anti-degludec antibodies that has a sensitivity consistent with FDA guidance. Your final report should include a summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay standard operating procedure (SOP).

PMC Schedule Milestones: Final Report Submission: September 2016

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☒ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The assessment of anti-degludec antibodies is appropriate for a PMC because development of anti-degludec antibodies could potentially impact efficacy rather than safety. Of note, the development of anti-insulin antibodies (AIA), which do have the potential to impact safety, have been assessed by an assay with high sensitivity (20 ng/mL). The Sponsor's AIA data do not show appreciable change from baseline upon administration of TRESIBA, and are comparable between TRESIBA and comparator arms. Therefore, TRESIBA administration does not appear to pose an immunogenicity safety issue that would preclude approval or necessitate a PMR.

2. Describe the particular review issue and the goal of the study.

The development of anti-degludec antibodies should be evaluated because their development may impact efficacy. However, the Sponsor's current assay for detection of anti-degludec antibodies has a very low sensitivity of 1800 ng/mL, making it impossible to accurately assess the incidence of anti-degludec antibodies. Therefore, the Sponsor will need to develop an assay with sensitivity of at least 250-500 ng/mL as recommended by FDA guidance, and submit validation of this assay to the FDA for approval.

3. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   - ☐ Dissolution testing
   - ☒ Assay
   - ☐ Sterility
   - ☐ Potency
   - ☐ Product delivery
   - ☐ Drug substance characterization
   - ☐ Intermediates characterization
   - ☐ Impurity characterization
   - ☐ Reformulation
   - ☐ Manufacturing process issues
   - ☐ Other

   Describe the agreed-upon study:

Development of an anti-degludec antibody assay that has sensitivity consistent with FDA guidance, and submission of assay validation to the FDA for approval.

4. To be completed by ONDQA/OBP Manager:

   - ☒ Does the study meet criteria for PMCs?
   - ☒ Are the objectives clear from the description of the PMC?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	NDA 203314
Product Name:	TRESIBA (insulin degludec)

PMC #4 Description: To assess the incidence and titers of anti-degludec antibodies in sera from patients treated with Tresiba (insulin degludec injection) in Tresiba (insulin degludec injection) clinical trials and determine whether they are associated with differences in pharmacokinetics parameters (e.g. exposure), efficacy (e.g. hemoglobin A1c, insulin dose), and safety (e.g. hypoglycemia and hypersensitivity). The clinical samples should not be tested until the results from the PMC for anti-degludec antibody assay development and validation have been submitted to and reviewed by the Agency.

PMC Schedule Milestones:		
	Final Protocol Submission:	January 2017
	Study Completion:	July 2017
	Final Report Submission:	October 2017

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☒ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The assessment of anti-degludec antibodies is appropriate for a PMC because development of anti-degludec antibodies could potentially impact efficacy rather than safety. Of note, the development of anti-insulin antibodies (AIA), which do have the potential to impact safety, have been assessed by an assay with high sensitivity (20 ng/mL). The Sponsor's AIA data do not show appreciable change from baseline upon administration of TRESIBA, and are comparable between TRESIBA and comparator arms. Therefore, TRESIBA administration does not appear to pose an immunogenicity safety issue that would preclude approval or necessitate a PMR.

2. Describe the particular review issue and the goal of the study.

Because the Sponsor's assay for detection of anti-degludec antibodies has a very low sensitivity of 1800 ng/mL, it is not possible to accurately assess the incidence of anti-degludec antibodies. Measurement of anti-degludec antibodies will need to be performed using an assay that has a sensitivity of at least 250-500 ng/mL consistent with FDA published guidance. The Sponsor will need to analyze patient serum samples using the assay developed in fulfillment of PMC #3. For this purpose, the Sponsor may use frozen sera from their completed trials, and/or conduct new trials to assess immunogenicity. The Sponsor should then provide these anti-degludec antibody data to the FDA for review.

3. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   - ☐ Dissolution testing
   - ☒ Assay
   - ☐ Sterility
   - ☐ Potency
   - ☐ Product delivery
   - ☐ Drug substance characterization
   - ☐ Intermediates characterization
   - ☐ Impurity characterization
   - ☐ Reformulation
   - ☐ Manufacturing process issues
   - ☐ Other

   Describe the agreed-upon study:

The Sponsor will need to use the anti-degludec antibody assay developed in fulfillment of PMC #3 to assess antibody incidence and levels in sera from patients treated in the TRESIBA and comparator arms of TRESIBA clinical trials, and submit these data to the FDA for review.

4. To be completed by ONDQA/OBP Manager:

   - ☒ Does the study meet criteria for PMCs?
   - ☒ Are the objectives clear from the description of the PMC?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs only)

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

/s/

JENNIFER R PIPPINS
09/25/2015

Memo

Date: August 18, 2015

updated August 27-Sept 2, 2015 to reflect Sponsor's responses to the 8/20/2015 IR

revised September 4-6, 2015

From: Fred Mills, Staff Scientist, Laboratory of Immunobiology, OBP, Division 4

To: Daniela Verthelyi, Chief, Laboratory of Immunology, OBP, BDRR 3

FDA designation: NDA 203314 and NDA 203313, original NDA submission

Sponsor: Novo Nordisk

Products: insulin degludec (IDeg, generic name insulin 454), for treatment of diabetes Designated as TRESIBA for single API studies and as RYZODEG when combined with IAsp, which is a licensed short acting insulin.
Subject: summary of IDeg (TRESIBA) and IDeg/IAsp (RYZODEG) clinical trial antibody results, immunogenicity label wording and PMCs.

Comments to the File

The Sponsor Novo Nordisk has conducted clinical trials for treatment of diabetes Type 1 (T1DM) and Type 2 (T2DM) using their long acting insulin degludec (IDeg) either alone (designated TRESIBA, under NDA 203314) or in combination with their licensed short acting insulin IAsp (designation RYZODEG, under NDA 203314). Relative to insulin, IDeg lacks the last amino acid of the B chain and has a di-carboxylic fatty acid coupled to the lysine at position B29, greatly increasing the IDeg half-life by promoting formation of stable multi-hexamers.

The Sponsor has conducted comprehensive antibody assessments on sera from their clinical studies using radioimmunoassays (RIA) to measure anti-degludec antibodies as well as anti-insulin antibodies (AIA), antibodies to the insulins used in the comparator arm of studies (IGlarg in almost all cases), and antibodies to the IAsp short acting insulin component in RYZODEG . The RIA method for AIA has high sensitivity (20 ng/ml), as do the methods for anti-IGlarg (50 ng/ ml) and anti-IAsp (33 ng/ ml). The assay to measure antibodies to degludec, however, has low sensitivity (see below).

Most significantly from a safety standpoint, as seen in Table 3, p. 8 in this review, the incidences of AIA in T1DM studies are high at baseline, but show a only modest increases during trials;i.e.
TRESIBA: T1DM baseline 89.7% , 95.9% anytime, sustained for degludec arms
RYZODEG: T1DM baseline 89.0% , 95.9% anytime, sustained for degludec arms

and is similar to comparator arms

TRESIBA: T1DM baseline 88.2%, 95.9% anytime, sustained for comparator arms
RYZODEG: T1DM baseline 88.3% , 97.2 % anytime sustained for comparator arms

For T2DM studies, AIA incidence increased during studies; i.e.

TRESIBA T2DM baseline 14.5%, 31.5 % anytime, sustained for degludec arms
RYZODEG T2DM baseline 45.4%, 67.5% anytime, sustained for degludec arms
While the levels of antibodies cannot be compared between treatments because the assays to detect antibodies to the products are different, the incidence of antibodies against treatment in the patients receiving degludec is similar to that of the patients receiving the comparator
TRESIBA: T2DM baseline 16.3%, 46.1 % anytime, sustained for comparator arms
RYZODEG: T2DM baseline 30.8%, 63.9% anytime, sustained for comparator arms

The Sponsor did not determine AIA titers, but the mean signal as (%B/T) provides some quantitative information on the levels of antibodies in patients (see Figure 40 p.16). For the T1DM data, there is little or no difference between the IDeg and comparator arms, providing reassurance that there is no increased immunogenicity risk mediated by IDeg relative to the comparators (IGlar or IDet). The plots show a lower incidence of anti-insulin antibodies in T2DM relative to T1DM, however these results should be considered carefuly since the reduced %B/T signal may to some extent result from assay interference from endogenous insulin in some patients in the T2DM studies. Importantly, for subjects that were positive at baseline the %B/T did not increase during treatment (see Figure 5-3 on p.15 of this review).

Furthermore, there was little change in the ratio of AEs to antibody levels for the degludec arms of studies, and the AE/anti-IGlarg ratios in comparator arms are the same or higher. These results support the view that degludec administration poses no safety risk vis a vis increased levels of AIA, which might in principle pose safety concerns due to loss of endogenous insulin activity. In RYZODEG trials, anti-IAsp antibodies show little change from baseline, and little difference between treatment and comparator arms, indicating RYZODEG administration does not generate an important antibody response to its short-acting component. Taken together, these AIA data indicate that there are no important antibody-mediated safety issues arising from administration of IDeg, and therefore nothing to preclude approval from an immunogenicity standpoint.

However, the Sponsor's specific anti-degludec assay has a low sensitivity of 1800 ng/ml, making it impossible to draw conclusions about the incidence and levels of antibodies raised to the product and their potential impact on safety and efficacy. For this reason, the Sponsor has been asked to agree to identical PMCs for TRESIBA and RYZODEG to develop and validate a new anti-degludec assay with sensitivity at least consistent with current FDA guidance (250-500 ng/ml), and also identical PMCs for TRESIBA and RYZODEG stipulating that the new assay be used to analyze degludec-treated patient sera to obtain interpretable data on anti-degludec antibody incidence and titer, and correlate these data with PK, safety, and efficacy. Moreover, the FDA has proposed label wording for the current approval stating that "The incidence of anti-degludec antibodies has not been accurately assessed." This language can be revised post-approval when the PMCs for analysis of sera with a new anti-degludec assay have been fulfilled.

Table of Contents

Proposed immunogenicity Labeling

Proposed wording for NDA 203313 TRESIBA (degludec)

6.2 Immunogenicity

(b) (4) The incidence of anti-degludec antibodies has not been accurately assessed. In studies of type 1 diabetes patients, 95.9% of patients who received TRESIBA once daily were positive for anti-insulin antibodies (AIA) at least once during the studies, including 89.7 % that were positive at baseline. In studies of type 2 diabetes patients, 31.5% of patients who received TRESIBA once daily were positive for AIA at least once during the studies, including 14.5% that were positive at baseline. The antibody incidence rates for type 2 diabetes may (b) (4) due to potential assay interference by endogenous insulin in samples (b) (4) patients. The presence of antibodies that affect clinical efficacy may necessitate dose adjustments to correct for tendencies toward hyper- or hypoglycemia.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to TRESIBA with the incidence of antibodies in other studies or to other products, may be misleading.

Proposed wording for NDA 203314 RYZODEG (degludec + insulin Aspart/ IAsp)

6.2 Immunogenicity

(b) (4) The incidence of anti-degludec antibodies has not been accurately assessed. In studies of type 1 diabetes patients, 95.9% of patients who received RYZODEG once daily were positive for anti-insulin antibodies (AIA) at least once during the studies, including 89% that were positive at baseline, while 13% of these patients were positive for anti-IAsp antibodies at least once during the studies, including 6.4% who were positive at baseline. In studies of type 2 diabetes patients, 67.5% of patients who received RYZODEG once daily were positive for AIA at least once during the studies, including 45.4% that were positive at baseline, while 17.1% of these patients were positive for anti-IAsp antibodies at least once during the studies, including 12.3% who were positive at baseline. The antibody incidence rates for type 2 diabetes may (b) (4) due to potential assay interference by endogenous insulin in samples (b) (4) patients. The presence of antibodies that affect clinical efficacy may necessitate dose adjustments to correct for tendencies toward hyper- or hypoglycemia.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to RYZODEG with the incidence of antibodies in other studies or to other products, may be misleading.

Immunogenicity PMCs (identical between TRESIBA and RYZODEG, except for name change)

PMC #1 Description: To develop and validate an assay to assess for the presence of anti-degludec antibodies that has a sensitivity consistent with FDA guidance. Your final report should include a summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay standard operating procedure (SOP).

PMC Schedule Milestones:		
	Final Protocol Submission:	Not needed
	Study/Trial Completion:	Not needed
	Final Report Submission:	10/01/2016
	Other:	MM/DD/YYYY

PMC #2 Description: To assess the incidence and titers of anti-degludec antibodies in sera from patients treated with TRESIBA in TRESIBA clinical studies and determine whether they are associated with differences in pharmacokinetics parameters (e.g. exposure), efficacy (e.g. hemoglobin A1c, insulin dose), and safety (e.g. hypoglycemia and hypersensitivity). The clinical samples should not be tested until the results from the PMC for anti-degludec antibody assay development and validation have been submitted to and reviewed by the Agency. (b) (4)

PMC Schedule Milestones:		
	Final Protocol Submission:	01/01/2017
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	04/01/2017

OBP information request (08-20-2015) and Novo Nordisk response (08-26-2015)
On August 20, 2015 the following Information Request was sent to the Sponsor (response requested by COB August 26), with the goal of clarifying the percentage of antibody positive patients, and correlation of antibodies with safety and efficacy.

Question 1
Provide a table containing data on antibody incidence rates and, if available, antibody titers for each study that assessed immunogenicity in Type I or Type 2 diabetes. The tables for each study should describe:
a) Number of patients (absolute number and percent) treated with degludec (TRESIBA), degludec + insulin aspart (RYZODEG), or comparator.
i. who were positive for ADA at any time during the study
ii. who were positive for ADA at baseline
iii. who had sustained ADA (defined as two or more positive for ADA samples or remained positive at the end of the study).
iv. For all subjects that have at least 1 positive sample provide the ADA titers if available in a table organized by treatment group, patient and sampling time.
b) Number of patients (absolute number and percent) treated with degludec (TRESIBA), degludec + insulin aspart (RYZODEG), or comparator.
i. who were positive for AIA at any time during the study
ii. who were positive for AIA at baseline
iii. who had sustained AIA (defined as two or more positive for ADA samples or remained positive at the end of the study).
iv. For all subjects that have at least 1 positive sample provide the AIA titers if available in a table organized by treatment group, patient and sampling time
c) Table showing whether there is a correlation between ADA or AIA with adverse events
d) Table showing whether there is a correlation between ADA or AIA and changes in efficacy with changes in antibody levels and/or titer.

Question 2
Your submission stated the sensitivity of each assay but does not state that an appropriate suitability control was used routinely to ensure that the sensitivity of the assays was consistent during the run of the study samples. Describe the system suitability controls that are routinely included as part of assay runs.

Responses to Question 1
The Sponsor responded on August 26, 2015. In this response the term 'ADA' is interpreted as meaning 'anti-drug-antibodies', i.e., specific antibodies against IDeg, insulin glargine (IGlar), insulin detemir (IDet) or insulin aspart (IAsp), while 'AIA' is interpreted as meaning 'anti-insulin-antibodies' and used to describe antibodies cross-reacting to human insulin. IDeg refers to degludec (Tresiba) while IDegAspr refers to the degludec+insulin Aspart (IAsp) combination (Ryzodeg).

Anti-Drug Antibodies

Table 1 Incidence of basal insulin (IDeg, IGlar and IDet) specific antibodies (ADA) - safety analysis set

Type	Trial ID	Treatment	Safety set	Positive for ADA		
				Anytime	Baseline	Sustained[§]
Pool IDeg T1DM trials		Comparator	467	166 (35.5)	65 (13.9)	155 (33.2)
		IDeg	1102	269 (24.4)	83 (7.5)	115 (10.4)
Pool IDeg T2DM trials		Comparator	1138	57 (5.0)	3 (0.3)	39 (3.4)
		IDeg	2287	255 (11.1)	68 (3.0)	120 (5.2)
Pool IDegAsp T1DM trial		Comparator	180	171 (95.0)	97 (53.9)	160 (88.9)
		IDegAsp	362	87 (24.0)	31 (8.6)	43 (11.9)
Pool IDegAsp T2DM trials		Comparator	261	13 (5.0)	1 (0.4)	12 (4.6)
		IDegAsp	544	93 (17.1)	17 (3.1)	40 (7.4)

Reviewer comments

The anti-degludec antibody assay has low sensitivity relative to the anti-IGlar and IDet comparator assays. The data for the IDeg T1DM and IDegAsp trials are consistent with this low sensitivity; i.e. reported incidence of IDeg antibodies is lower than comparator-suggesting inadequate detection.

Anti-IAsp levels in RYZODEG trial

Table 2 Incidence of IAsp-specific antibodies (ADA) - safety analysis set

Type	Trial ID	Treatment	Safety set	Positive for ADA		
				Anytime	Baseline	Sustained[§]
T1DM	NN5401-3594-3645	IDet	180	18 (10.0)	10 (5.6)	16 (8.9)
		IDegAsp	362	47 (13.0)	23 (6.4)	42 (11.6)
Pool IDegAsp T1DM trial		Comparator	180	18 (10.0)	10 (5.6)	16 (8.9)
		IDegAsp	362	47 (13.0)	23 (6.4)	42 (11.6)
T2DM	NN5401-3590-3726[#]	IDegAsp	265	33 (12.5)	24 (9.1)	28 (10.6)
T2DM	NN5401-3597	BIAsp 30	141	32 (22.7)	23 (16.3)	30 (21.3)
		IDegAsp	279	60 (21.5)	43 (15.4)	49 (17.6)
Pool IDegAsp T2DM trials		Comparator	141	32 (22.7)	23 (16.3)	30 (21.3)
		IDegAsp	544	93 (17.1)	67 (12.3)	77 (14.2)
Phase 2 trials						
T2DM	NN5401-1791	IDegAsp	118	16 (13.6)	14 (11.9)	14 (11.9)
T2DM	NN5401-1792	BIAsp 30	62	16 (25.8)	6 (9.7)	16 (25.8)
		IDegAsp	119	18 (15.1)	15 (12.6)	18 (15.1)

[#]IAsp was not included in the comparator arm (IGlar); [§]More than one or at follow-up

Pools contain only confirmatory therapeutic trials. Phase 2 trials were analyzed separately.

Reviewer comments

Anti-IAsp antibodies are detected by a sensitive assay, and show little change from baseline, and little difference between treatment and comparator arms, indicating RYZODEG administration does not generate an important antibody response to its short-acting component.

Anti-Insulin Antibodies (AIA)

Table 3 Incidence of cross reacting antibodies (AIA) - safety set

Type	Trial ID	Treatment	Safety set	Positive for AIA Anytime	Positive for AIA Baseline	Positive for AIA Sustained[$]
T1DM	NN1250-3583-3644	IGlar	154	145 (94.2)	136 (88.3)	141 (91.6)
		IDeg	472	455 (96.4)	425 (90.0)	445 (94.3)
T1DM	NN1250-3585-3725	IDet	152	149 (98.0)	130 (85.5)	147 (96.7)
		IDeg	301	285 (94.7)	268 (89.0)	282 (93.7)
T1DM	NN1250-3770 main-ext	IGlar	161	154 (95.7)	146 (90.7)	151 (93.8)
		IDeg	329	317 (96.4)	295 (89.7)	306 (93.0)
Pool IDeg T1DM trials		Comparator	467	448 (95.9)	412 (88.2)	439 (94.0)
		IDeg	1102	1057 (95.9)	988 (89.7)	1033 (93.7)
T2DM	NN1250-3579-3643	IGlar	257	120 (46.7)	19 (7.4)	96 (37.4)
		IDeg	766	248 (32.4)	60 (7.8)	169 (22.1)
T2DM	NN1250-3586	IGlar	146	72 (49.3)	21 (14.4)	62 (42.5)
		IDeg	284	63 (22.2)	28 (9.9)	40 (14.1)
T2DM	NN1250-3587	IGlar	278	114 (41.0)	44 (15.8)	102 (36.7)
		IDeg	553	152 (27.5)	84 (15.2)	137 (24.8)
T2DM	NN1250-3668	IGlar	229	123 (53.7)	79 (34.5)	100 (43.7)
		IDeg	456	200 (43.9)	140 (30.7)	169 (37.1)
T2DM	NN1250-3672	IGlar	228	96 (42.1)	22 (9.6)	72 (31.6)
		IDeg	228	58 (25.4)	19 (8.3)	39 (17.1)
Pool IDeg T2DM trials		Comparator	1138	525 (46.1)	185 (16.3)	432 (38.0)
		IDeg	2287	721 (31.5)	331 (14.5)	554 (24.2)
T1DM	NN5401-3594-3645	IDet	180	175 (97.2)	159 (88.3)	174 (96.7)
		IDegAsp	362	347 (95.9)	322 (89.0)	343 (94.8)
Pool IDegAsp T1DM trial		Comparator	180	175 (97.2)	159 (88.3)	174 (96.7)
		IDegAsp	362	347 (95.9)	322 (89.0)	343 (94.8)
T2DM	NN5401-3590-3726	IGlar	261	132 (50.6)	20 (7.7)	121 (46.4)
		IDegAsp	265	138 (52.1)	42 (15.8)	118 (44.5)
T2DM	NN5401-3597	BIAsp 30	141	125 (88.7)	104 (73.8)	117 (83.0)
		IDegAsp	279	229 (82.1)	205 (73.5)	211 (75.6)
Pool IDegAsp T2DM trials		Comparator	402	257 (63.9)	124 (30.8)	238 (59.2)
		IDegAsp	544	367 (67.5)	247 (45.4)	329 (60.5)
Phase 2 Trials						
T2DM	NN1250-1836	IDeg	178	53 (29.8)	15 (8.4)	45 (25.3)

[$]More than one or at follow-up

Pools contain only confirmatory therapeutic trials. Phase 2 trials were analyzed separately

For anti-insulin antibodies, the incidence of baseline, anytime antibodies, and sustained antibody levels in the IDeg or IDegAsp treatments are similar, or in some cases lower than the incidence rates for the corresponding comparator arms, suggesting no increased safety risk relative to comparator that is mediated by increases in anti-insulin antibodies.

Adverse effect association

Table 4 Adverse event rates according to change in absolute values in ADA and AIA, therapeutic confirmatory trials

Trial	IDeg (AE-rates/100 PYE)				Comparator (AE-rates/100 PYE)			
IDeg	≥5%B/T ADA	≤5%B/T ADA	≥10%B/T AIA	≤10%B/T AIA	≥5%B/T ADA	≤5%B/T ADA	≥10%B/T AIA	≤10%B/T AIA
T1DM								
3585-3725	213.2	464.3	429.2	464.3	476.7	394.2	490.7	359.2
3770-EX	130.7	450.3	453.7	444.2	1389.5	478.0	431.5	498.5
3583-3644	395.2	382.9	411.7	375.2	0.0	374.0	414.1	363.4
Pooled	306.1	413.4	424.8	408.2	487.5	407.7	449.3	399.9
T2DM								
3586	0.0	293.1	334.5	292.6	299.4	289.9	316.4	284.2
3672	0.0	451.3	401.4	452.5	600.4	485.2	643.2	473.7
3668	438.9	397.1	399.7	398.1	0.0	390.9	401.9	381.9
3579-3643	0.0	361.7	401.7	360.7	646.1	331.2	288.6	346.2
3587	0.0	229.2	152.7	232.6	376.7	285.6	240.9	298.4
Pooled	366.1	347.2	336.7	347.6	456.3	349.0	320.0	356.4
IDegAsp								
T1DM								
3594-3645	318.1	410.9	304.7	436.8	406.2	467.1	427.2	469.4
T2DM								
3590-3726	341.9	312.2	320.8	312.0	261.5	237.1	253.6	234.4
3597	517.7	344.3	334.2	350.4	802.7	389.4	364.9	401.9
Pooled	401.8	324.2	324.5	326.7	314.5	270.5	286.6	267.8

PYE: patient year of exposure

Reviewer comments

These data indicate that for anti-insulin antibodies (AIA), which are detected by a sensitive assay, there is no association between antibody levels and adverse events for the IDeg arms, and no difference between the IDeg arms and the comparator arms, except for the comparator arm of two studies (3770-EX, 3672, and 3597), where there AE-rates/100PYE are actually higher. This reinforces the view that degludec administration poses no safety risk vis a vis increased level of AIA, which might in principle mediate pose safety concerns due to los of endogenous insulin activity.

Table 5 Spearman Correlation Coefficients – Antibodies vs. HbA_{1c} and vs. Dose – SAS

IDeg confirmatory trials	IDeg Group			Comparator Group		
T1DM Pooled	HbA_{1c} at end-of trial	Change from baseline in HbA_{1c}	Total daily dose at end-of-trial	HbA_{1c} at end-of-trial	Change from baseline in HbA_{1c}	Total daily dose at end-of trial
ADA (IDeg/Comp)	0.02	-0.01	0.01	-0.07	-0.11	**0.30***
ADA (IAsp)	0.02	**0.07***	0.05	-0.01	-0.04	0.07
AIA	0.02	0.02	0.04	-0.06	-0.10	**0.20***
Trial 3583-3644, T1DM						
ADA (IDeg/Comp)	0.05	-0.04	0.01	-0.11	0.01	-0.04
ADA (IAsp)	0.00	0.09	0.10	-0.04	0.04	0.01
AIA	-0.02	0.06	-0.02	-0.10	-0.17	0.13
Trial 3585-3725, T1DM						
ADA (IDeg/Comp)	0.10	0.10	0.04	-0.12	0.13	0.09
ADA (IAsp)	0.08	0.13*	-0.01	0.04	-0.04	0.13
AIA	**0.13***	-0.04	**0.24***	0.01	0.06	0.11
Trial 3770-3770 Ex, T1DM						
ADA (IDeg/Comp)	-0.12	-0.05	-0.02	-	-	-
ADA (IAsp)	-0.08	0.02	0.03	-0.02	-0.05	-0.05
AIA	-0.06	0.10	-0.00	-0.10	-0.04	0.17
T2DM Pooled						
ADA (IDeg/Comp)	0.01	-0.00	0.01	0.02	-0.02	0.00
AIA	**0.10***	0.02	**0.12***	**0.08***	0.01	0.05
Trial 3579-3643, T2DM						
ADA (IDeg/Comp)	0.06	0.02	-0.00	-0.01	-0.04	0.13
AIA	0.08	0.02	**0.12***	0.04	-0.09	**0.24***
Trial 3672, T2DM						
ADA (IDeg/Comp)	-0.04	-0.10	0.09	-0.06	-0.06	0.01
AIA	0.07	-0.03	**0.14***	-0.12	-0.13	-0.07
Trial 3586, T2DM						
ADA (IDeg/Comp)	0.07	0.11	0.02	0.06	0.01	0.08
AIA	-0.03	-0.07	**0.17***	0.07	0.03	0.14
Trial 3668, T2DM						
ADA (IDeg/Comp)	0.03	**0.21***	0.13	0.02	-0.06	-0.02
AIA	**0.20***	0.11	**0.20***	**0.24***	0.13	0.08
Trial 3587						
ADA (IDeg/Comp)	-0.02	-0.05	-0.02	0.05	0.05	-0.10
AIA	0.08	-0.01	0.05	0.06	0.03	0.10

abs. antibodies; comparator: IGlar (3583-3644, 3770-3770 Ex, 3579-3643, 3672, 3586, 3668; 3587); IDet (3585-3725).

* Statistically significant different from 0

Reviewer comments

Because of the low sensitivity of the anit-degludec antibody assay, no statement can be made about correlation of these antibodies with efficacy. However, there is no apparent effect of AIA, which are detected with a sensitive assay, on efficacy in T1D, and only modest effects in T2DM. On this basis degludec administration does not seem to have a significant effect on efficacy that is mediated by immunogenicity.

Response to Question 2

System suitability control samples were included in every assay run for each of the four analyses for determination of ADA's (IDeg specific, IDet specific, IAsp specific, IGlar specific antibodies) and for determination of AIA (insulin human binding antibodies). The control samples for each of the four ADA assays was generated by spiking monoclonal drug specific antibodies into human serum. The control sample for the AIA assay was spiked with a polyclonal antibody towards human insulin. The levels of antibody in the controls were based on titration and selected to be on the linear part of the titration curve (25-45%B/T) in order to reduce the assay variation. Assay acceptance is based on the system suitability controls included three times

in each assay run. For an assay to be accepted, two out of the three control sample results should be within their acceptance range (nominal values ± 20% based on assay variation). The nominal value for each control sample was determined as the mean %B/T value in at least 6 assay runs. All data presented were derived from successful assay runs. The assay rejection rate was below 5% (the exact number may be found in the antibody analytical report placed in Appendix 16.1.10 of the clinical trial report for each individual trial). The composition of the control samples were not changed during the clinical development program. This ensures consistent analysis performance throughout the program.

Reviewer comments

The Sponsor includes suitability controls in all assay runs that utilize multiple samples of positive control antibody in the linear range of response, where optimal reproducibility is expected. Two out of three control results must meet specification for an assay to be acceptable, and the Sponsor's experience has been that the assay rejection rate is less than 5%, indicating the assay is consistently performing within this specification. Of note, the sponsor does not use a Low positive control to confirm the sensitivity of the assay on each run. This will be brought to their attention so that such a control is included when the testing needed to fulfill the PMC is conducted.

This assay's antibody incidence rate and measurement of antibody levels is consistent with that observed in literature and by other Sponsors e.g.

Mianowska et al. Pediatric Diabetes (2011) 12, pp.78-84
T1D insulin naïve patients baseline 80% 6 and 24 month treatment 97.9%

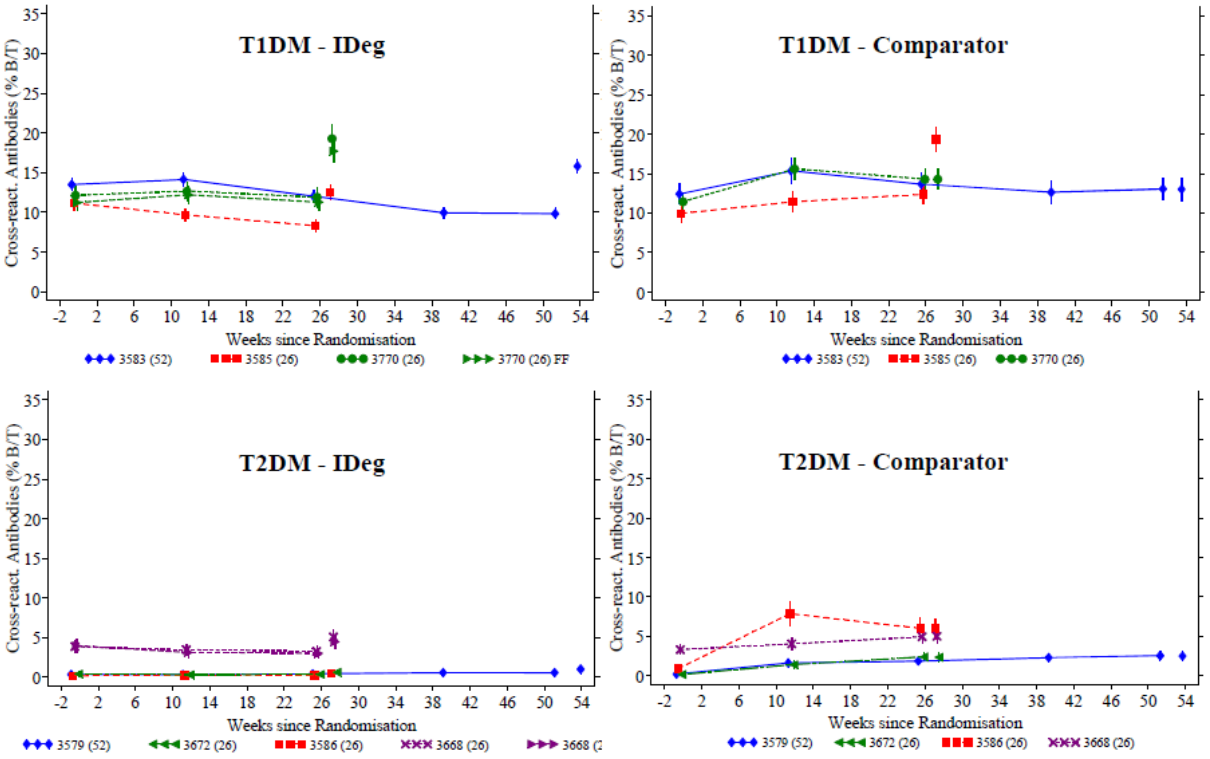
TOUJEO (Sanofi Iglarg) label

T1D baseline	62%	ever positive 6 month	79%
T2D baseline	42%	ever positive 6 month	25%

In addition, for studies of cross-reacting antibodies in trials with Lispro (Lilly)
Fineberg et al., Diabetes Care (2003) 26 pp.89-96; .

Figure 3—*Percent binding of cross-reactive antibodies from parallel studies in insulin-treated patients with type 1 or type 2 diabetes. Mean and 95% CIs over time are shown. The vertical dotted line separates parent and extension studies. The inset graph is the fitted quadratic random mixed model.*

These levels are similar for those from the Novo Nordisk assay; i.e.



% B/T:% bound over total radioactivity; Subjects temporarily discontinued trial product for a 1-week washout with NPH insulin at Weeks 26 and 52; Last antibody assessment was made 1 week after last trial product administration;

Comparator: IGlar (3583, 3770, 3579, 3672, 3586, 3668), IDet (3585).

Therefore the Novo Nordisk antibody assay appears to be detecting expected incidence and antibody levels and thus performing adequately.

Product Description

The structure of IDeg is based on that of human insulin. Compared with human insulin, IDeg contains no amino acid substitutions, but the last amino acid (b) (4) (threonine at position B30), which does not impact receptor recognition, has been omitted. In addition, a di-carboxylic fatty acid (hexadecanedioic acid) has been coupled to the lysine at position B29 via a glutamic acid spacer. The addition of this specific di-carboxylic fatty acid via the glutamic acid spacer is what enables IDeg to form soluble and stable multi-hexamers when injected into subcutaneous tissue. In contrast human insulin remains as hexamers. The biologically active monomers of IDeg gradually separate from the multi-hexamers in the subcutaneous depot, providing a slow, stable and continuous delivery of IDeg into the circulation resulting in the observed pharmacokinetic and pharmacodynamic (PD) profiles. Tresiba (NDA 203314)n is a formulation of IDeg, while Ryzodeg (NDA 302213) is a formulation of IDeg + insulin aspart. Both are licensed in the EU, and EMA statements regarding antibody formation are provided below.

EMA Tresiba product information

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002498/WC500138940.pdf

Section 4.4 Special Warnings and Precautions for Use p.5

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Section 5.1 Pharmacodynamic Properties, p.12

Antibody development was sparse and had no clinical impact.

EMA Ryzodeg product information

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002499/WC500139011.pdf

Section 4.4 Special Warnings and Precautions for Use p.18

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Section 5.1 Pharmacodynamic Properties, p. 23

There is no clinically relevant development of insulin antibodies after long-term treatment of Ryzodeg

From Novo Nordisk backgrounder for November 8, 2012 Advisory Committee

Insulin antibodies were measured in 7 IDeg trials: 4 T2DM trials (Trials 3579, 3586, 3668 and 3672) and 3 T1DM trials (Trials 3583, 3585 and 3770). Insulin antibodies were also measured in 3 IDegAsp trials: T2DM Trials 3590 and 3597 and T1DM Trial 3594. Antibody development against IDeg, IAsp, IDet and IGlar was measured by a validated subtraction radio-immunoassay using radioactively labeled IDeg, Asp, IDet, IGlar or human insulin. The amount of precipitated radioactivity was measured and expressed as percent bound radioactivity (B) of the total amount of radioactivity (T) applied to the sample. The %B/T value is proportional to the amount of anti-insulin antibody present in the sample.

Antibody Assay Description

The Sponsor's antibody assay is a RadioImmunoPrecipitation (RIA). Briefly, the assay is a subtraction radioimmunoassay. The samples were incubated with ^{125}I labeled tracer ± excess insulin/insulin analogue. After incubation overnight the immunoglobulin was precipitated together with any antigen that may have bound. The precipitate was counted in a gamma counter and the amount of radioactivity was expressed in percent of the total amount of added radioactivity (%B *(bound)* /T*(total)*). The %B/T value is proportional to the amount of anti-insulin antibody present in the sample. This is the assay methodology most widely used for detection of anti-insulin antibodies (Fineberg et al. 2007 Endocrine Reviews 28 pp.625-652)

The sensitivity of the anti-degludec antibody assay is low (1800 ng/ml) and not consistent with FDA guidance, which currently recommends a minimum sensitivity of 250-ng/ml. Adequate sensitivity was demonstrated for the assay for antibodies to the comparator IGlarg insulin (50 ng/ml), antibodies to the short-acting IAsp in RYZODEG (33 ng/ ml) and Anti-Insulin Antibodies or AIA (20 ng/ml)

Reviewer comment

As discussed above, the Agency has proposed PMCs for the Sponsor to develop an anti-ideg antibody assay with adequate sensitivity, and to analyze clinical samples with this new assay.

Summaries of Antibody Data from NDAs 203314 and 203313

NDA 203313 –Tresiba / IDeg/ degludec

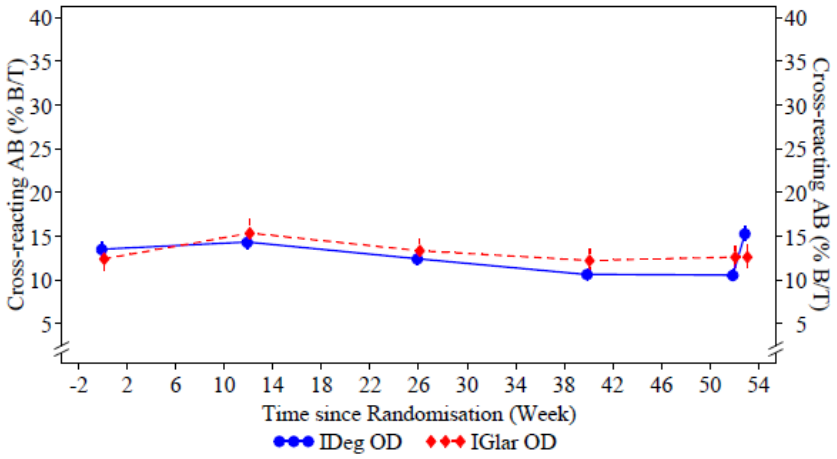
From IDeg 2.5 Clinical Overview

Under NDA 203314, there were three T1DM trials using IDeg, with IDet or IGlar as a comparator. There were eight T2DM trials using IDeg, with IGlar or (in one trial) sitagliptin as comparators.

Insulin antibody development was investigated in all trials in T1DM and in a total of 4 trials in subjects with T2DM according to guidelines from EMA. In Trials 3583 and 3579, subjects with T1DM and T2DM, respectively, were treated with IDeg for a period of 52 weeks, and data from these trials are therefore of primary interest. In T1DM, the majority of subjects treated with IDeg had little or no change in IDeg-specific antibodies. The mean level of antibodies cross-reacting between IDeg (and IGlar) and human insulin remained low (10-15% B/T) throughout the trials in both treatment groups. The increase in antibody levels from Week 52 to Week 53 are due to the fact that subjects were transferred to NPH prior to the last antibody measurement to reduce interference from IDeg or comparator in the antibody assay.

In the 12-month trials (3583 and 3579), IDeg specific, IGlar specific and antibodies cross-reacting to human insulin were measured at baseline (Week 0) and after 26 and 53 weeks of treatment. In the 6-month trials, IDeg specific, IGlar specific or IDet specific and antibodies cross-reacting to human insulin were measured at baseline (Week 0) and after 27 weeks of treatment. At Weeks 26 for 26-week trials and 52 for 52-week trials, a wash-out period of at least 7 days was included where the subjects discontinued the trial products and were switched to intermediate acting NPH insulin in order to provide basal insulin coverage while reducing the level of exogenous insulin present at antibody sampling and consequently to reduce the

possibility for interference with antibody measurements. No washout period was performed before antibody measurements at the remaining time points and consequently, the detection of insulin antibodies was lower at these time points. In the following figures, only observed values with a wash-out period are presented. Data are presented based on the completer population.



Safety; LOCF imputed data. Error bars: + Standard Error (Mean). %B/T: percent antibody bound/total radioactivity

Cross-reference: Trial 3583 (M 5.3.5.1), Figure 12-7

Figure 5–2 Cross-reacting Antibodies to Human Insulin (%B/T) – Subjects with T1DM (Trial 3583) Mean Plot – SAS

Reviewer Comments

These data for anti-insulin antibodies in T1DM patients are interpretable because of the high sensitivity of the assay and expected lack of interference from endogenous samples. The time courses for both IDeg and comparator patients stable and very similar, suggesting that IDeg mediates no new immunological effects

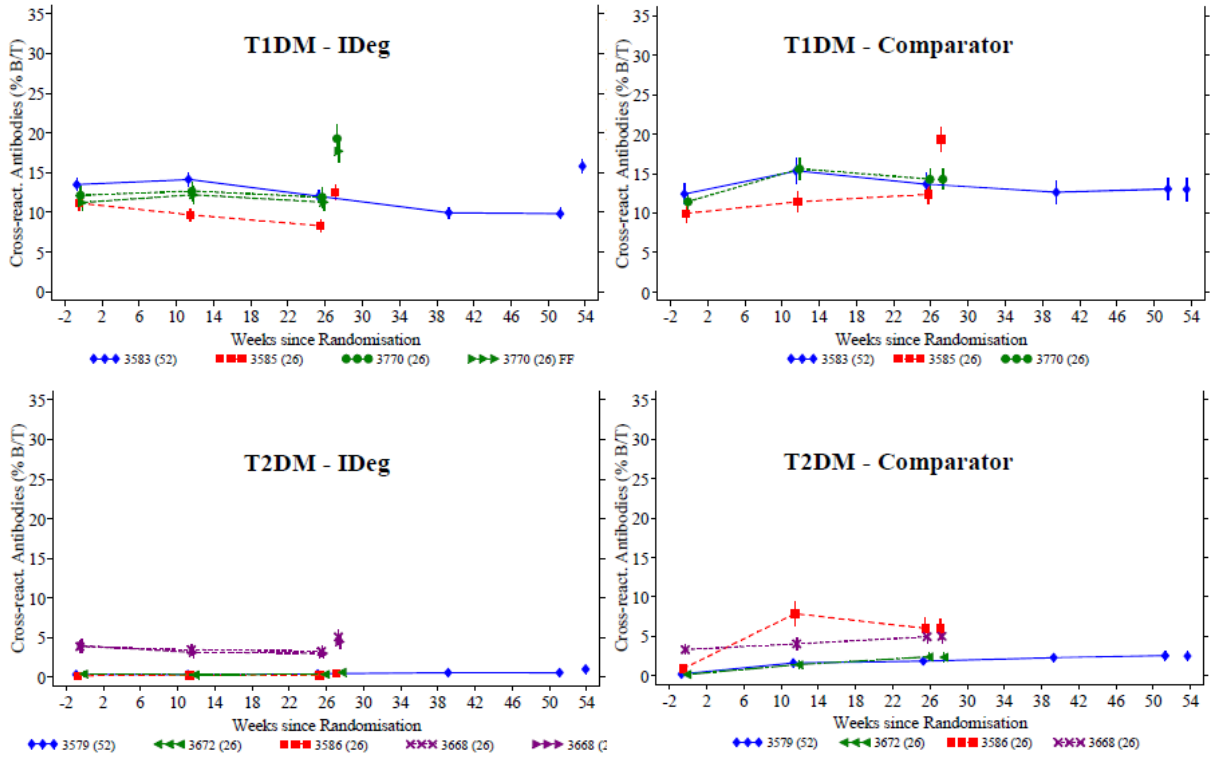
In subjects with T2DM, very few subjects experienced changes in IDeg and comparator specific antibodies. The mean level of cross-reacting antibodies remained < 5% with IDeg throughout the trials and marginal increases were observed with comparator insulin products.

Reviewer Comment

As discussed further in subsequent sections, the relatively low detected antibody levels in T2DM studies may result in part from assay interference stemming from increased levels of endogenous insulin.

From IDeg 2.7.3 Summary of Clinical Efficacy

Figure 5-3 antibodies cross-reactive with human insulin



% B/T:% bound over total radioactivity; Subjects temporarily discontinued trial product for a 1-week washout with NPH insulin at Weeks 26 and 52; Last antibody assessment was made 1 week after last trial product administration;

Comparator: IGlar (3583, 3770, 3579, 3672, 3586, 3668), IDet (3585).

Reviewer comments

These data should be interpretable, because they represent the results of anti-insulin antibody assays, which have a high sensitivity (20 ng/ml). The Sponsor did not determine titers, and these have been requested as part of a PMC. However, the mean signal as (%B/T) does provide quantitative information on the levels of antibodies raised in patients. For the T1DM data, there seems to be little or no difference between the IDeg and comparator arms, providing reassurance that there is no immunogenicity mediated by IDeg relative to the comparators (IGlar or IDet).The plots show a reduced detection of anti-insulin antibodies in T2DM relative to T1DM, although a caveat is that reduced %B/T signal may to some extent result from assay interference from endogenous insulin in some patients in the T2DM studies.

Table 5–1 Spearman Correlation Coefficients – Antibodies vs. HbA_{1c} and vs. Dose – SAS

	IDeg Group			Comparator Group		
Trial 3583, T1DM	**HbA_{1c} at EOT**	**Change from baseline in HbA_{1c}**	**Total daily dose at EOT**	**HbA_{1c} at EOT**	**Change from baseline in HbA_{1c}**	**Total daily dose at EOT**
IDeg/Comp specific abs	-0.02	0.05	0.01	0.08	0.04	0.05
IAsp specific abs	0.05	0.01	0.13	0.05	0.04	0.06
Abs cross reacting to human insulin	0.04	0.09	0.02	-0.01	-0.07	0.13
Trial 3585, T1DM						
IDeg/Comp specific abs	0.10	0.09	0.06	-0.09	0.05	0.09
IAsp specific abs	0.10	0.14	-0.05	-0.17	-0.18	0.17
Abs cross reacting to human insulin	**0.17***	0.03	**0.14***	-0.04	0.03	0.16
Trial 3770, T1DM						
IDeg/Comp specific abs	-0.05	-0.10	-0.03	0.05	-0.02	-0.03
IAsp specific abs	-0.02	0.08	-0.08	-0.05	0.02	0.00
Abs cross reacting to human insulin	0.07	-0.07	0.06	0.01	0.05	0.10
Trial 3579, T2DM						
IDeg/Comp specific abs	0.05	0.02	-0.02	-0.08	-0.05	-0.03
Abs cross reacting to human insulin	**0.15***	0.03	0.03	0.02	-0.03	0.13
Trial 3672, T2DM						
IDeg/Comp specific abs	-0.04	-0.10	0.09	-0.06	-0.06	0.01
Abs cross reacting to human insulin	0.07	-0.03	**0.14***	-0.12	-0.13	-0.07
Trial 3586, T2DM						
IDeg/Comp specific abs	0.07	0.11	0.02	0.06	0.01	0.08
Abs cross reacting to human insulin	-0.03	-0.07	**0.17***	0.07	0.02	0.14
Trial 3668, T2DM						
IDeg/Comp specific abs	0.03	**0.21***	0.13	0.02	-0.06	-0.02
Abs cross reacting to human insulin	**0.20***	0.11	**0.20***	**0.24***	**0.14***	0.08

EOT: end of trial; abs. antibodies; comparator: IGlar (3583, 3770, 3579, 3672, 3586, 3668), IDet (3585).

* **Statistically significant different from 0**

Reviewer comments

Here, the data for cross-reactive insulin antibodies (20 ng/ ml sensitivity) and anti-IAsp(33 ng/ml sensitivity) are interpretable in T1DM, because no assay interference from endogenous insulin is expected. For two of the Trials (3585 and 3770) there is no statistically significant correlation with antibodies. However, for the third T1DM trial (3585), there are significant correlations of anti-insulin antibodies with HbA1c and daily dose. Moreover, in the T2DM trials, where detection of antibodies may be reduced by interference from endogenous insulin, there are nonetheless statistically significant correlations of HbA1c and/or daily dose and detected antibodies. These data indicate some modest impact of antibodies on efficacy, but I defer to the clinical review team for interpretation of their significance.

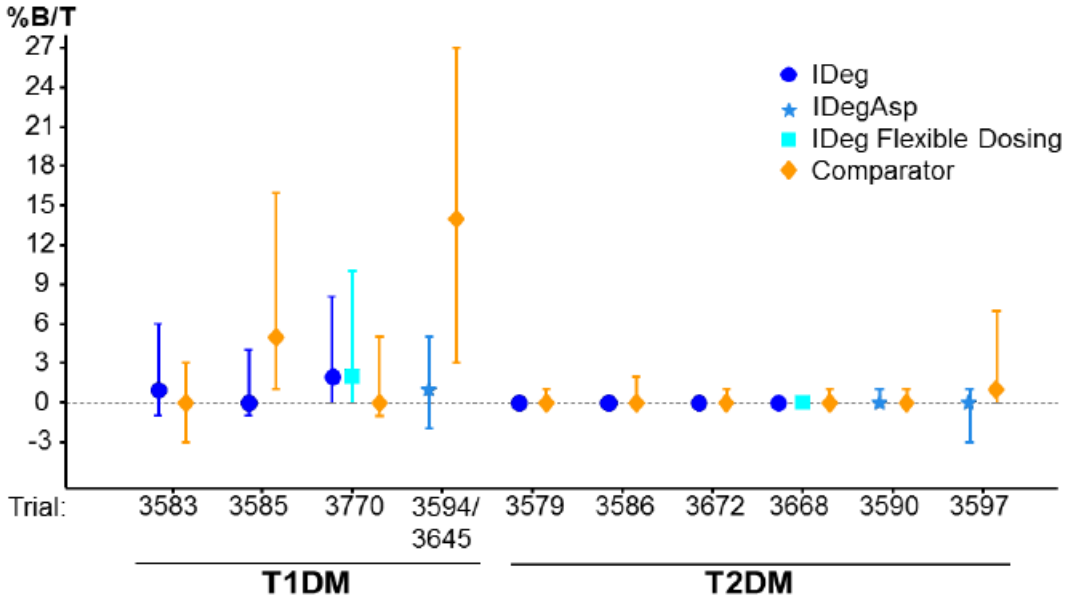
A total of 220 (5%) subjects with T1DM and T2DM in the IDeg group and 145 (6%) subjects in the comparator group had an increase of 10% B/T (absolute value) or more in antibodies cross-reacting with human insulin or an increase in anti-insulin specific antibodies of 5% B/T or more.

Reviewer comments

The overall antibody incidence across T1DM and T2DM studies added together is likely higher in both the treatment and comparator groups, because, as stated above, the detection rate in the T2DM trials may be reduced by interference by endogenous insulin. It would be helpful to have separate incidence calculation for T1DM and T2DM studies. These data were requested in the August 20, 2015 Information Request, to which the Sponsor responded on August 26, and are discussed at the beginning of this review. Briefly, for anti-insulin antibodies, the incidence of baseline, anytime antibodies, and sustained

antibody levels in the IDeg or IDegAsp treatments are similar, or in some cases lower than the incidence rates for the corresponding comparator arms, suggesting no increased safety risk relative to comparator that is mediated by increases in anti-insulin antibodies.

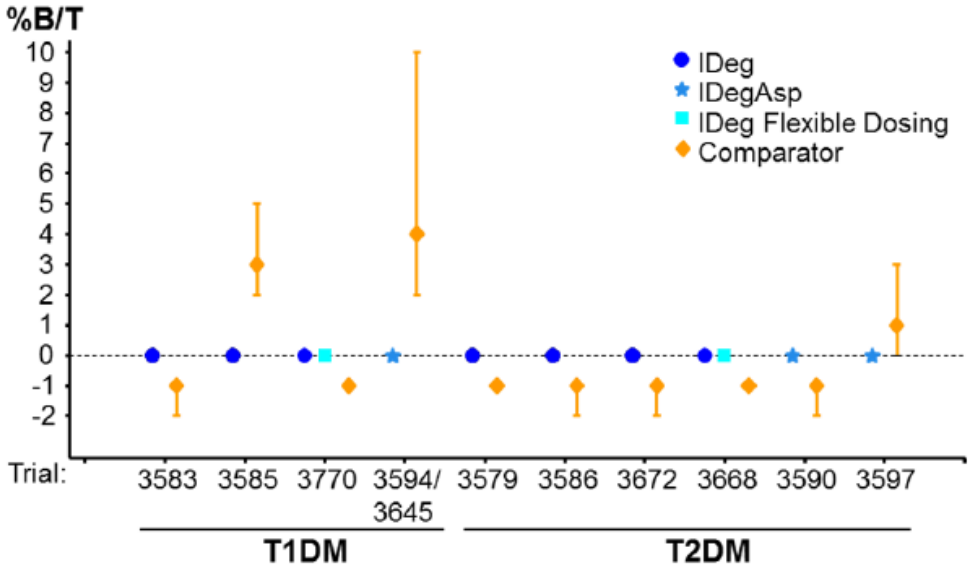
From Summary 2.7.4, Section 3.3.1 Clinical Safety Summary
Summary across trials



Observed values with 25 and 75 percentiles. %B/T: percent bound over total. Comparators: IGlar (Trials 3583, 3770, 3579, 3586, 3672, 3668 and 3590), IDet (Trials 3585 and 3594) and BIAsp 30 (Trial 3597). Safety analysis set.

Figure 40 Cross-reacting Antibodies at Week 27/53 – Change from Baseline – Phase 3 Trials – IDeg or IDegAsp versus Comparator – NDA

The Sponsor states that the mean level of antibodies cross-reacting with human insulin at baseline and at end of trial (following 27 or 53 weeks of treatment) was similar in the IDeg or IDegAsp and the comparator group. Shown below is a plot of the levels of insulin-analogue specific antibodies in the Phase 3 trials. This plot doesn't differentiate IDeg, Asp, IDet, or IGlar specific antibodies.



Reviewer comment

The increased detection of antibodies in the T1DM vs T2DM studies is consistent with assay interference from endogenous insulin in T2DM samples, which was in fact observed in the Sponsor's validation studies;i.e. at 160 pM insulin (normal individual's concentration) the AIA signal is reduced to 80% of no insulin control, while at 320 pM insulin the signal is reduced to 70 % of the control value.

Summary of Cross-reacting antibodies (AIA/ Anti-Insulin Antibodies)

These data provide an overview of the antibody levels, indicating no difference in T1DM studies for IDeg arms versus comparator arms. However, from the standpoint of providing information to physicians, it would be more useful to have incidence rates, with these rates calculated separately for T1DM and T2DM studies. These data were requested in the August 20,2015 Information Request, to which the Sponsor responded on August 26, and are discussed at the beginning of this review. Briefly for T1DM the incidence rates are high at baseline, and show a modest increase during treatment, with baseline and treatment incidences similar between degludec and comparator arms.

Allergic reactions

Two immunogenicity-related events (allergic reactions) were
reported for these subjects: one event of 'urticaria' in each treatment group. Both events were mild, non-serious and considered unlikely to be related to trial product by the investigator. Both subjects recovered and had no increase in anti-insulin specific antibodies.

Reviewer comments

This low incidence of allergic response is consistent with that seen for other insulins (see labels for HUMULIN, LISPRO, LEVIMIR, NOVOLOG)

NDA 203314 –Ryzodeg IDeg/ degludec (long acting)+Insulin aspart (short acting)

From 2.5 Clinical Overview

The following trials were conducted under NDA 203314

3594/3645 T1DM

3590, 3592, 3593, 3597 T2DM

In the therapeutic confirmatory trial programm, insulin antibodies were measured in T1DM (Trial 3594/3645) and in T2DM (Trials 3590 and 3597)
In T1DM, the mean level of cross-reacting insulin antibodies remained low (10-15% B/T) throughout the trial in the IDegAsp group, whereas a small increase was observed in the comparator group. A total of 13% of subjects treated with IDegAsp and 49% of subjects treated with comparator products had an increase in cross-reacting antibodies of 10% B/T or more and/or an increase of 5% B/T or more in insulin-specific antibodies.

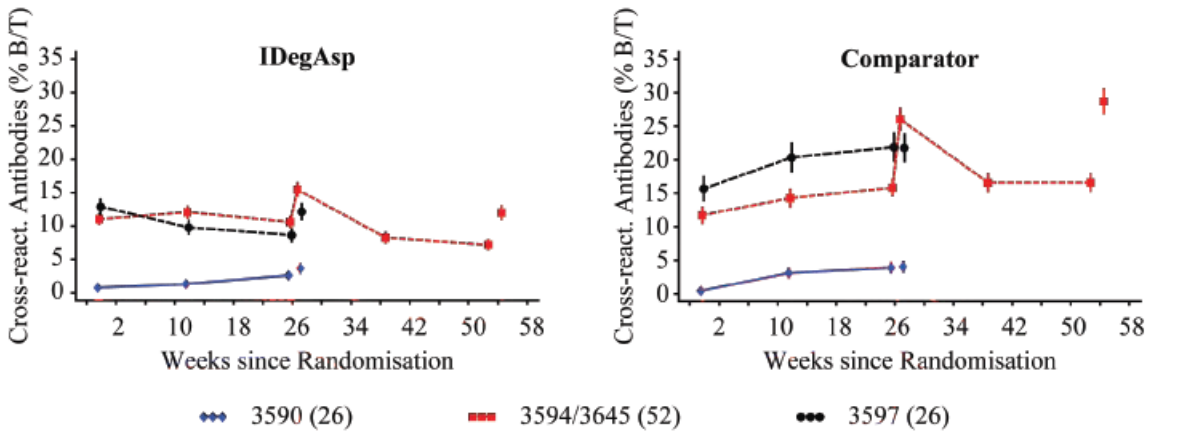
In insulin-naïve subjects with T2DM (Trial 3590), the mean level of cross-reacting insulin antibodies remained below 5% throughout the trial. Only 4% of subjects treated with IDegAsp and 6% of subjects treated with comparators demonstrated an increase in cross-reacting or insulin-specific antibodies.

Reviewer comments

The anti-IDeg incidence rates for the IDeg arms of the T1DM studies appear to show lower incidence rates than the comparator(IDet+IAsp) arms, howeverthe Agency finds that these results are uninterpretable due to the low sensitivity of the anit-IDeg assay. The Sponsor has been asked to agree PMCs for development of a more sensitive assay and to use this new assay to measure anit-IDeg levels in patient sera.

From 2.7.3 Summary of clinical efficacy, pp 169-170

Insulin antibodies were measured in Trials 3583, 3585, 3770, 3579, 3672, 3586, 3668 in order to include a broad population of subjects with T1DM and T2DM in different regions, with different races and with different treatment regimens. Insulin antibodies were measured at baseline and after 12 and 26 weeks of treatment. In addition, insulin antibodies were measured after 52 weeks of treatment in Trial 3583 (T1DM) and Trial 3579 (T2DM). A follow-up visit was scheduled at least 7 days after end of treatment to allow for a washout period and thereby less interference of exogenous insulin with the antibody assay. In the 1-week washout period, the subjects were treated with NPH insulin, which causes less interference with the assay due to a lower plasma concentration during treatment and a shorter half-life. The main analyses of insulin antibody development were therefore based on antibody measurements performed at baseline and at follow up (post-treatment period after the wash-out period). Antibody development against IDeg, IAsp, IDet and IGlar was measured by a validated subtraction radio-immunoassay using radioactively labelled IDeg, IAsp, IDet, IGlar or human insulin. The amount of precipitated radioactivity was measured and expressed as percent bound radioactivity (B) of the total amount of radioactivity (T) applied to the sample. The %B/T value is proportional to the amount of anti-insulin antibody present in the sample.



%B/T = Percent bound over total.
Subjects temporarily discontinued trial product for a 1-week washout with NPH at Weeks 26 and 52.
Comparator: IDet (3594/3645), IGlar OD (3590), BIAsp 30 BID (3597)

Reviewer comments

The T1DM studies (3594/3645) create little concern, since the IDegAsp arm actually shows a slight decrease in antibody levels with time, whereas the levels for comparator are higher and increase with time. The antibody levels for IDegAsp patients in the T2DM studies also appear low relative to the comparator arms, although the true incidence for both treatment and comparator may be higher due to assay interference from endogenous insulin.

Table 5–1 Spearman Correlation Coefficients – Antibodies versus HbA_{1c} and versus Dose

	IDegAsp Group			Comparator Group		
Trial 3594/3645, T1DM	**HbA_{1c} at EOT**	**Change from Baseline in HbA_{1c}**	**Total Daily Dose at EOT**	**HbA_{1c} at EOT**	**Change from Baseline in HbA_{1c}**	**Total Daily Dose at EOT**
IDeg/Comp-specific abs	-0.06	0.00	-0.05	0.05	0.04	0.04
IAsp-specific abs	-0.10	0.00	-0.10	**0.21***	**0.22***	-0.08
Abs cross-reacting to human insulin	0.05	0.08	-0.05	0.07	0.15	0.01
Trial 3590, T2DM						
IDeg/Comp-specific abs	0.01	0.06	0.02	-0.04	-0.01	-0.04
IAsp-specific abs	-0.07	-0.06	-0.02			
Abs cross-reacting to human insulin	0.04	-0.05	**0.19***	-0.03	-0.06	0.11
Trial 3597, T2DM						
IDeg/Comp-specific abs	0.02	-0.02	0.03	See IAsp row below		
IAsp-specific abs	-0.07	0.08	-0.08	**-0.19***	-0.15	0.08
Abs cross-reacting to human insulin	0.00	**0.13***	0.09	-0.02	-0.09	**0.30***

*** Statistically significant different from 0**; abs: antibodies, EOT: End of trial
Comparator: IDet (3594/3645), IGlar OD (3590), BIAsp 30 BID (3597)

Reviewer comments

The treatment group in the T1DM study shows no effect of antibodies on efficacy, whereas there is some statistically significant correlation between antibody levels and HbA1c in the comparator group. This is perhaps expected due to the higher antibody levels in the comparator group. For the T2DM studies there are statistically significant effects for both treatment and comparator, but these are difficult to interpret due to the caveat regarding assay interference from endogenous insulin in T2DM samples.

From Summary 2.7.4, Section 3.3.1 Clinical Safety Summary
Allergic responses
Three patients in the T2DM trials had hypersensitivity reactions. These patients withdrew from the study.

Reviewer comment
This low incidence of allergic response is consistent with that seen for other insulins (see labels for HUMULIN, LISPRO, LEVIMIR, NOVOLOG)

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

/s/

FREDERICK C MILLS
09/10/2015

DANIELA I VERTHELYI
09/21/2015

Memo

Date: August 18, 2015

updated August 27-Sept 2, 2015 to reflect Sponsor's responses to the 8/20/2015 IR

revised September 4-6, 2015

From: Fred Mills, Staff Scientist, Laboratory of Immunobiology, OBP, Division 4

To: Daniela Verthelyi, Chief, Laboratory of Immunology, OBP, BDRR 3

FDA designation: NDA 203314 and NDA 203313, original NDA submission

Sponsor: Novo Nordisk

Products: insulin degludec (IDeg, generic name insulin 454), for treatment of diabetes Designated as TRESIBA for single API studies and as RYZODEG when combined with IAsp, which is a licensed short acting insulin.
Subject: summary of IDeg (TRESIBA) and IDeg/IAsp (RYZODEG) clinical trial antibody results, immunogenicity label wording and PMCs.

Comments to the File

The Sponsor Novo Nordisk has conducted clinical trials for treatment of diabetes Type 1 (T1DM) and Type 2 (T2DM) using their long acting insulin degludec (IDeg) either alone (designated TRESIBA, under NDA 203314) or in combination with their licensed short acting insulin IAsp (designation RYZODEG, under NDA 203314). Relative to insulin, IDeg lacks the last amino acid of the B chain and has a di-carboxylic fatty acid coupled to the lysine at position B29, greatly increasing the IDeg half-life by promoting formation of stable multi-hexamers.

The Sponsor has conducted comprehensive antibody assessments on sera from their clinical studies using radioimmunoassays (RIA) to measure anti-degludec antibodies as well as anti-insulin antibodies (AIA), antibodies to the insulins used in the comparator arm of studies (IGlarg in almost all cases), and antibodies to the IAsp short acting insulin component in RYZODEG . The RIA method for AIA has high sensitivity (20 ng/ml), as do the methods for anti-IGlarg (50 ng/ ml) and anti-IAsp (33 ng/ ml). The assay to measure antibodies to degludec, however, has low sensitivity (see below).

Most significantly from a safety standpoint, as seen in Table 3, p. 8 in this review, the incidences of AIA in T1DM studies are high at baseline, but show a only modest increases during trials;i.e.
TRESIBA: T1DM baseline 89.7% , 95.9% anytime, sustained for degludec arms
RYZODEG: T1DM baseline 89.0% , 95.9% anytime, sustained for degludec arms

and is similar to comparator arms

TRESIBA: T1DM baseline 88.2%, 95.9% anytime, sustained for comparator arms
RYZODEG: T1DM baseline 88.3% , 97.2 % anytime sustained for comparator arms

For T2DM studies, AIA incidence increased during studies; i.e.

TRESIBA T2DM baseline 14.5%, 31.5 % anytime, sustained for degludec arms
RYZODEG T2DM baseline 45.4%, 67.5% anytime, sustained for degludec arms
While the levels of antibodies cannot be compared between treatments because the assays to detect antibodies to the products are different, the incidence of antibodies against treatment in the patients receiving degludec is similar to that of the patients receiving the comparator
TRESIBA: T2DM baseline 16.3%, 46.1 % anytime, sustained for comparator arms
RYZODEG: T2DM baseline 30.8%, 63.9% anytime, sustained for comparator arms

The Sponsor did not determine AIA titers, but the mean signal as (%B/T) provides some quantitative information on the levels of antibodies in patients (see Figure 40 p.16). For the T1DM data, there is little or no difference between the IDeg and comparator arms, providing reassurance that there is no increased immunogenicity risk mediated by IDeg relative to the comparators (IGlar or IDet). The plots show a lower incidence of anti-insulin antibodies in T2DM relative to T1DM, however these results should be considered carefuly since the reduced %B/T signal may to some extent result from assay interference from endogenous insulin in some patients in the T2DM studies. Importantly, for subjects that were positive at baseline the %B/T did not increase during treatment (see Figure 5-3 on p.15 of this review).

Furthermore, there was little change in the ratio of AEs to antibody levels for the degludec arms of studies, and the AE/anti-IGlarg ratios in comparator arms are the same or higher. These results support the view that degludec administration poses no safety risk vis a vis increased levels of AIA, which might in principle pose safety concerns due to loss of endogenous insulin activity. In RYZODEG trials, anti-IAsp antibodies show little change from baseline, and little difference between treatment and comparator arms, indicating RYZODEG administration does not generate an important antibody response to its short-acting component. Taken together, these AIA data indicate that there are no important antibody-mediated safety issues arising from administration of IDeg, and therefore nothing to preclude approval from an immunogenicity standpoint.

However, the Sponsor's specific anti-degludec assay has a low sensitivity of 1800 ng/ml, making it impossible to draw conclusions about the incidence and levels of antibodies raised to the product and their potential impact on safety and efficacy. For this reason, the Sponsor has been asked to agree to identical PMCs for TRESIBA and RYZODEG to develop and validate a new anti-degludec assay with sensitivity at least consistent with current FDA guidance (250-500 ng/ml), and also identical PMCs for TRESIBA and RYZODEG stipulating that the new assay be used to analyze degludec-treated patient sera to obtain interpretable data on anti-degludec antibody incidence and titer, and correlate these data with PK, safety, and efficacy. Moreover, the FDA has proposed label wording for the current approval stating that "The incidence of anti-degludec antibodies has not been accurately assessed." This language can be revised post-approval when the PMCs for analysis of sera with a new anti-degludec assay have been fulfilled.

Table of Contents

Proposed immunogenicity Labeling

Proposed wording for NDA 203313 TRESIBA (degludec)

6.2 Immunogenicity

(b) (4). The incidence of anti-degludec antibodies has not been accurately assessed. In studies of type 1 diabetes patients, 95.9% of patients who received TRESIBA once daily were positive for anti-insulin antibodies (AIA) at least once during the studies, including 89.7 % that were positive at baseline. In studies of type 2 diabetes patients, 31.5% of patients who received TRESIBA once daily were positive for AIA at least once during the studies, including 14.5% that were positive at baseline. The antibody incidence rates for type 2 diabetes may (b) (4) due to potential assay interference by endogenous insulin in samples (b) (4) patients. The presence of antibodies that affect clinical efficacy may necessitate dose adjustments to correct for tendencies toward hyper- or hypoglycemia.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to TRESIBA with the incidence of antibodies in other studies or to other products, may be misleading.

Proposed wording for NDA 203314 RYZODEG (degludec + insulin Aspart/ IAsp)

6.2 Immunogenicity

(b) (4). The incidence of anti-degludec antibodies has not been accurately assessed. In studies of type 1 diabetes patients, 95.9% of patients who received RYZODEG once daily were positive for anti-insulin antibodies (AIA) at least once during the studies, including 89% that were positive at baseline, while 13% of these patients were positive for anti-IAsp antibodies at least once during the studies, including 6.4% who were positive at baseline. In studies of type 2 diabetes patients, 67.5% of patients who received RYZODEG once daily were positive for AIA at least once during the studies, including 45.4% that were positive at baseline, while 17.1% of these patients were positive for anti-IAsp antibodies at least once during the studies, including 12.3% who were positive at baseline. The antibody incidence rates for type 2 diabetes may (b) (4) due to potential assay interference by endogenous insulin in samples (b) (4) patients. The presence of antibodies that affect clinical efficacy may necessitate dose adjustments to correct for tendencies toward hyper- or hypoglycemia.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to RYZODEG with the incidence of antibodies in other studies or to other products, may be misleading.

Immunogenicity PMCs (identical between TRESIBA and RYZODEG, except for name change)

PMC #1 Description: To develop and validate an assay to assess for the presence of anti-degludec antibodies that has a sensitivity consistent with FDA guidance. Your final report should include a summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay standard operating procedure (SOP).

PMC Schedule Milestones:		
	Final Protocol Submission:	Not needed
	Study/Trial Completion:	Not needed
	Final Report Submission:	10/01/2016
	Other:	MM/DD/YYYY

PMC #2 Description: To assess the incidence and titers of anti-degludec antibodies in sera from patients treated with TRESIBA in TRESIBA clinical studies and determine whether they are associated with differences in pharmacokinetics parameters (e.g. exposure), efficacy (e.g. hemoglobin A1c, insulin dose), and safety (e.g. hypoglycemia and hypersensitivity). The clinical samples should not be tested until the results from the PMC for anti-degludec antibody assay development and validation have been submitted to and reviewed by the Agency. (b) (4)

PMC Schedule Milestones:		
	Final Protocol Submission:	01/01/2017
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	04/01/2017

OBP information request (08-20-2015) and Novo Nordisk response (08-26-2015)
On August 20, 2015 the following Information Request was sent to the Sponsor (response requested by COB August 26), with the goal of clarifying the percentage of antibody positive patients, and correlation of antibodies with safety and efficacy.

Question 1
Provide a table containing data on antibody incidence rates and, if available, antibody titers for each study that assessed immunogenicity in Type I or Type 2 diabetes. The tables for each study should describe:
a) Number of patients (absolute number and percent) treated with degludec (TRESIBA), degludec + insulin aspart (RYZODEG), or comparator.
i. who were positive for ADA at any time during the study
ii. who were positive for ADA at baseline
iii. who had sustained ADA (defined as two or more positive for ADA samples or remained positive at the end of the study).
iv. For all subjects that have at least 1 positive sample provide the ADA titers if available in a table organized by treatment group, patient and sampling time.
b) Number of patients (absolute number and percent) treated with degludec (TRESIBA), degludec + insulin aspart (RYZODEG), or comparator.
i. who were positive for AIA at any time during the study
ii. who were positive for AIA at baseline
iii. who had sustained AIA (defined as two or more positive for ADA samples or remained positive at the end of the study).
iv. For all subjects that have at least 1 positive sample provide the AIA titers if available in a table organized by treatment group, patient and sampling time
c) Table showing whether there is a correlation between ADA or AIA with adverse events
d) Table showing whether there is a correlation between ADA or AIA and changes in efficacy with changes in antibody levels and/or titer.

Question 2
Your submission stated the sensitivity of each assay but does not state that an appropriate suitability control was used routinely to ensure that the sensitivity of the assays was consistent during the run of the study samples. Describe the system suitability controls that are routinely included as part of assay runs.

Responses to Question 1
The Sponsor responded on August 26, 2015. In this response the term 'ADA' is interpreted as meaning 'anti-drug-antibodies', i.e., specific antibodies against IDeg, insulin glargine (IGlar), insulin detemir (IDet) or insulin aspart (IAsp), while 'AIA' is interpreted as meaning 'anti-insulin-antibodies' and used to describe antibodies cross-reacting to human insulin. IDeg refers to degludec (Tresiba) while IDegAspr refers to the degludec+insulin Aspart (IAsp) combination (Ryzodeg).

Anti-Drug Antibodies

Table 1 Incidence of basal insulin (IDeg, IGlar and IDet) specific antibodies (ADA) - safety analysis set

Type	Trial ID	Treatment	Safety set	Positive for ADA		
				Anytime	Baseline	Sustained[§]
Pool IDeg T1DM trials		Comparator	467	166 (35.5)	65 (13.9)	155 (33.2)
		IDeg	1102	269 (24.4)	83 (7.5)	115 (10.4)
Pool IDeg T2DM trials		Comparator	1138	57 (5.0)	3 (0.3)	39 (3.4)
		IDeg	2287	255 (11.1)	68 (3.0)	120 (5.2)
Pool IDegAsp T1DM trial		Comparator	180	171 (95.0)	97 (53.9)	160 (88.9)
		IDegAsp	362	87 (24.0)	31 (8.6)	43 (11.9)
Pool IDegAsp T2DM trials		Comparator	261	13 (5.0)	1 (0.4)	12 (4.6)
		IDegAsp	544	93 (17.1)	17 (3.1)	40 (7.4)

Reviewer comments

The anti-degludec antibody assay has low sensitivity relative to the anti-IGlar and IDet comparator assays. The data for the IDeg T1DM and IDegAsp trials are consistent with this low sensitivity; i.e. reported incidence of IDeg antibodies is lower than comparator-suggesting inadequate detection.

Anti-IAsp levels in RYZODEG trial

Table 2 Incidence of IAsp-specific antibodies (ADA) - safety analysis set

Type	Trial ID	Treatment	Safety set	Positive for ADA		
				Anytime	Baseline	Sustained[§]
T1DM	NN5401-3594-3645	IDet	180	18 (10.0)	10 (5.6)	16 (8.9)
		IDegAsp	362	47 (13.0)	23 (6.4)	42 (11.6)
Pool IDegAsp T1DM trial		Comparator	180	18 (10.0)	10 (5.6)	16 (8.9)
		IDegAsp	362	47 (13.0)	23 (6.4)	42 (11.6)
T2DM	NN5401-3590-3726[#]	IDegAsp	265	33 (12.5)	24 (9.1)	28 (10.6)
T2DM	NN5401-3597	BIAsp 30	141	32 (22.7)	23 (16.3)	30 (21.3)
		IDegAsp	279	60 (21.5)	43 (15.4)	49 (17.6)
Pool IDegAsp T2DM trials		Comparator	141	32 (22.7)	23 (16.3)	30 (21.3)
		IDegAsp	544	93 (17.1)	67 (12.3)	77 (14.2)
Phase 2 trials						
T2DM	NN5401-1791	IDegAsp	118	16 (13.6)	14 (11.9)	14 (11.9)
T2DM	NN5401-1792	BIAsp 30	62	16 (25.8)	6 (9.7)	16 (25.8)
		IDegAsp	119	18 (15.1)	15 (12.6)	18 (15.1)

[#]IAsp was not included in the comparator arm (IGlar); [§]More than one or at follow-up

Pools contain only confirmatory therapeutic trials. Phase 2 trials were analyzed separately.

Reviewer comments

Anti-IAsp antibodies are detected by a sensitive assay, and show little change from baseline, and little difference between treatment and comparator arms, indicating RYZODEG administration does not generate an important antibody response to its short-acting component.

Anti-Insulin Antibodies (AIA)

Table 3 Incidence of cross reacting antibodies (AIA) - safety set

Type	Trial ID	Treatment	Safety set	Positive for AIA Anytime	Positive for AIA Baseline	Positive for AIA Sustained[$]
T1DM	NN1250-3583-3644	IGlar	154	145 (94.2)	136 (88.3)	141 (91.6)
		IDeg	472	455 (96.4)	425 (90.0)	445 (94.3)
T1DM	NN1250-3585-3725	IDet	152	149 (98.0)	130 (85.5)	147 (96.7)
		IDeg	301	285 (94.7)	268 (89.0)	282 (93.7)
T1DM	NN1250-3770 main-ext	IGlar	161	154 (95.7)	146 (90.7)	151 (93.8)
		IDeg	329	317 (96.4)	295 (89.7)	306 (93.0)
Pool IDeg T1DM trials		Comparator	467	448 (95.9)	412 (88.2)	439 (94.0)
		IDeg	1102	1057 (95.9)	988 (89.7)	1033 (93.7)
T2DM	NN1250-3579-3643	IGlar	257	120 (46.7)	19 (7.4)	96 (37.4)
		IDeg	766	248 (32.4)	60 (7.8)	169 (22.1)
T2DM	NN1250-3586	IGlar	146	72 (49.3)	21 (14.4)	62 (42.5)
		IDeg	284	63 (22.2)	28 (9.9)	40 (14.1)
T2DM	NN1250-3587	IGlar	278	114 (41.0)	44 (15.8)	102 (36.7)
		IDeg	553	152 (27.5)	84 (15.2)	137 (24.8)
T2DM	NN1250-3668	IGlar	229	123 (53.7)	79 (34.5)	100 (43.7)
		IDeg	456	200 (43.9)	140 (30.7)	169 (37.1)
T2DM	NN1250-3672	IGlar	228	96 (42.1)	22 (9.6)	72 (31.6)
		IDeg	228	58 (25.4)	19 (8.3)	39 (17.1)
Pool IDeg T2DM trials		Comparator	1138	525 (46.1)	185 (16.3)	432 (38.0)
		IDeg	2287	721 (31.5)	331 (14.5)	554 (24.2)
T1DM	NN5401-3594-3645	IDet	180	175 (97.2)	159 (88.3)	174 (96.7)
		IDegAsp	362	347 (95.9)	322 (89.0)	343 (94.8)
Pool IDegAsp T1DM trial		Comparator	180	175 (97.2)	159 (88.3)	174 (96.7)
		IDegAsp	362	347 (95.9)	322 (89.0)	343 (94.8)
T2DM	NN5401-3590-3726	IGlar	261	132 (50.6)	20 (7.7)	121 (46.4)
		IDegAsp	265	138 (52.1)	42 (15.8)	118 (44.5)
T2DM	NN5401-3597	BIAsp 30	141	125 (88.7)	104 (73.8)	117 (83.0)
		IDegAsp	279	229 (82.1)	205 (73.5)	211 (75.6)
Pool IDegAsp T2DM trials		Comparator	402	257 (63.9)	124 (30.8)	238 (59.2)
		IDegAsp	544	367 (67.5)	247 (45.4)	329 (60.5)
Phase 2 Trials						
T2DM	NN1250-1836	IDeg	178	53 (29.8)	15 (8.4)	45 (25.3)

[$]More than one or at follow-up

Pools contain only confirmatory therapeutic trials. Phase 2 trials were analyzed separately

For anti-insulin antibodies, the incidence of baseline, anytime antibodies, and sustained antibody levels in the IDeg or IDegAsp treatments are similar, or in some cases lower than the incidence rates for the corresponding comparator arms, suggesting no increased safety risk relative to comparator that is mediated by increases in anti-insulin antibodies.

Adverse effect association

Table 4 Adverse event rates according to change in absolute values in ADA and AIA, therapeutic confirmatory trials

Trial	IDeg (AE-rates/100 PYE)				Comparator (AE-rates/100 PYE)			
IDeg	≥5%B/T ADA	≤5%B/T ADA	≥10%B/T AIA	≤10%B/T AIA	≥5%B/T ADA	≤5%B/T ADA	≥10%B/T AIA	≤10%B/T AIA
T1DM								
3585-3725	213.2	464.3	429.2	464.3	476.7	394.2	490.7	359.2
3770-EX	130.7	450.3	453.7	444.2	1389.5	478.0	431.5	498.5
3583-3644	395.2	382.9	411.7	375.2	0.0	374.0	414.1	363.4
Pooled	306.1	413.4	424.8	408.2	487.5	407.7	449.3	399.9
T2DM								
3586	0.0	293.1	334.5	292.6	299.4	289.9	316.4	284.2
3672	0.0	451.3	401.4	452.5	600.4	485.2	643.2	473.7
3668	438.9	397.1	399.7	398.1	0.0	390.9	401.9	381.9
3579-3643	0.0	361.7	401.7	360.7	646.1	331.2	288.6	346.2
3587	0.0	229.2	152.7	232.6	376.7	285.6	240.9	298.4
Pooled	366.1	347.2	336.7	347.6	456.3	349.0	320.0	356.4
IDegAsp								
T1DM								
3594-3645	318.1	410.9	304.7	436.8	406.2	467.1	427.2	469.4
T2DM								
3590-3726	341.9	312.2	320.8	312.0	261.5	237.1	253.6	234.4
3597	517.7	344.3	334.2	350.4	802.7	389.4	364.9	401.9
Pooled	401.8	324.2	324.5	326.7	314.5	270.5	286.6	267.8

PYE: patient year of exposure

Reviewer comments

These data indicate that for anti-insulin antibodies (AIA), which are detected by a sensitive assay, there is no association between antibody levels and adverse events for the IDeg arms, and no difference between the IDeg arms and the comparator arms, except for the comparator arm of two studies (3770-EX, 3672, and 3597), where there AE-rates/100PYE are actually higher. This reinforces the view that degludec administration poses no safety risk vis a vis increased level of AIA, which might in principle mediate pose safety concerns due to los of endogenous insulin activity.

Table 5 Spearman Correlation Coefficients – Antibodies vs. HbA_{1c} and vs. Dose – SAS

IDeg confirmatory trials	IDeg Group			Comparator Group		
T1DM Pooled	HbA_{1c} at end-of trial	Change from baseline in HbA_{1c}	Total daily dose at end-of-trial	HbA_{1c} at end-of-trial	Change from baseline in HbA_{1c}	Total daily dose at end-of trial
ADA (IDeg/Comp)	0.02	-0.01	0.01	-0.07	-0.11	**0.30***
ADA (IAsp)	0.02	**0.07***	0.05	-0.01	-0.04	0.07
AIA	0.02	0.02	0.04	-0.06	-0.10	**0.20***
Trial 3583-3644, T1DM						
ADA (IDeg/Comp)	0.05	-0.04	0.01	-0.11	0.01	-0.04
ADA (IAsp)	0.00	0.09	0.10	-0.04	0.04	0.01
AIA	-0.02	0.06	-0.02	-0.10	-0.17	0.13
Trial 3585-3725, T1DM						
ADA (IDeg/Comp)	0.10	0.10	0.04	-0.12	0.13	0.09
ADA (IAsp)	0.08	0.13*	-0.01	0.04	-0.04	0.13
AIA	**0.13***	-0.04	**0.24***	0.01	0.06	0.11
Trial 3770-3770 Ex, T1DM						
ADA (IDeg/Comp)	-0.12	-0.05	-0.02	-	-	-
ADA (IAsp)	-0.08	0.02	0.03	-0.02	-0.05	-0.05
AIA	-0.06	0.10	-0.00	-0.10	-0.04	0.17
T2DM Pooled						
ADA (IDeg/Comp)	0.01	-0.00	0.01	0.02	-0.02	0.00
AIA	**0.10***	0.02	**0.12***	**0.08***	0.01	0.05
Trial 3579-3643, T2DM						
ADA (IDeg/Comp)	0.06	0.02	-0.00	-0.01	-0.04	0.13
AIA	0.08	0.02	**0.12***	0.04	-0.09	**0.24***
Trial 3672, T2DM						
ADA (IDeg/Comp)	-0.04	-0.10	0.09	-0.06	-0.06	0.01
AIA	0.07	-0.03	**0.14***	-0.12	-0.13	-0.07
Trial 3586, T2DM						
ADA (IDeg/Comp)	0.07	0.11	0.02	0.06	0.01	0.08
AIA	-0.03	-0.07	**0.17***	0.07	0.03	0.14
Trial 3668, T2DM						
ADA (IDeg/Comp)	0.03	**0.21***	0.13	0.02	-0.06	-0.02
AIA	**0.20***	0.11	**0.20***	**0.24***	0.13	0.08
Trial 3587						
ADA (IDeg/Comp)	-0.02	-0.05	-0.02	0.05	0.05	-0.10
AIA	0.08	-0.01	0.05	0.06	0.03	0.10

abs. antibodies; comparator: IGlar (3583-3644, 3770-3770 Ex, 3579-3643, 3672, 3586, 3668; 3587); IDet (3585-3725).

* Statistically significant different from 0

Reviewer comments

Because of the low sensitivity of the anit-degludec antibody assay, no statement can be made about correlation of these antibodies with efficacy. However, there is no apparent effect of AIA, which are detected with a sensitive assay, on efficacy in T1D, and only modest effects in T2DM. On this basis degludec administration does not seem to have a significant effect on efficacy that is mediated by immunogenicity.

Response to Question 2

System suitability control samples were included in every assay run for each of the four analyses for determination of ADA's (IDeg specific, IDet specific, IAsp specific, IGlar specific antibodies) and for determination of AIA (insulin human binding antibodies). The control samples for each of the four ADA assays was generated by spiking monoclonal drug specific antibodies into human serum. The control sample for the AIA assay was spiked with a polyclonal antibody towards human insulin. The levels of antibody in the controls were based on titration and selected to be on the linear part of the titration curve (25-45%B/T) in order to reduce the assay variation. Assay acceptance is based on the system suitability controls included three times

in each assay run. For an assay to be accepted, two out of the three control sample results should be within their acceptance range (nominal values ± 20% based on assay variation). The nominal value for each control sample was determined as the mean %B/T value in at least 6 assay runs. All data presented were derived from successful assay runs. The assay rejection rate was below 5% (the exact number may be found in the antibody analytical report placed in Appendix 16.1.10 of the clinical trial report for each individual trial). The composition of the control samples were not changed during the clinical development program. This ensures consistent analysis performance throughout the program.

Reviewer comments

The Sponsor includes suitability controls in all assay runs that utilize multiple samples of positive control antibody in the linear range of response, where optimal reproducibility is expected. Two out of three control results must meet specification for an assay to be acceptable, and the Sponsor's experience has been that the assay rejection rate is less than 5%, indicating the assay is consistently performing within this specification. Of note, the sponsor does not use a Low positive control to confirm the sensitivity of the assay on each run. This will be brought to their attention so that such a control is included when the testing needed to fulfill the PMC is conducted.

This assay's antibody incidence rate and measurement of antibody levels is consistent with that observed in literature and by other Sponsors e.g.

Mianowska et al. Pediatric Diabetes (2011) 12, pp.78-84
T1D insulin naïve patients baseline 80% 6 and 24 month treatment 97.9%

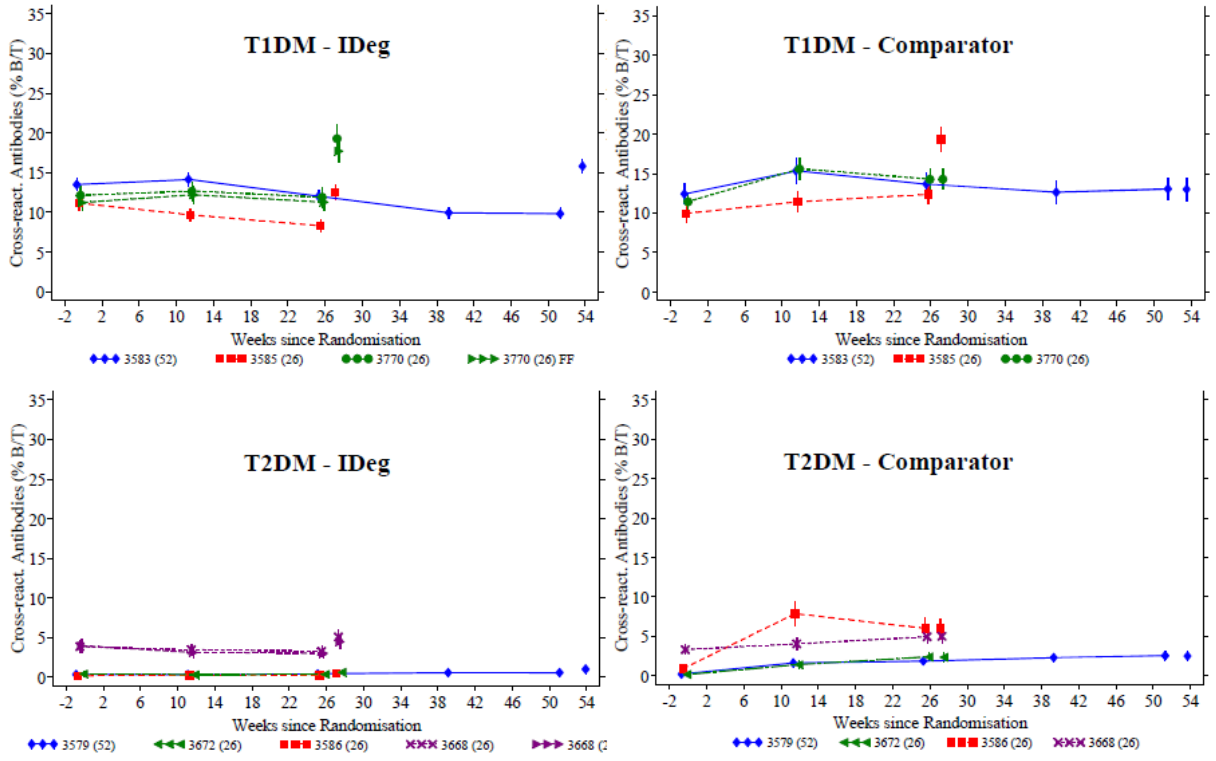
TOUJEO (Sanofi Iglarg) label

T1D baseline	62%	ever positive 6 month	79%
T2D baseline	42%	ever positive 6 month	25%

In addition, for studies of cross-reacting antibodies in trials with Lispro (Lilly)
Fineberg et al., Diabetes Care (2003) 26 pp.89-96; .

Figure 3—*Percent binding of cross-reactive antibodies from parallel studies in insulin-treated patients with type 1 or type 2 diabetes. Mean and 95% CIs over time are shown. The vertical dotted line separates parent and extension studies. The inset graph is the fitted quadratic random mixed model.*

These levels are similar for those from the Novo Nordisk assay; i.e.



% B/T:% bound over total radioactivity; Subjects temporarily discontinued trial product for a 1-week washout with NPH insulin at Weeks 26 and 52; Last antibody assessment was made 1 week after last trial product administration;

Comparator: IGlar (3583, 3770, 3579, 3672, 3586, 3668), IDet (3585).

Therefore the Novo Nordisk antibody assay appears to be detecting expected incidence and antibody levels and thus performing adequately.

Product Description

The structure of IDeg is based on that of human insulin. Compared with human insulin, IDeg contains no amino acid substitutions, but the last amino acid (b) (4) (threonine at position B30), which does not impact receptor recognition, has been omitted. In addition, a di-carboxylic fatty acid (hexadecanedioic acid) has been coupled to the lysine at position B29 via a glutamic acid spacer. The addition of this specific di-carboxylic fatty acid via the glutamic acid spacer is what enables IDeg to form soluble and stable multi-hexamers when injected into subcutaneous tissue. In contrast human insulin remains as hexamers. The biologically active monomers of IDeg gradually separate from the multi-hexamers in the subcutaneous depot, providing a slow, stable and continuous delivery of IDeg into the circulation resulting in the observed pharmacokinetic and pharmacodynamic (PD) profiles. Tresiba (NDA 203314)n is a formulation of IDeg, while Ryzodeg (NDA 302213) is a formulation of IDeg + insulin aspart. Both are licensed in the EU, and EMA statements regarding antibody formation are provided below.

EMA Tresiba product information

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002498/WC500138940.pdf

Section 4.4 Special Warnings and Precautions for Use p.5

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Section 5.1 Pharmacodynamic Properties, p.12

Antibody development was sparse and had no clinical impact.

EMA Ryzodeg product information

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002499/WC500139011.pdf

Section 4.4 Special Warnings and Precautions for Use p.18

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Section 5.1 Pharmacodynamic Properties, p. 23

There is no clinically relevant development of insulin antibodies after long-term treatment of Ryzodeg

From Novo Nordisk backgrounder for November 8, 2012 Advisory Committee

Insulin antibodies were measured in 7 IDeg trials: 4 T2DM trials (Trials 3579, 3586, 3668 and 3672) and 3 T1DM trials (Trials 3583, 3585 and 3770). Insulin antibodies were also measured in 3 IDegAsp trials: T2DM Trials 3590 and 3597 and T1DM Trial 3594. Antibody development against IDeg, IAsp, IDet and IGlar was measured by a validated subtraction radio-immunoassay using radioactively labeled IDeg, Asp, IDet, IGlar or human insulin. The amount of precipitated radioactivity was measured and expressed as percent bound radioactivity (B) of the total amount of radioactivity (T) applied to the sample. The %B/T value is proportional to the amount of anti-insulin antibody present in the sample.

Antibody Assay Description

The Sponsor's antibody assay is a RadioImmunoPrecipitation (RIA). Briefly, the assay is a subtraction radioimmunoassay. The samples were incubated with ^{125}I labeled tracer ± excess insulin/insulin analogue. After incubation overnight the immunoglobulin was precipitated together with any antigen that may have bound. The precipitate was counted in a gamma counter and the amount of radioactivity was expressed in percent of the total amount of added radioactivity (%B *(bound)* /T*(total)*). The %B/T value is proportional to the amount of anti-insulin antibody present in the sample. This is the assay methodology most widely used for detection of anti-insulin antibodies (Fineberg et al. 2007 Endocrine Reviews 28 pp.625-652)

The sensitivity of the anti-degludec antibody assay is low (1800 ng/ml) and not consistent with FDA guidance, which currently recommends a minimum sensitivity of 250-ng/ml. Adequate sensitivity was demonstrated for the assay for antibodies to the comparator IGlarg insulin (50 ng/ml), antibodies to the short-acting IAsp in RYZODEG (33 ng/ ml) and Anti-Insulin Antibodies or AIA (20 ng/ml)

Reviewer comment

As discussed above, the Agency has proposed PMCs for the Sponsor to develop an anti-ideg antibody assay with adequate sensitivity, and to analyze clinical samples with this new assay.

Summaries of Antibody Data from NDAs 203314 and 203313

NDA 203313 –Tresiba / IDeg/ degludec

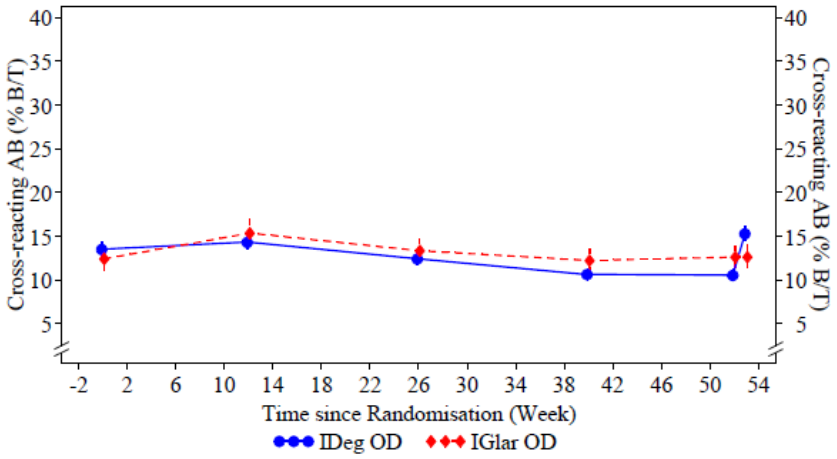
From IDeg 2.5 Clinical Overview

Under NDA 203314, there were three T1DM trials using IDeg, with IDet or IGlar as a comparator. There were eight T2DM trials using IDeg, with IGlar or (in one trial) sitagliptin as comparators.

Insulin antibody development was investigated in all trials in T1DM and in a total of 4 trials in subjects with T2DM according to guidelines from EMA. In Trials 3583 and 3579, subjects with T1DM and T2DM, respectively, were treated with IDeg for a period of 52 weeks, and data from these trials are therefore of primary interest. In T1DM, the majority of subjects treated with IDeg had little or no change in IDeg-specific antibodies. The mean level of antibodies cross-reacting between IDeg (and IGlar) and human insulin remained low (10-15% B/T) throughout the trials in both treatment groups. The increase in antibody levels from Week 52 to Week 53 are due to the fact that subjects were transferred to NPH prior to the last antibody measurement to reduce interference from IDeg or comparator in the antibody assay.

In the 12-month trials (3583 and 3579), IDeg specific, IGlar specific and antibodies cross-reacting to human insulin were measured at baseline (Week 0) and after 26 and 53 weeks of treatment. In the 6-month trials, IDeg specific, IGlar specific or IDet specific and antibodies cross-reacting to human insulin were measured at baseline (Week 0) and after 27 weeks of treatment. At Weeks 26 for 26-week trials and 52 for 52-week trials, a wash-out period of at least 7 days was included where the subjects discontinued the trial products and were switched to intermediate acting NPH insulin in order to provide basal insulin coverage while reducing the level of exogenous insulin present at antibody sampling and consequently to reduce the

possibility for interference with antibody measurements. No washout period was performed before antibody measurements at the remaining time points and consequently, the detection of insulin antibodies was lower at these time points. In the following figures, only observed values with a wash-out period are presented. Data are presented based on the completer population.



Safety; LOCF imputed data. Error bars: + Standard Error (Mean). %B/T: percent antibody bound/total radioactivity

Cross-reference: Trial 3583 (M 5.3.5.1), Figure 12-7

Figure 5–2 Cross-reacting Antibodies to Human Insulin (%B/T) – Subjects with T1DM (Trial 3583) Mean Plot – SAS

Reviewer Comments

These data for anti-insulin antibodies in T1DM patients are interpretable because of the high sensitivity of the assay and expected lack of interference from endogenous samples. The time courses for both IDeg and comparator patients stable and very similar, suggesting that IDeg mediates no new immunological effects

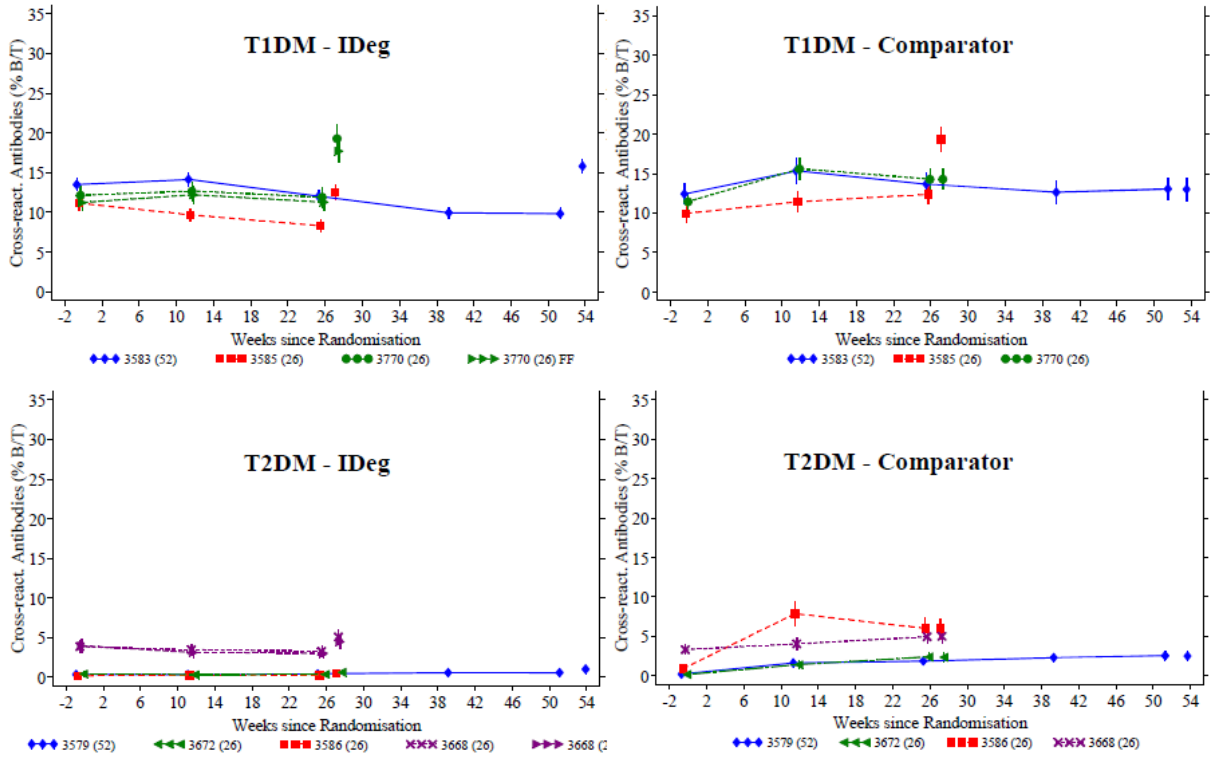
In subjects with T2DM, very few subjects experienced changes in IDeg and comparator specific antibodies. The mean level of cross-reacting antibodies remained < 5% with IDeg throughout the trials and marginal increases were observed with comparator insulin products.

Reviewer Comment

As discussed further in subsequent sections, the relatively low detected antibody levels in T2DM studies may result in part from assay interference stemming from increased levels of endogenous insulin.

From IDeg 2.7.3 Summary of Clinical Efficacy

Figure 5-3 antibodies cross-reactive with human insulin



% B/T:% bound over total radioactivity; Subjects temporarily discontinued trial product for a 1-week washout with NPH insulin at Weeks 26 and 52; Last antibody assessment was made 1 week after last trial product administration;

Comparator: IGlar (3583, 3770, 3579, 3672, 3586, 3668), IDet (3585).

Reviewer comments

These data should be interpretable, because they represent the results of anti-insulin antibody assays, which have a high sensitivity (20 ng/ml). The Sponsor did not determine titers, and these have been requested as part of a PMC. However, the mean signal as (%B/T) does provide quantitative information on the levels of antibodies raised in patients. For the T1DM data, there seems to be little or no difference between the IDeg and comparator arms, providing reassurance that there is no immunogenicity mediated by IDeg relative to the comparators (IGlar or IDet).The plots show a reduced detection of anti-insulin antibodies in T2DM relative to T1DM, although a caveat is that reduced %B/T signal may to some extent result from assay interference from endogenous insulin in some patients in the T2DM studies.

Table 5–1 Spearman Correlation Coefficients – Antibodies vs. HbA_{1c} and vs. Dose – SAS

	IDeg Group			Comparator Group		
Trial 3583, T1DM	**HbA_{1c} at EOT**	**Change from baseline in HbA_{1c}**	**Total daily dose at EOT**	**HbA_{1c} at EOT**	**Change from baseline in HbA_{1c}**	**Total daily dose at EOT**
IDeg/Comp specific abs	-0.02	0.05	0.01	0.08	0.04	0.05
IAsp specific abs	0.05	0.01	0.13	0.05	0.04	0.06
Abs cross reacting to human insulin	0.04	0.09	0.02	-0.01	-0.07	0.13
Trial 3585, T1DM						
IDeg/Comp specific abs	0.10	0.09	0.06	-0.09	0.05	0.09
IAsp specific abs	0.10	0.14	-0.05	-0.17	-0.18	0.17
Abs cross reacting to human insulin	**0.17***	0.03	**0.14***	-0.04	0.03	0.16
Trial 3770, T1DM						
IDeg/Comp specific abs	-0.05	-0.10	-0.03	0.05	-0.02	-0.03
IAsp specific abs	-0.02	0.08	-0.08	-0.05	0.02	0.00
Abs cross reacting to human insulin	0.07	-0.07	0.06	0.01	0.05	0.10
Trial 3579, T2DM						
IDeg/Comp specific abs	0.05	0.02	-0.02	-0.08	-0.05	-0.03
Abs cross reacting to human insulin	**0.15***	0.03	0.03	0.02	-0.03	0.13
Trial 3672, T2DM						
IDeg/Comp specific abs	-0.04	-0.10	0.09	-0.06	-0.06	0.01
Abs cross reacting to human insulin	0.07	-0.03	**0.14***	-0.12	-0.13	-0.07
Trial 3586, T2DM						
IDeg/Comp specific abs	0.07	0.11	0.02	0.06	0.01	0.08
Abs cross reacting to human insulin	-0.03	-0.07	**0.17***	0.07	0.02	0.14
Trial 3668, T2DM						
IDeg/Comp specific abs	0.03	**0.21***	0.13	0.02	-0.06	-0.02
Abs cross reacting to human insulin	**0.20***	0.11	**0.20***	**0.24***	**0.14***	0.08

EOT: end of trial; abs. antibodies; comparator: IGlar (3583, 3770, 3579, 3672, 3586, 3668), IDet (3585).

*** Statistically significant different from 0**

Reviewer comments

Here, the data for cross-reactive insulin antibodies (20 ng/ ml sensitivity) and anti-IAsp(33 ng/ml sensitivity) are interpretable in T1DM, because no assay interference from endogenous insulin is expected. For two of the Trials (3585 and 3770) there is no statistically significant correlation with antibodies. However, for the third T1DM trial (3585), there are significant correlations of anti-insulin antibodies with HbA1c and daily dose. Moreover, in the T2DM trials, where detection of antibodies may be reduced by interference from endogenous insulin, there are nonetheless statistically significant correlations of HbA1c and/or daily dose and detected antibodies. These data indicate some modest impact of antibodies on efficacy, but I defer to the clinical review team for interpretation of their significance.

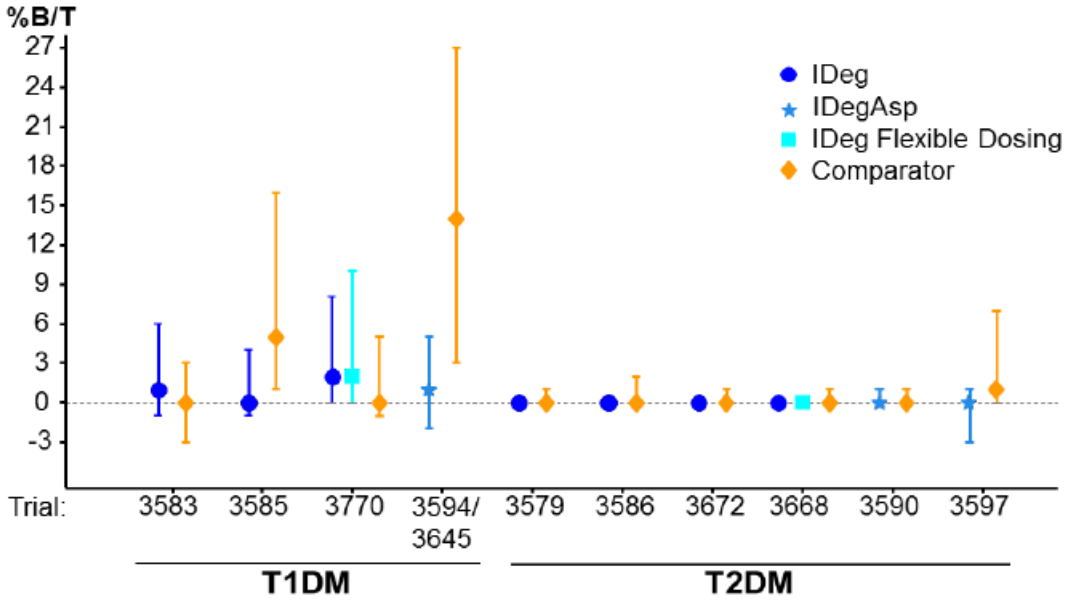
A total of 220 (5%) subjects with T1DM and T2DM in the IDeg group and 145 (6%) subjects in the comparator group had an increase of 10% B/T (absolute value) or more in antibodies cross-reacting with human insulin or an increase in anti-insulin specific antibodies of 5% B/T or more.

Reviewer comments

The overall antibody incidence across T1DM and T2DM studies added together is likely higher in both the treatment and comparator groups, because, as stated above, the detection rate in the T2DM trials may be reduced by interference by endogenous insulin. It would be helpful to have separate incidence calculation for T1DM and T2DM studies. These data were requested in the August 20, 2015 Information Request, to which the Sponsor responded on August 26, and are discussed at the beginning of this review. Briefly, for anti-insulin antibodies, the incidence of baseline, anytime antibodies, and sustained

antibody levels in the IDeg or IDegAsp treatments are similar, or in some cases lower than the incidence rates for the corresponding comparator arms, suggesting no increased safety risk relative to comparator that is mediated by increases in anti-insulin antibodies.

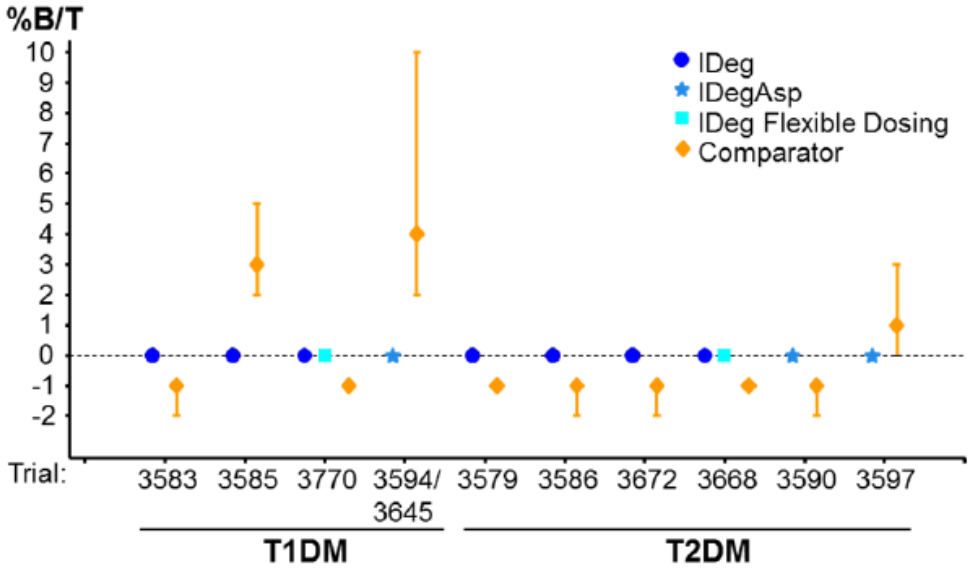
From Summary 2.7.4, Section 3.3.1 Clinical Safety Summary
Summary across trials



Observed values with 25 and 75 percentiles. %B/T: percent bound over total. Comparators: IGlar (Trials 3583, 3770, 3579, 3586, 3672, 3668 and 3590), IDet (Trials 3585 and 3594) and BIAsp 30 (Trial 3597). Safety analysis set.

Figure 40 Cross-reacting Antibodies at Week 27/53 – Change from Baseline – Phase 3 Trials – IDeg or IDegAsp versus Comparator – NDA

The Sponsor states that the mean level of antibodies cross-reacting with human insulin at baseline and at end of trial (following 27 or 53 weeks of treatment) was similar in the IDeg or IDegAsp and the comparator group. Shown below is a plot of the levels of insulin-analogue specific antibodies in the Phase 3 trials. This plot doesn't differentiate IDeg, Asp, IDet, or IGlar specific antibodies.



Reviewer comment

The increased detection of antibodies in the T1DM vs T2DM studies is consistent with assay interference from endogenous insulin in T2DM samples, which was in fact observed in the Sponsor's validation studies;i.e. at 160 pM insulin (normal individual's concentration) the AIA signal is reduced to 80% of no insulin control, while at 320 pM insulin the signal is reduced to 70 % of the control value.

Summary of Cross-reacting antibodies (AIA/ Anti-Insulin Antibodies)

These data provide an overview of the antibody levels, indicating no difference in T1DM studies for IDeg arms versus comparator arms. However, from the standpoint of providing information to physicians, it would be more useful to have incidence rates, with these rates calculated separately for T1DM and T2DM studies. These data were requested in the August 20,2015 Information Request, to which the Sponsor responded on August 26, and are discussed at the beginning of this review. Briefly for T1DM the incidence rates are high at baseline, and show a modest increase during treatment, with baseline and treatment incidences similar between degludec and comparator arms.

Allergic reactions

Two immunogenicity-related events (allergic reactions) were
reported for these subjects: one event of 'urticaria' in each treatment group. Both events were mild, non-serious and considered unlikely to be related to trial product by the investigator. Both subjects recovered and had no increase in anti-insulin specific antibodies.

Reviewer comments

This low incidence of allergic response is consistent with that seen for other insulins (see labels for HUMULIN, LISPRO, LEVIMIR, NOVOLOG)

NDA 203314 –Ryzodeg IDeg/ degludec (long acting)+Insulin aspart (short acting)

From 2.5 Clinical Overview

The following trials were conducted under NDA 203314

3594/3645 T1DM

3590, 3592, 3593, 3597 T2DM

In the therapeutic confirmatory trial programm, insulin antibodies were measured in T1DM (Trial 3594/3645) and in T2DM (Trials 3590 and 3597)
In T1DM, the mean level of cross-reacting insulin antibodies remained low (10-15% B/T) throughout the trial in the IDegAsp group, whereas a small increase was observed in the comparator group. A total of 13% of subjects treated with IDegAsp and 49% of subjects treated with comparator products had an increase in cross-reacting antibodies of 10% B/T or more and/or an increase of 5% B/T or more in insulin-specific antibodies.

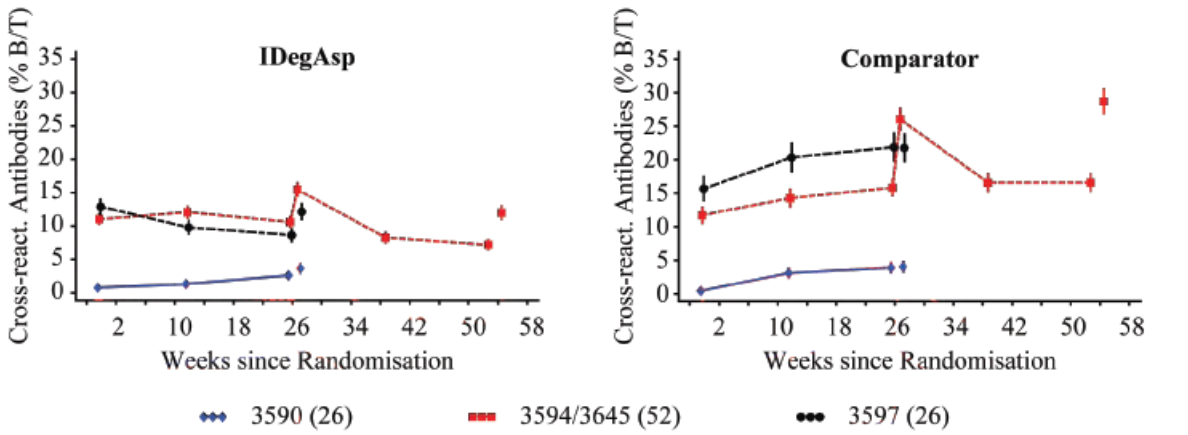
In insulin-naïve subjects with T2DM (Trial 3590), the mean level of cross-reacting insulin antibodies remained below 5% throughout the trial. Only 4% of subjects treated with IDegAsp and 6% of subjects treated with comparators demonstrated an increase in cross-reacting or insulin-specific antibodies.

Reviewer comments

The anti-IDeg incidence rates for the IDeg arms of the T1DM studies appear to show lower incidence rates than the comparator(IDet+IAsp) arms, howeverthe Agency finds that these results are uninterpretable due to the low sensitivity of the anit-IDeg assay. The Sponsor has been asked to agree PMCs for development of a more sensitive assay and to use this new assay to measure anit-IDeg levels in patient sera.

From 2.7.3 Summary of clinical efficacy, pp 169-170

Insulin antibodies were measured in Trials 3583, 3585, 3770, 3579, 3672, 3586, 3668 in order to include a broad population of subjects with T1DM and T2DM in different regions, with different races and with different treatment regimens. Insulin antibodies were measured at baseline and after 12 and 26 weeks of treatment. In addition, insulin antibodies were measured after 52 weeks of treatment in Trial 3583 (T1DM) and Trial 3579 (T2DM). A follow-up visit was scheduled at least 7 days after end of treatment to allow for a washout period and thereby less interference of exogenous insulin with the antibody assay. In the 1-week washout period, the subjects were treated with NPH insulin, which causes less interference with the assay due to a lower plasma concentration during treatment and a shorter half-life. The main analyses of insulin antibody development were therefore based on antibody measurements performed at baseline and at follow up (post-treatment period after the wash-out period). Antibody development against IDeg, IAsp, IDet and IGlar was measured by a validated subtraction radio-immunoassay using radioactively labelled IDeg, IAsp, IDet, IGlar or human insulin. The amount of precipitated radioactivity was measured and expressed as percent bound radioactivity (B) of the total amount of radioactivity (T) applied to the sample. The %B/T value is proportional to the amount of anti-insulin antibody present in the sample.



%B/T = Percent bound over total.
Subjects temporarily discontinued trial product for a 1-week washout with NPH at Weeks 26 and 52.
Comparator: IDet (3594/3645), IGlar OD (3590), BIAsp 30 BID (3597)

Reviewer comments

The T1DM studies (3594/3645) create little concern, since the IDegAsp arm actually shows a slight decrease in antibody levels with time, whereas the levels for comparator are higher and increase with time. The antibody levels for IDegAsp patients in the T2DM studies also appear low relative to the comparator arms, although the true incidence for both treatment and comparator may be higher due to assay interference from endogenous insulin.

Table 5–1 Spearman Correlation Coefficients – Antibodies versus HbA_{1c} and versus Dose

	IDegAsp Group			Comparator Group		
Trial 3594/3645, T1DM	**HbA_{1c} at EOT**	**Change from Baseline in HbA_{1c}**	**Total Daily Dose at EOT**	**HbA_{1c} at EOT**	**Change from Baseline in HbA_{1c}**	**Total Daily Dose at EOT**
IDeg/Comp-specific abs	-0.06	0.00	-0.05	0.05	0.04	0.04
IAsp-specific abs	-0.10	0.00	-0.10	**0.21***	**0.22***	-0.08
Abs cross-reacting to human insulin	0.05	0.08	-0.05	0.07	0.15	0.01
Trial 3590, T2DM						
IDeg/Comp-specific abs	0.01	0.06	0.02	-0.04	-0.01	-0.04
IAsp-specific abs	-0.07	-0.06	-0.02			
Abs cross-reacting to human insulin	0.04	-0.05	**0.19***	-0.03	-0.06	0.11
Trial 3597, T2DM						
IDeg/Comp-specific abs	0.02	-0.02	0.03	See IAsp row below		
IAsp-specific abs	-0.07	0.08	-0.08	**-0.19***	-0.15	0.08
Abs cross-reacting to human insulin	0.00	**0.13***	0.09	-0.02	-0.09	**0.30***

*** Statistically significant different from 0**; abs: antibodies, EOT: End of trial
Comparator: IDet (3594/3645), IGlar OD (3590), BIAsp 30 BID (3597)

Reviewer comments

The treatment group in the T1DM study shows no effect of antibodies on efficacy, whereas there is some statistically significant correlation between antibody levels and HbA1c in the comparator group. This is perhaps expected due to the higher antibody levels in the comparator group. For the T2DM studies there are statistically significant effects for both treatment and comparator, but these are difficult to interpret due to the caveat regarding assay interference from endogenous insulin in T2DM samples.

From Summary 2.7.4, Section 3.3.1 Clinical Safety Summary
Allergic responses
Three patients in the T2DM trials had hypersensitivity reactions. These patients withdrew from the study.

Reviewer comment
This low incidence of allergic response is consistent with that seen for other insulins (see labels for HUMULIN, LISPRO, LEVIMIR, NOVOLOG)

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/s/

FREDERICK C MILLS
09/10/2015

DANIELA I VERTHELYI
09/21/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 18, 2015
To:	Jean-Marc Guettier, MD Director **Division of Metabolism and Endocrinology (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kendra Y. Jones Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	RYZODEG (70% insulin degludec and 30% insulin aspart [rDNA origin] injection) TRESIBA (insulin degludec [rDNA origin] injection)
Dosage Form and Route:	solution for subcutaneous injection
Application Type/Number:	NDA 203313 NDA 203314
Applicant:	Novo Nordisk Inc.

1 INTRODUCTION

On September 29, 2011, Novo Nordisk submitted for the Agency's review an original New Drug Application (NDA) for RYZODEG (70% insulin degludec and 30% insulin aspart [rDNA origin] injection) and TRESIBA (insulin degludec [rDNA origin] injection) solution for subcutaneous use as a treatment for patients with diabetes mellitus (b) (4). On February 8, 2013, the Agency issued a Complete Response Letter to the Applicant citing cardiovascular safety deficiencies for both products. On March 26, 2015, the Applicant resubmitted the application.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on April 8, 2015 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for RYZODEG (70% insulin degludec and 30% insulin aspart [rDNA origin] injection) and TRESIBA (insulin degludec [rDNA origin] injection) solution for subcutaneous use.

2 MATERIAL REVIEWED

- Draft RYZODEG (70% insulin degludec and 30% insulin aspart [rdna origin] injection) and TRESIBA (insulin degludec [rdna origin] injection) PPIs and IFUs received on March 26, 2015, and received by DMPP on September 8, 2015.
- Draft RYZODEG (70% insulin degludec and 30% insulin aspart [rdna origin] injection) and TRESIBA (insulin degludec [rdna origin] injection) PPIs and IFUs received on March 26, 2015, and received by OPDP on September 8, 2015
- Draft Draft RYZODEG (70% insulin degludec and 30% insulin aspart [rdna origin] injection) and TRESIBA (insulin degludec [rdna origin] injection) Prescribing Information (PI) received on March 26, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on September 8, 2015.
- Draft Draft RYZODEG (70% insulin degludec and 30% insulin aspart [rdna origin] injection) and TRESIBA (insulin degludec [rdna origin] injection) Prescribing Information (PI) received on March 26, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on September 8, 2015.
- Approved Novolog (insulin aspart [rDNA origin] injection) comparator labeling dated April 17, 2015.

3 REVIEW METHODS

In 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as

Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the PPIs and IFUs we have:

- simplified wording and clarified concepts where possible
- ensured that the PPIs and IFUs are consistent with the Prescribing Information (PI)
- ensured that the PPIs and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPIs and IFUs meet the Regulations as specified in 21 CFR 208.20
- ensured that the PPIs and IFUs are consistent with the approved comparator labeling where applicable.
- ensured that the PPIs and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPIs and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPIs and IFUs is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPIs and IFUs.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
09/18/2015

MARCIA B WILLIAMS
09/18/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)

****Pre-decisional Agency Information****

Memorandum

Date: September 16, 2015

To: Callie Cappel-Lynch, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Kendra Y. Jones, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 203313
OPDP labeling comments for RYZODEG ® 70/30 (70% insulin degludec and 30% insulin aspart injection), for subcutaneous use

---

OPDP has reviewed the proposed draft labeling for RYZODEG ® 70/30 (70% insulin degludec and 30% insulin aspart injection), for subcutaneous use submitted for consult on April 8, 2015.

OPDP's comments (please see below) on the proposed draft labeling are based on the version sent by Callie Cappel-Lynch (RPM) on September 9, 2015.

Thank you for the opportunity to comment on the proposed draft labeling.

If you have any questions, please contact Kendra Jones at 301.796.3917 or Kendra.jones@fda.hhs.gov.

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/s/

ANKUR S KALOLA on behalf of KENDRA Y JONES
09/16/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)

****Pre-decisional Agency Information****

Memorandum

Date: September 16, 2015

To: Callie Cappel-Lynch, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Kendra Y. Jones, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 203114
OPDP labeling comments for TRESIBA ® (insulin degludec injection), for subcutaneous use

---

OPDP has reviewed the proposed draft labeling for TRESIBA ® (insulin degludec injection), for subcutaneous use submitted for consult on April 8, 2015.

OPDP's comments (please see below) on the proposed draft labeling are based on the version sent by Callie Cappel-Lynch (RPM) on September 9, 2015.

Thank you for the opportunity to comment on the proposed draft labeling.

If you have any questions, please contact Kendra Jones at 301.796.3917 or Kendra.jones@fda.hhs.gov.

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

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/s/

ANKUR S KALOLA on behalf of KENDRA Y JONES
09/16/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, and Ophthalmic Device Branch

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DATE: September 3, 2015

TO: Muthu Ramaswamy, Ph.D., ONDP, OPQ, CDER
Juandria Williams, OPF, OPQ, CDER

Through: Dr. Nina Nwaba, PharmD., MPH, MSC., Acting Chief, REGO, DMQ, OC, CDRH, REGO WO-66, Room 3544

Nina C. Mezu-nwaba -S

Digitally signed by Nina C. Mezu-nwaba -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300161791, cn=Nina C. Mezu-nwaba -S
Date: 2015.09.03 12:10:34 -04'00'

From: Crystal Lewis, REGO DMQ, OC, CDRH, OMPT. WO-66, Room 2628

Applicant: Novo Nordisk Incorporated
1100 Campus Rd
Princeton, NJ 08540-6650
FEI# 2244771

Application # NDA 203313 and NDA 203314

Consult # ICC1500307, ICC1500428 follow-up to ICC# 1500306

Product Name: Insulin Degludec / Insulin Aspart injection, 100units/ml PDS290 Pen Injector - NDA203313

Insulin Degludec injection, 100 and 200units/ml – NDA203314

Consult Instructions: CDRH and the Office of Compliance received consults to assess the suitability of the new combination products Insulin/Degludec/Insulin Aspart injection and Insulin Degludec injection and the need for an inspection of the involved sites.

Inspection Needed: No

Documentation Review: No Additional Information Required

Final Recommendation: Approval

The Office of Compliance at CDRH received consult requests from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of Insulin Degludec/Insulin Aspart PDS290 Pen Injector, NDA203313 and Insulin Degludec PDS290 Pen Injector, NDA203314.

PRODUCT DESCRIPTION

NDA 203313: The Insulin Degludec is a new generation of long acting basal insulin to be available as a pre-filled pen in two strengths (100U/ml; and 200U/ml) under the trade name Tresiba.

NDA 203314: The proposed product (Ryzodeg injection 100U/ml) is a 70/30 mixture of long acting insulin (insulin degludec) and immediate acting insulin (insulin aspart) provided as a prefilled pen.

Both Ryzodeg injection and Tresiba injection are intended for subcutaneous administration and utilize a common pen injector known as (PDS290 pen injector) for drug administration.

The PDS290 pen-injector for Insulin Degludec/Insulin Aspart 100 U/ml, see Figure 1, and PDS290 pen-injector for Insulin Degludec 100 U/ml and 200U/ml (Figure 2) are prefilled multi-dose disposable delivery device. The devices contain the drug solution, , in a (b) (4). The device is intended to function with (b) (4) needle (b) (4)

PDS290 pen-injector is based on (b) (4). (b) (4) Aside from this feature, the PDS290 prefilled pen is used in the same way as FlexPen®.

The pen consists of (b) (4).
The plastic components in the device are made from the following materials:
(b) (4)

(b) (4)

Both Insulin Degludec and Insulin Aspart are indicated to improve glycemic control on adult patients with diabetes mellitus. Patients with diabetes mellitus are treated by individualizing the insulin doses. The standard product strength in the PDS290 pen is U100 and provides up to 80U per injection which accommodates 70% of patients' once-daily dose requirements in a single injection. The Insulin Degludec 200U/ml pen-injector provides a maximum of 160U per injection and addresses about 30% of individuals whose insulin resistance cannot be addressed through a single daily injection with the standard U100 product. Therefore, these patients increased dose requirements are addressed by the pen-injector providing up to 160U per injection.

Figure 1. Ryzodeg U-100

Figure 2 Tresiba pen injector U-200 U-100

REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820 for both NDA 203313 and NDA203314:

1. Novo Nordisk
   1100 Campus Rd
   Princeton, NJ 08540-6650
   FEI: 2244771

An analysis of the firm's inspection history was performed over the past two years. An inspection conducted from 6/3/2014 to 6/19/2014 was classified as No Action Indicated (NAI). This inspection was specific to the firm's drug product activity.

Update (Date: 08/26/15):
An inspection is not required for this firm because this facility is not responsible for the design, manufacture and assembly of the final combination product. This facility performs drug manufacturing including the Insulin drug product for the combination product. This site was last inspected June 3, 2014 to June 19, 2014 and was classified NAI.

2. Novo Nordisk Pharmaceutical Industries Incorporated
   3612 Powhatan Rd
   Clayton, NC 27527-9217
   FEI: 1000158576

An analysis of the firm's inspection history over the past 2 years revealed that a drug inspection was performed and classified as NAI. The inspection was conducted from August 18, 2014, to August 21, 2014. A request was sent for the firm to identify specific activities performed at this manufacturing site for the combination product.

Update (Date: 08/26/15):
An inspection is not required for this firm because this facility is not responsible for the design, manufacture and assembly of the final combination product. This is a sterile drug manufacturing facility and includes the manufacture of Insulin for the combination product. The last inspection was performed August 18 to August 21, 2014 and was classified NAI.

3. Novo Nordisk A/S
   Brennum Park
   DK-3400 Hillerod
   Denmark
   FEI: 3002807752

An analysis of the firm's inspection history was performed over the past two years. Novo Nordisk has indicated they have the ultimate responsibility for the final combination product. This facility where the final assembly of the final combination product occurs was last inspected 6/15/2015 to 6/18/2015 and was classified NAI. A level II inspection was also performed at this facility from 10/6/2014 to 10/10/2014 and was classified NAI.

Therefore, a device inspection is not required for this firm.

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

Novo Nordisk did not identify the name of the firm who is ultimately responsible for the overall combination product.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.20.

Update Date: 08/26/15):

The firm's response dated 08/17/15 is adequate. Novo Nordisk specified they have the ultimate responsibility for the overall combination product. In Appendix A, the firm provided a group of documents which covered management controls. They included:

- Novo Nordisk Way (017854)
- Novo Nordisk Policies (128363)
- Novo Nordisk Quality Manual (166087)
- Product Supply Quality Manual (019436)
- R & D Quality Manual (053775)
- Document Control of QBIQ Documents (100084)

These procedures document policies that ensure compliance with the quality system requirements for Management Controls. These documents control the firm's overall Management Controls including: quality policy, quality system procedures, quality planning, management review and training of personnel.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30
The firm details the design and development plan of the PDS290 pen injector delivery device in the validation of device use for the container closure system of the Risk Management Conclusions final report. The formative evaluations and design modifications section captures the design control plan. Also, the validation testing section of the Risk Management Conclusions final report details development and design control activities. Multiple studies were conducted by the firm to verify the design of both the Insulin/Degludec/Insulin Aspart PDS290 Pen Injector and the Insulin Degludec PDS290 Pen Injector devices.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50
The firm's procedures or descriptions for purchasing controls are not provided in the submission. The firm does however identify the following firms as component manufacturers: (b) (4)

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.50.

Update (Date: 08/26/15):
The firm's response dated 08/17/15 is adequate. The firm's procedures or descriptions for purchasing controls were provided in the submission. The firm identified the following procedures that are in place for purchasing controls. The firm included Selection and Approval of Direct Spend Suppliers (103259); Re-evaluation of Suppliers – Direct Spend (103203); and Sourcing – Direct Spend (019443) and they are located in the firm's supplement labeled Appendix A. Also, the firm identified the following firms as component manufacturers: (b) (4)

These documents demonstrate the firm's Purchasing Controls through the maintenance of records of acceptable suppliers. Also, the firm's procedures for supplier evaluation criteria are documented to demonstrate control over its suppliers to comply with the quality system regulations for Purchasing Controls.
The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100
The firm has not provided a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System.

Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.100.

Update (Date: 08/26/15):
The firm's response dated 08/17/15 is adequate. The firm provided a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System and they are identified as CAPA system (150266) and Corrective Actions and Preventive Actions (019470). These procedures can be found in Appendix A.

These CAPA procedures demonstrate the firm's control over policies for identifying and addressing problems in order to prevent their occurrence or reoccurrence to ensure compliance with quality system regulations. The documents include procedures to investigate the cause of nonconformities; to validate corrective or preventive actions and to implement and record changes in procedures.

Therefore, the information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170
Installation is not required for this combination product.

Servicing, 21 CFR 820.200
Servicing is not required for this combination product.

MANUFACTURING
Production and Process Controls
The firm provided a summary of its process controls in section 3.2.P.3.3 Description of Manufacturing Process and Process Controls. Description of the manufacturing process for the finished combination product includes controls for the pre-treatment of primary packaging material, (b) (4) caps, (b) (4), filling as well as a description of the packaging operation.

Production Flow
The firm also provided a production flow diagram identifying the steps involved in the manufacture of the finished Insulin/Degludec/insulin combination product. See Figure 1 below.

Figure 1 Manufacturing of insulin degludec/insulin aspart 100 U/ml

Acceptance Activities

The firm does not provide information describing how it will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities.

Update (Date: 08/26/15):
The firm's response dated 08/17/15 is inadequate. The firm states the use of drug CGMPs to provide evidence of compliance with acceptance activities for the finished combination product. Specifically 21CFR 211 Subpart E – Control of Components and Drug Product Containers and Closures and Subpart F – Production and Process Controls were applied by the firm to ensure compliance of the finished combination product.

However, the firm did not provide any descriptions of the incoming, in-process, and releasing acceptance tests/activities to assure that the final combination products are manufactured within specifications. This is not considered an approvability issue; however, it is recommended that an additional request for information be submitted to the firm and a response submitted as an Annual Report. The following should be sent to the firm:

Your firm did not provide any information on its procedure(s) for acceptance activities. Please provide a description of the incoming, in-process, and releasing acceptance tests/activities your firm performs to ensure the final combination products are manufactured within specifications. You may submit your response through an Annual Report.

Documentation Review Recommendation

The document review of the Insulin/Degludec/Insulin Aspart injection and Insulin Degludec injection combination products noted the following deficiency in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product.

1. Your firm did not provide any information on its procedures for acceptance activities. Please provide a description of the incoming, in-process, and releasing acceptance tests/activities your firm performs to assure that the final combination products are manufactured within specifications. This information can be submitted through an annual report.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of application NDA203313 and NDA203314 and has the following recommendations:

The applications for NDA203313 and NDA203314 are approvable from the perspective of the applicable Quality System Requirements.

Crystal Lewis -S

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Date: 2015.09.03 11:39:56 -04'00'

Crystal Lewis

Prepared: CLewis: 07/17/2015
Reviewed: VVerna: 7/22/2015; 8/4/2015; 8/12/15; 8/27/15; 8/28/2015\
Reviewed: NMezu-Nwaba: 9/2/2015

CTS No.: ICC1500306 - ICC1500428
NDA203313

Review Cycle Meeting Attendance:
Month/Day/Year
Month/Day/Year
Month/Day/Year

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

/s/

CALLIE C CAPPEL-LYNCH
09/03/2015
signing for Crystal Lewis

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: August 30, 2015

From: Lana Shiu, M.D.
General Hospital Devices Branch, DAGRID, ODE, CDRH

To: Callie Cappel-Lynch
Division of Metabolism and Endocrine Products, Office of New Drugs, CDER

Via: Keith Marin and Ryan McGowan
Combination Products Team Leaders, GHDB, DAGRID, CDRH

Rick Chapman
Branch Chief, General Hospital Devices Branch, DAGRID, ODE, CDRH

Subject: NDA 203313 Ryzodeg and NDA 203314 Tresiba /Applicant: NovoNordisk
CDRH Tracking: ICC1500179

Indication: Injection for treatment of diabetes.
Background: Inter-center consult received from DMEP RPM stating the following:

Novo Nordisk has submitted a class 2 resubmission for Ryzodeg and Tresiba (NDA 203313 and 203314). The resubmission was received on 3/26/15 and material is available via the links below. The original submission was received on September 29, 2011 . A CR letter was issued after the first review cycle on 2/8/13. We request that you review the device portion of the resubmission as well as reviewing the device information contained in the original submission to ensure there are no outstanding device issues.

EDR Location: \\CDSESUB1\evsprod\NDA203313\0045 (CVOT data)

EDR Location: \\CDSESUB1\evsprod\NDA203313\0043 (safety update)

EDR Location: \\CDSESUB1\evsprod\NDA203314\0047 (safety update)

EDR Location: \\CDSESUB1\EVSPROD\NDA203314\203314.enx (CVOT data)

EDR Location: \\CDSESUB1\evsprod\NDA203313\203313.enx
EDR Location: \\CDSESUB1\evsprod\NDA203314\203314.enx

The submission describes the drug will be injected using FlexTouch (PDS290) is an improved version of NovoNordisk's previous FlexPen.

- The new FlexTouch pen has [redacted] (b) (4)
- [redacted] (b) (4)

Approved and marketed US products using the PDS290 platform injector

Product	Presentation	Application	Approval date
Norditropin® FlexPro®	5mg/1.5mL 10mg/1.5mL 15 mg/1.5mL	NDA 21-148 (S-27)	May 1, 2010
Levemir® FlexTouch®	100 U/mL in 3 mL	NDA 20-986 (S-33)	October 31, 2013
NovoLog® FlexTouch®	100 U/mL in 3mL	NDA 20-986 (S-61)	October 31, 2013
Saxenda®	6 mg/mL in 3 mL	NDA 206321 (original)	December 23, 2014
Norditropin® FlexPro®	30 mg/3 mL	NDA 21-148 (S-42)	January 23, 2015

[redacted] (b) (4) To accommodate new drugs/biologicals, the following components are modified:

[redacted] (b) (4)

Device Description:

PDS290 is a pen-shaped, prefilled device containing a non-replaceable, fixed, 3 ml cartridge with insulin.

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NDA 203313 - Performance Testing using degludec/insulin aspart 100U/ml:

Density of insulin degludec/insulin aspart 100 U/ml

Temperature	Density [1]
5°C	(b) (4)
20°C	
40°C	

According to ISO 11608-1, all dosage values in mg should be converted to volumes using the density. To keep the raw-data intact the acceptance criteria have been converted to mg using the density.

Acceptance Criteria in mg

Dose (U)	Nominal value µl	Tolerance µl	Acceptance criteria converted to mg using the density					
			5 °C		20 °C		40 °C	
			Lower	Upper	Lower	Upper	Lower	Upper
1 U			(b) (4)					
40 U								
80 U								

Test results according to ISO 11608-1:

Requirement	ISO 11608-1 subject	Results	Comments
The device must be designed according to instructions in 5. General requirements	5. General Requirements	All general requirements in section 5 have been visually verified and accepted.	5.b, 5.c and 5.i were tested in "Total/last content of device"
When the pen-injector is ready for injection, the cartridge holder shall allow visibility of the deliverable volume. It shall be possible to determine whether sufficient medicinal product remains in order to administer the maximum pre-settable dose.	5. General Requirements (a)	This is visually inspected during the tests in 290.QA.034R and found true.	No comments
The pen-injector shall be designed such that it is able to deliver the labeled volume from the cartridge for which it is designed.	5. General Requirements (b)	The total content (Total dose) fulfills the specifications. Table 5	No comments
The pen-injector shall be designed such that the last dose delivered from a cartridge satisfies requirements for dose accuracy.	5. General Requirements (c)	The last dose ("end of content (EOC)") fulfills the requirements for dose accuracy. Table 5	No comments
The pen-injector shall indicate the pre-set dose.	5. General Requirements (d)	This is visually inspected during the tests in 290.QA.034R and found true.	No comments
The pen-injector shall indicate, at least by visual means, that it is ready for injection. There shall be an indication of the pre-setting procedure by tactile or audible means, or both.	5. General Requirements (e)	This is visually inspected during the tests in 290.QA.034R and found true.	No comments

Requirement	ISO 11608-1 subject	Results	Comments
The state of the pen-injector, when ready to deliver a dose, shall be different to its state when the dose has been delivered. The difference shall be visible.	5. General Requirements (f)	This is visually inspected during the tests in 290.QA.034R and found true.	No comments
The pen-injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed.	5. General Requirements (g)	This is visually inspected during the tests in 290.QA.034R and found true.	No comments
If the pen-injector is designed for variable doses, it shall be so designed that it is impossible to deliver a second dose after delivery of the first dose without a second pre-setting.	5. General Requirements (h)	This is visually inspected during the tests in 290.QA.034R and found true.	No comments
The pen-injector shall be so designed that it: 1) does not allow a larger dose to be pre-set than is left in the cartridge; or 2) does not allow dose delivery if the pre-set amount exceeds the amount of medicinal product left in the cartridge; or 3) indicates the amount of medicinal product delivered; or 4) indicates the amount of medicinal product not delivered of the pre-set dose.	5. General Requirements (i)	The last dose ("end of content (EOC)") fulfills the requirements for dose accuracy. Table 5	1) The PDS290 pen-injector does not allow a larger dose to be pre-set than is left in the cartridge. 4) The PDS290 pen-injector indicates the amount of medicinal product not delivered of the pre-set dose, in the dose scale window.
The pen-injector shall be designed to function with a needle fulfilling the specifications of ISO 11608-2.	5. General Requirements (j)	This is visually inspected during the tests in 290.QA.034R and found true.	All tests have been performed with NovoTwist® or NovoFine® needle fulfilling specifications of ISO 11608-2: 2000.

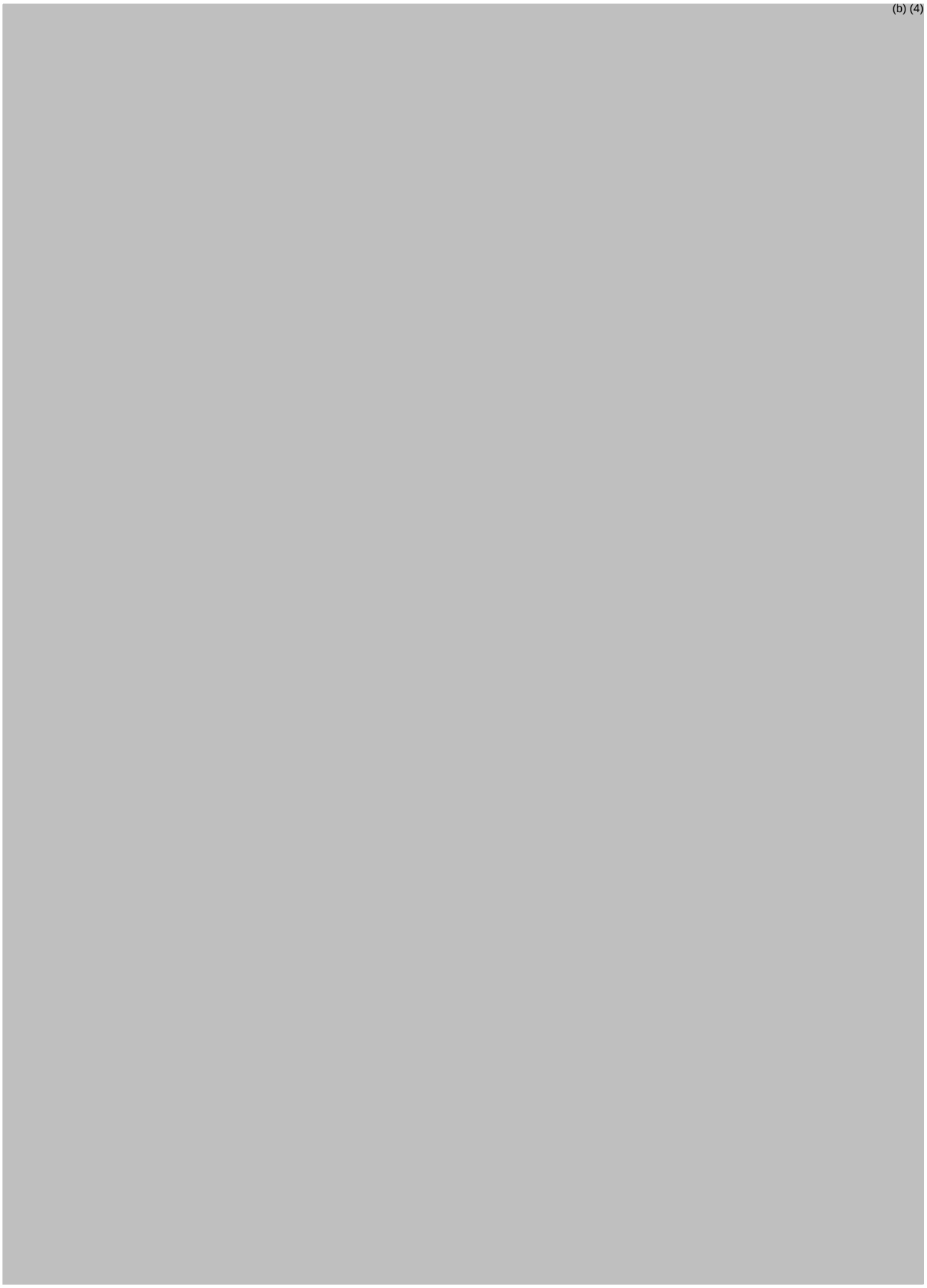
Requirement	ISO 11608-1 subject	Results	Comments
(b) (4)			
Dose accuracy when subjected to standard atmosphere Temperature: from 18 °C to 28 °C Relative humidity: from 25 % RH to 75 % RH after having been subjected to storage for at least 4 h in this atmosphere.	9.2.2 /9.1/ 6.1	Fulfills the requirements for dose accuracy at standard atmosphere. Protocol 290.QA.034P: Table 6	No comments
Dose accuracy when subjected to cool atmosphere. The assembled pen-injector with the cartridge and needle is placed in a test chamber for at least 4 h in the following cool atmosphere: Temperature: (5 ± 3) °C.	9.2.2/9.1 / 6.2	Fulfills the requirements for dose accuracy at cool atmosphere. Protocol 290.QA.034P: Table 6	No comments
Dose accuracy when subjected to hot atmosphere. The assembled pen-injector with the cartridge and needle is placed in a test chamber for at least 4 h in the following hot atmosphere: Temperature: (40 ± 2) °C Relative humidity: (50 ± 10) % RH.	9.2.2/9.1 / 6.3	Fulfills the requirements for dose accuracy at hot atmosphere. Protocol 290.QA.034P: Table 6	No comments
(b) (4)			

Requirement	ISO 11608-1 subject	Results	Comments
Dose accuracy after being subjected to dry heat storage preconditioning. The pen-injector without the cartridge and needle is placed in a test chamber for at least 96 h in the following hot atmosphere: Temperature: (70 ± 2) °C Relative humidity: (50 ± 10) % RH. None of the pen-injectors shall have visible defects after removal from the hot storage atmosphere when inspected in accordance with clause 12. Return the pen-injectors to the standard conditions and determine the dose accuracy of the pen-injectors. Pen-injectors with a lower acceptable storage temperature, e.g. pen-injectors with non-replaceable cartridges, shall be subjected to preconditioning at the acceptable temperature, and this acceptable temperature shall be stated in the instructions for use.	9.2.4 / 7.1 / 12 / 9.1	No PDS290 pen-injectors have been damaged during storage. Fulfills the requirements for dose accuracy. Protocol 290.QA.034P; Table 6	PDS290 pen-injector has been stored for 96 h at: temperature: (40 ± 2) °C relative humidity: (50 ± 10) % RH followed by dose accuracy test at standard conditions.
Dose accuracy after being subjected to cold storage preconditioning. The pen-injector without the cartridge and needle is placed in a test chamber for at least 96 h in the following cold atmosphere: Temperature: (-40 ± 3) °C. None of the pen-injectors shall have visible defects after removal from the cold storage atmosphere when inspected in accordance with clause 12. Return the pen-injectors to the standard conditions and determine the dose accuracy of the pen-injectors in accordance with 9.1. Pen-injectors with a higher acceptable storage temperature, e.g. pen-injectors with non-replaceable cartridges, shall be subjected to preconditioning at the acceptable temperature, and this acceptable temperature shall be stated in the instructions for use.	9.2.5 / 7.2 / 12 / 9.1	No PDS290 pen-injectors have been damaged during storage. Fulfills the requirements for dose accuracy. Protocol 290.QA.034P; Table 6	PDS290 pen-injector has been stored for 96 h at: temperature: (5 ± 3) °C followed by dose accuracy test at standard conditions.

Requirement	ISO 11608-1 subject	Results	Comments
[redacted] (b) (4)			
Freedom from defects after being subjected to free fall. None of the pen-injectors shall have visible defects after the free fall when inspected in accordance with clause 12.None of the pen-injectors shall have functional defects after the free fall when inspected in accordance with clause 13.	10.3 / 7.4 / 9.1 / 12 / 13	No errors were observed during the freefall test. Fulfills the requirements for dose accuracy. Table 7, Table 8	No comments

Acceptance criteria:	Method used:
EOC: Must comply with Dose accuracy in ISO 11608-1:2000 [1] / JIS T 3226-1:2005 [2] (Must be between LSL and USL) Total content: [redacted] (b) (4)	• Perform an air-shot on the balance (b) (4) according to the method description • Dose [redacted] (b) (4) out of PDS290 pen-injector to prepare it for EOC dose. • Preset the remaining amount in PDS290 pen-injector and note dose size. • Dose out on balance • Calculate Total content in U: [redacted] (b) (4)

LSL = L = Lower Specification Limit
USL = U =Upper specification Limit
EOC = End of Content


(b) (4)

NDA 203314 - Performance Testing using degludec 100U/ml

Density of insulin degludec 100 U/ml

Temperature	Density [1]
5°C	(b) (4)
20°C	
40°C	

According to ISO 11608-1, all dosage values in mg should be converted to volumes using the density. To keep the raw-data intact the acceptance criteria have been converted to mg using the density.

Acceptance Criteria in mg

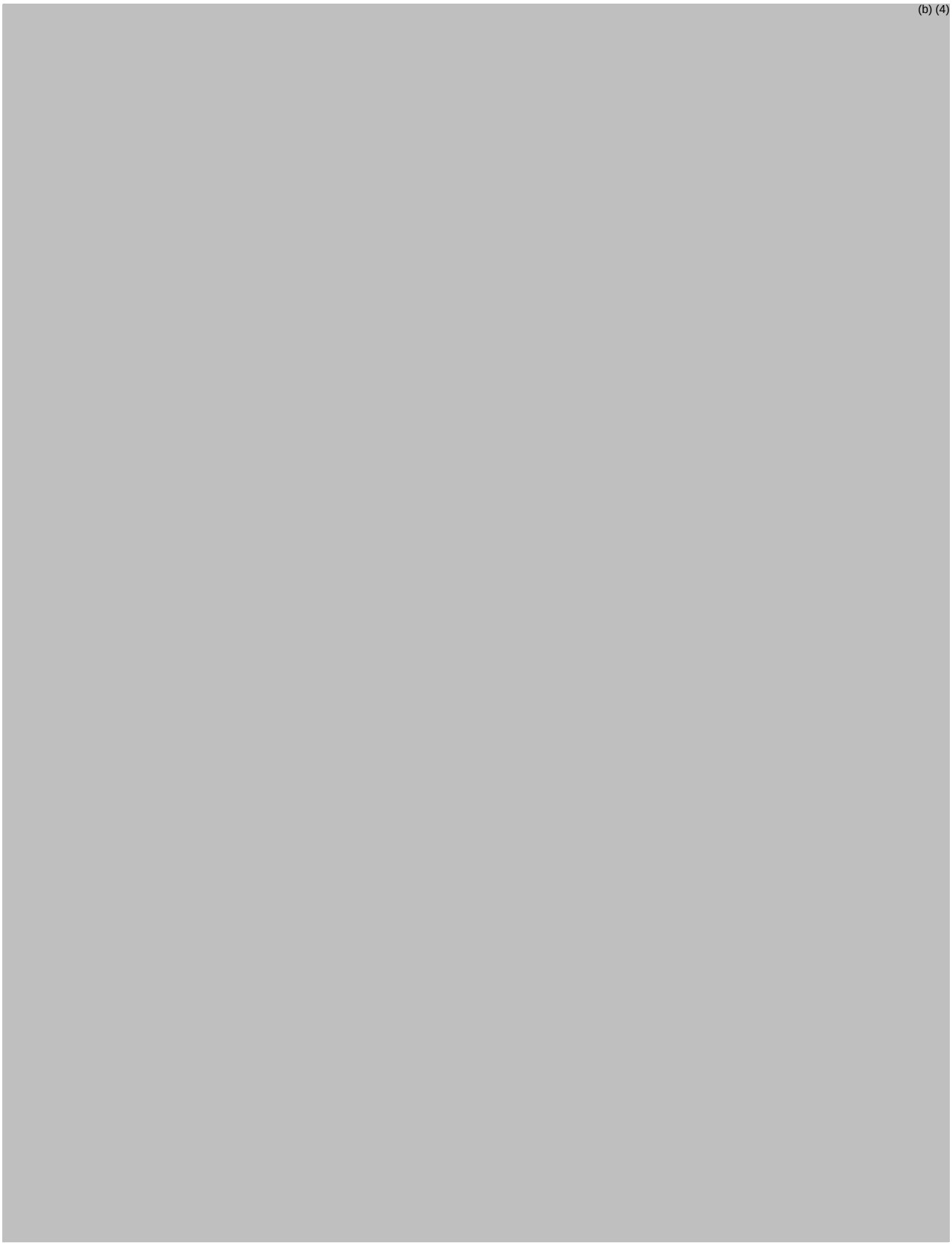
Dose (U)	Nominal value µl	Tolerance µl	Acceptance criteria converted to mg using the density					
			5 °C		20 °C		40 °C	
			Lower	Upper	Lower	Upper	Lower	Upper
1 U	(b) (4)							
40 U								
80 U								

Acceptance criteria:	Method used:
EOC: Must comply with Dose accuracy in ISO 11608-1:2000 [1] / JIS T 3226-1:2005 [2] (Must be between LSL and USL) Total content: (b) (4)	• Perform an air-shot on the balance (b) (4) according to the method description • Dose (b) out of PDS290 pen-injector to prepare it for EOC dose. • Preset the remaining amount in PDS290 pen-injector and note dose size. • Dose out on balance • Calculate Total content in U (b) (4)

LSL = L = Lower Specification Limit
USL = U =Upper specification Limit
EOC = End of Content

Table 5 Total content of device / last dose accuracy (290.QA.032P)

	Total content of device / last dose accuracy																		
	Pen 1	Pen 2	Pen 3	Pen 4	Pen 5	Pen 6	Pen 7	Pen 8	Pen 9	Pen 10	Pen 11	Pen 12	Pen 13	Pen 14	Pen 15	Pen 16	Pen 17	Pen 18	Pen 19	Pen 20
Pre-set EOC [U]	(b) (4)																		
EOC [mg]																			
LSL EOC [mg]																			
USL EOC [mg]																			
Total content [U]																			


(b) (4)

NDA 203314 - Performance Testing using degludec 200U/ml

Density of insulin degludec 200 U/ml

Temperature	Density [1]
5°C	(b) (4)
20°C	
40°C	

According to ISO 11608-1, all dosage values in mg should be converted to volumes using the density. To keep the raw-data intact the acceptance criteria have been converted to mg using the density.

Acceptance Criteria in mg

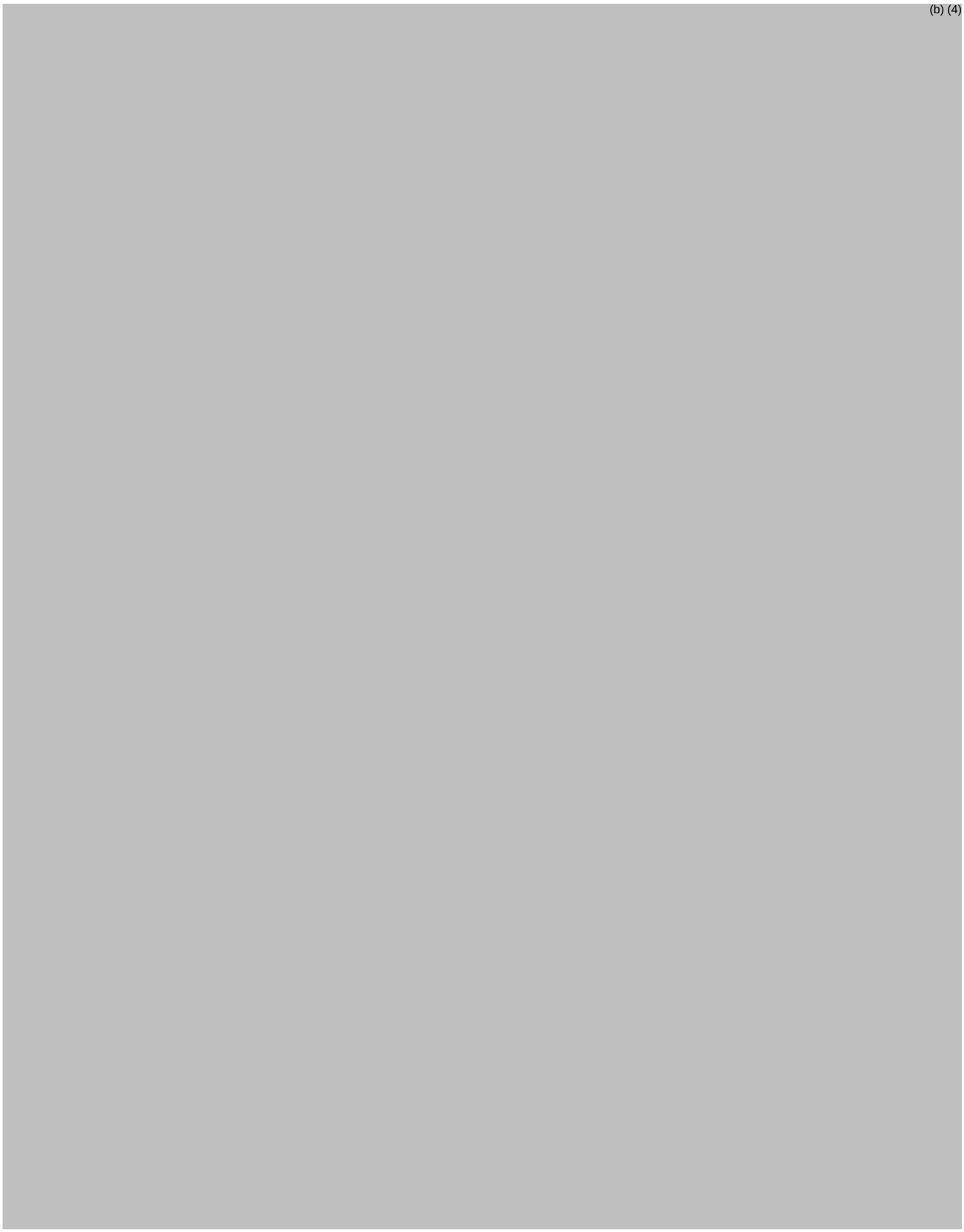
Dose (U)	Nominal value µl	Tolerance µl	Acceptance criteria converted to mg using the density					
			5 °C		20 °C		40 °C	
			Lower	Upper	Lower	Upper	Lower	Upper
2 U			(b) (4)					
80 U								
160 U								

Table 5 Total content of device / last dose accuracy (290.QA.033P)

	Total content of device / last dose accuracy																			
	Pen 1	Pen 2	Pen 3	Pen 4	Pen 5	Pen 6	Pen 7	Pen 8	Pen 9	Pen 10	Pen 11	Pen 12	Pen 13	Pen 14	Pen 15	Pen 16	Pen 17	Pen 18	Pen 19	Pen 20
Pre-set EOC [clicks]	(b) (4)																			
EOC [mg]																				
LSL EOC [mg]																				
USL EOC [mg]																				
Total content [U]																				

Acceptance criteria:	Method used:
EOC: Must comply with Dose accuracy in ISO 11608-1:2000 [1] / JIS T 3226-1:2005 [2] (Must be between LSL and USL)	• Perform an air-shot on the balance (b) (4) according to the method description • Dose (b) (4) out of PDS290 pen-injector to prepare it for EOC dose. • Preset the remaining amount in PDS290 pen-injector and note dose size. • Dose out on balance • Calculate Total content in U: (b) (4)
Total content: Minimum (b) (4) (b) (4)	

LSL = L = Lower Specification Limit
USL = U =Upper specification Limit
EOC = End of Content


(b) (4)

NovoNordisk responded to CDRH/ODE deficiencies on 6/10/2015:

You provided a comparison table in your NDA comparing FlexPen and FlexTouch, however, you have not specified what are the internal mechanical differences. We are looking for specifications in your submission for spring force/trigger force/injection force.

Novo Nordisk Response

The FlexPen® function on the principle of dialing up a dose with a corresponding extension of the dose button as the dose increases and subsequent manual depression of the dose button to deliver the dose (see Figure below).

FlexTouch® (PDS290) has no dose button extension at any dose (see Figure below). The injection is driven (b) (4)

(b) (4)

What is the shelf life of your injector device and where is that information located in the submission?

Novo Nordisk Response

The shelf life of the Tresiba® 100 U/mL, Tresiba® 200 U/mL, (b) (4) peninjectors is 30 months. The shelf life of the pen-injector is supported by testing dose accuracy for the complete drug/device combination product (i.e., 3 mL cartridge assembled in the PDS290 pen injector), as part of the stability studies on the finished products. Dose accuracy data are included in 3.2.P.8.3 Stability Data in the respective primary stability data reports for the products.

What is the Life Cycle of your injector meaning just before expiry of your device and it is distributed from the shelf to the user then how many injection can your device perform? Is the testing performed to 2x or 3x? Where is this testing information located in your submission? Although the injector device uses a non-replaceable cartridge, it is not a one-time use and discard injector in that patients can dial numerous doses on the injector before emptying out the cartridge. Thus the Agency is seeking data (not exactly the Life Cycle per ISO 11608-1) regarding the maximum of number of actuations/drug delivery doses can this injector device perform per the life time of the fixed cartridge.

Novo Nordisk Response

The PDS290 pen-injector is prefilled with a non-replaceable cartridge, and thus, the pen-injector cannot deliver more than the content of the cartridge (i.e., 3 mL or 300 increments) in contrast to a durable pen-injector. The number of movements of the internal components is restricted by the total content of the cartridge, not the individual actuations. Per the life time of the fixed cartridge, the pen-injector has been verified to be able to deliver the entire labelled volume (300 increments). See 3.2.P.7, Summary Report of Qualification Testing, Appendix A, Table 5.
Since the design mechanism only shall deliver 300 increments, it will not be exposed to any systematic wear, and the pen-injector is tested to ensure that it will be able to deliver the required dose throughout the expected life time.

Verification of the pen-injector includes dose accuracy testing of the pen-injector measured at different dose sizes throughout the entire volume of the cartridge. By doing this, it is ensured that the internal dosing mechanism is exerted to the highest possible stress level combined with the prefilled pen-injectors ability not to deliver more than the content of the cartridge.

Appendix A Test Results from protocol 290.QA.034P

Table 5 Total content of device / last dose accuracy (290.QA.034P)

Total content of device / last dose accuracy																			
	Pen 1	Pen 2	Pen 3	Pen 4	Pen 5	Pen 6	Pen 7	Pen 8	Pen 9	Pen 10	Pen 11	Pen 12	Pen 13	Pen 14	Pen 15	Pen 16	Pen 17	Pen 18	Pen 19	Pen 20
Pre-set EOC [U]	(b) (4)																			
EOC [mg]																				
LSL EOC [mg]																				
USL EOC [mg]																				
Total content [U]																				

Acceptance criteria:		**Method used:**
EOC:	Must comply with Dose accuracy in ISO 11608-1:2000 [1] / JIS T 3226-1:2005 [2] (Must be between LSL and USL)	• Perform an air-shot on the balance (b) (4) according to the method description • Dose (b) (4) out of PDS290 pen-injector to prepare it for EOC dose. • Preset the remaining amount in PDS290 pen-injector and note dose size. • Dose out on balance • Calculate Total content in U: (b) (4)
Total content:	(b) (4)	

LSL = L = Lower Specification Limit
USL = U =Upper specification Limit
EOC = End of Content

Did you track device performance during the clinical trials in terms of device-related medication errors, device malfunctions or failures or adverse events related to the device use? If yes, please provide the detailed data and root cause analysis as well as the location of this information in the 2 submissions.

Novo Nordisk Response
Novo Nordisk did track device performance during the clinical trials in terms of device-related medication errors, device malfunctions or failures or adverse events related to the device use.

During the IDeg and IDegAsp development programmes, the PDS290 pen-injector was used in fourteen phase 3 trials with IDeg and in six phase 3 trials with IDegAsp including extension trials. These trials encompassed exposure/use of the pen-injector in more than 5000 subjects exposed to trial products up to 30 months. A search was done of all completed trials with IDeg and IDegAsp, in which subjects administered trial product with the FlexTouch® pen injector as of 12 June 2015. This identified two device-related adverse events in subjects treated with IDeg with use of the FlexTouch® pen injector.

The two device-related events originated from Trial NN1250-3643 (extension to Trial 3579) and Trial NN1250 3718. Both events were reported as 'injection site bruising' and were non-serious and mild in severity. The events occurred after 409 and 23 days of treatment, respectively and both were judged by the investigator as having a probable related to trial product. The subjects recovered completely.

Technical complaints associated with adverse events were reported for three subjects treated with IDeg using the FlexTouch® pen. This included the two events of 'injection site bruising' mentioned above, as well as one complaint in Trial NN1250-3846 related to defective needles causing an adverse event of 'injection site haematoma'. The FlexTouch® injection device was not sent to the Customer Compliance Center at Novo Nordisk A/S for further investigation for these 3 events, only the needles from the latter case.

We are also looking for the biocompatibility (ISO 10993) testing and data for this surface contacting injector device.

Novo Nordisk Response
A biological evaluation of the PDS290 pen-injector has been performed in accordance with EN ISO 10993-1:2009 *"Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process"* considering all parts of the pen-injector which come in direct contact with the users. According to the standard, identification of biological (toxicological) hazards, and, if any, an evaluation of the associated risks, are required for devices which come in direct or indirect contact with the users. The PDS290 pen-injector is a surface contacting injector device Category B Prolonged duration of contact (> 24 h to 30 days). This categorization is based on the accumulated life time exposure.

The Tresiba®/Ryzodeg® FlexTouch® pen-injectors are intended for subcutaneous injection of insulin. Based on the intended use of the Tresiba®/Ryzodeg® FlexTouch® pen-injectors, brief, repeated contact to intact skin will occur during handling of the pen-injector. According to EN ISO

10993-1:2009, for non-invasive devices, which will only be in user contact with intact skin, an evaluation of testing for the following biological hazards, shall be considered:

☐ Cytotoxicity
☐ Sensitisation
☐ Irritation or intracutaneous reactivity

All PDS290 pen-injector components which come into direct or indirect contact with users consist of (b) (4)

The PDS290 pen-injector components that are identical to the currently marketed FlexPen® or FlexTouch® are evaluated as toxicologically qualified as the materials are equivalent (*according to ISO 10993-18:2009 Annex C*) and have a demonstrable safe history of use for the same intended use, physical form, formulation, processing, component interactions, and storage conditions. (b) (4)) meets the requirements for Class VI Medical Grade Plastic Materials (b) (4) In addition, the material is in compliance with the test requirements of (b) (4) covering irritation and delayed-type hypersensitivity. Finally, (b) (4) has passed an *in vitro* cytotoxicity test in cultured mammalian cells (L929 mouse fibroblasts). Based on the concordance between *in vivo* irritation and *in vitro* cytotoxicity and the weight of evidence for irritation as a prerequisite in the sensitisation pathway, a negative *in vitro* cytotoxicity test is considered sufficient to rule out any relevant hazard for skin irritation and sensitization caused by dermal exposure to leaching substances.

(b) (4) . Furthermore, the material has passed an *in vitro* cytotoxicity test in cultured mammalian cells (L929 mouse fibroblasts). Based on this, it is concluded that this material does not contain any substances with a potential to cause skin irritation and/or sensitization at relevant exposure levels.

(b) (4) all listed constituents were evaluated for their potential to cause irritation and sensitization. The evaluations of the constituents were based on toxicological data in the scientific literature published on four publicly available websites, supplier data, or a worst exposure assessment. In conclusion, (b) (4) do not contain any component with a potential to cause skin irritation and sensitization at relevant exposure levels.

(b) (4) all constituents were evaluated for their potential to cause irritation and sensitization based on four websites containing toxicological data publicly available in the scientific literature. In conclusion, the master batches do not contain any component with a potential to cause skin irritation and sensitization.

Based on the biological evaluation performed above, it is concluded that the Tresiba®/Ryzodeg® FlexTouch® pen-injectors do not pose a risk of cytotoxicity, skin irritation and sensitisation, or any other biological hazard as defined in EN ISO 10993-1and are safe for the intended use.

CDRH/ODE/DAGRID Review Comments 8/24/2015:

Although the mechanical engineering testing provided by the sponsor appear to be adequate for PDS290 but the biocompatibility area has some deficiencies (please see below for the 3 deficiency questions from Dr. Bifeng Qian).

The Tresiba®/Ryzodeg® FlexTouch® pen-injectors (PDS290) proposed in NDA 203313 and NDA 203314 are intended for subcutaneous injection of insulin. Based on the intended use, the PDS290 pen-injectors are categorized as a surface device, intact skin contact, and prolonged duration (> 24 h to 30 days) due to the accumulated life time exposure.

In the response dated 15 June 2015, the sponsor claims "*All PDS290 pen-injector components which come into direct or indirect contact with users consist of* (b) (4) However, the sponsor has not provided adequate information to support the biocompatibility of the modified PDS290 pen-injector platform. Below, please see the recommended deficiencies to be communicated with the sponsor.

Recommended Biocompatibility Deficiencies:

1. You state "*All PDS290 pen-injector components which come into direct or indirect contact with users consist of* (b) (4) To support the biocompatibility of the device components (b) (4) please provide a material certification statement from the device manufacturer as below:

(b) (4)

2. The (b) (4) have been modified from the previous NDA/BLA approved devices. It appears that these modified patient contacting device components have introduced new materials (b) (4). However, the material information provided in your 15 June 2015 response is unclear and inadequate. To address the safety concern, please clearly identify all materials used in the modified (b) (4) Please specify the new materials that are not used in the previously approved pen-injectors.

Please provide the chemical identity, composition, CAS number if there is, currently known health problems associated with the chemical and toxicological data, for each of the new materials identified above. This information may be contained in the Material Safety Data Sheets (MSDS) or Technical Specification Sheets.

3. Based on analysis of the raw materials used, you state "*the Tresiba®/Ryzodeg® FlexTouch® pen-injectors do not pose a risk of cytotoxicity, skin irritation and sensitization, or any other biological hazard as defined in EN ISO 10993-1 and are safe for the intended use*". However, you have not provided any biocompatibility testing for the modified pen-injector in its final finished form. Please be advised that biocompatibility testing or risk analysis based on raw materials may have limitations and may not represent the final finished subject device or device components. Based on the FDA recognized standard ISO 10993-1: 2009/(R)2013 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process, biocompatibility testing shall be performed on the final product, or representative samples from the final product or materials processed in the same manner as the final product (including sterilization). ISO 10993-1 also indicates that biocompatibility of the final product shall be re-evaluated if there is any change a) in the source or in the specification of the materials used in the manufacture of the product; b) in the formulation, processing, primary packaging or sterilization of the product; c) in the manufacturer's instructions or expectations concerning storage, e.g. changes in shelf life and/or transport; etc.
To demonstrate that the modified PDS290 pen-injector is biocompatible, please provide complete biocompatibility study reports of the following using the final finished new device components, based on the exposure type and duration and a worst case scenario:

- *In vitro* cytotoxicity (ISO 10993-5)
- Skin irritation or intracutaneous reactivity (ISO 10993-10)
- Sensitization (ISO 10993-10)

NovoNordisk responded to CDRH/ODE deficiencies with 163 page document on 8/31/2015:

Novo Nordisk Response Q1:

Novo Nordisk is the manufacturer of the PDS290 pen-injector, and all pen-injector components are controlled by the Novo Nordisk quality system. To support the biocompatibility of the pen-injector (b) (4) (b) (4), a material certification statement is provided in Appendix A.

Novo Nordisk Response Q2:

Novo Nordisk would like to clarify that (b) (4) material components of the Tresiba® 100 U/mL FlexTouch® / Tresiba® 200 U/mL FlexTouch® / Ryzodeg® 70/30 FlexTouch® *have not* been modified from the previous NDA approved NovoLog® and Levemir® FlexTouch® pen-injectors[2]. (b) (4)

(b) (4)

(b) (4)

Table 1 Same materials used in the previously approved FlexTouch® pen-injector

Component	Tresiba® 100 U/mL FlexTouch®	Tresiba® 200 U/mL FlexTouch®	Ryzodeg® 70/30 FlexTouch®	Approved FlexTouch®
(b) (4)				

Table 2 New materials not used in the previously approved FlexTouch® pen-injectors with references to the sections in the Biological Evaluation Report

Component	Tresiba® 100 U/mL FlexTouch®	Tresiba® 200 U/mL FlexTouch®	Ryzodeg® 70/30 FlexTouch®
(b) (4)			

The overall chemical composition of all materials is specified and the full chemical composition is included for the color masterbatches by CAS number and weight percentage in the Biological Evaluation Report for Tresiba® FlexTouch® and Biological Evaluation Report for Ryzodeg® 70/30 FlexTouch® (references in Table 1 and Table 2 above).

Novo Nordisk Response Q3:

The assessment of the biocompatibility of the color masterbatches in the (b) (4) (b) (4) 100 U/mL FlexTouch® / Tresiba® 200 U/mL FlexTouch® / Ryzodeg® 70/30 FlexTouch®) is based on information on the full chemical composition of the color masterbatches. All the color masterbatches are manufactured under change control. All constituents with potential to migrate were evaluated for their potential to cause irritation and sensitization based on four websites containing toxicological data publicly available in the scientific literature, supplier data, or a worst case exposure assessment; further details are provided in the Biological Evaluation Report for Tresiba® FlexTouch® and Biological Evaluation Report for Ryzodeg® 70/30 FlexTouch®. The color masterbatches do not contain any component with a potential to cause skin irritation or sensitization at relevant exposure levels.

In conclusion, the biological evaluation is considered as sufficient to assess the biological safety of the Tresiba®/Ryzodeg® 70/30 FlexTouch® pen-injectors when used as intended. The risk of cytotoxicity, skin irritation and skin sensitization, or any other biological hazard as defined in ISO 10993-1, caused by potential leachables are considered as negligible for the FlexTouch® pen-injectors which only have brief contact to intact and dry skin.

As noted in the response to FDA Comment 2 above, it is (b) (4) (b) (4) for the Tresiba® 100 U/mL FlexTouch® / Tresiba® 200 U/mL FlexTouch® / Ryzodeg® 70/30 FlexTouch® that are new/different from the previous NDA approved FlexTouch® pen-injectors.

In accordance with ISO 10993-1, biocompatibility of the final Tresiba® 100 U/mL FlexTouch® / Tresiba® 200 U/mL FlexTouch® / Ryzodeg® 70/30 FlexTouch® was evaluated with respect to the changes from the previous NDA approved FlexPen®/FlexTouch® pen-injectors. The evaluation of safety was based on both the risk of the material (i.e., the level of toxicological concern) and the duration of exposure for the user. In accordance with ISO 10993-1: 2009/(R)2013, for components where evaluation of raw materials is combined with biocompatibility testing, the testing has been performed on the final product, or representative samples from the final product, or materials processed in the same manner as the final product.

CDRH/ODE/DAGRID Review Recommendation 8/31/2015:

IR Response provided by the sponsor to Dr. Qian's deficiency questions regarding PDS 290 biocompatibility for NDA 203313 and NDA203314 has been deemed adequate by Dr. Bifeng Qian.

As previously discussed with Dr. Lisa Yanoff and also during the Internal Wrap Up meeting, the device is (b) (4) **. Note, this is not a new problem as PDS 290 is a platform device and 2014 approved NDA supplements for insulins Levemir and Novolog both use this injector device as well as other endocrine drug products from NovoNordisk. We defer to CDER's clinical expertise regarding whether labeling material should note this device characteristic.**

All other engineering questions have been adequately addressed. No further device/engineering issues.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Lana Shiu, M.D. Digitally signed by Lana L. Shiu -S Date: 2015.09.01 13:06:07 -04'00'
Branch Chief Sign-Off	Richard C. Chapman -S 2015.09.02 01:59:56 -04'00'

Ryan J. Mcgowan -S
Digitally signed by Ryan J. Mcgowan -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=20003 52462, cn=Ryan J. Mcgowan -S
Date: 2015.09.01 16:25:16 -04'00'

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

/s/

CALLIE C CAPPEL-LYNCH
09/02/2015
signing for Lana Shiu

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, and Ophthalmic Device Branch

DATE: August 26, 2015

TO: Su Tran
Catherine.TranZwanetz@fda.hhs.gov
RPM: Muthu Ramaswamy

Through: CAPT Nina Nwaba, Acting Chief, REGO, DMQ, OC, CDRH, REGO WO-66, Room 3544

Nina C. Mezu-nwaba -S Digitally signed by Nina C Mezu nwaba S
DN: c=US, o=U S Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300161791, cn=Nina C Mezu nwaba S
Date: 2015.09.01 11:29:08 04'00'

From: Crystal Lewis, REGO DMQ, OC, CDRH, OMPT. WO-66, Room 2628

Applicant: Novo Nordisk Incorporated
1100 Campus Rd
Princeton, NJ 08540-6650
FEI# 2244771

Application # NDA 203313

Consult # ICC1500428 follow-up to ICC# 1500306

Product Name: Insulin Degludec / Insulin PDS290 Pen Injector

Consult Instructions: CDRH and the Office of Compliance received a consult to assess the suitability of the new combination product Insulin/Degludec/Insulin and the need for an inspection of the involved sites.

Inspection Needed: Yes - Decision Date: 8/26/2015

Documentation Review: No Additional Information Required

Final Recommendation: **DELAYED** – Pending pre-approval inspection

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of Insulin/Degludec/insulin PDS290 Pen Injector, NDA203313.

PRODUCT DESCRIPTION

The Insulin Degludec is a new generation of ultra-long acting basal insulin. It is formulated in two strengths and in one co-formulation of 70% Insulin Degludec and 30% insulin aspart. The PDS290 pen-injector is a new insulin prefilled pen-injector developed to increase user convenience. The PDS290 pen-injector's intended use is for the subcutaneous administration of Insulin Degludec (100U/m; and 200U/ml) and Insulin Degludec/Insulin Aspart (100U/ml). The three PDS290 pen-injectors have the proposed brand names under evaluation (b) (4).

Both Insulin Degludec and Insulin Aspart are indicated to improve glycemic control on adult patients with diabetes mellitus. Patients with diabetes mellitus are treated by individualizing the insulin doses. The standard product strength in the PDS290 pen is U100 and provides up to 80U per injection which accommodates 70% of patients' once-daily dose requirements in a single injection. The Insulin Degludec 200U/ml pen-injector provides a maximum of 160U per injection and addresses about 30% of individuals whose insulin resistance cannot be addressed through a single daily injection with the standard U100 product. Therefore, these patients increased dose requirements are addressed by the pen-injector providing up to 160U per injection.

(b) (4)

REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Novo Nordisk
   1100 Campus Rd
   Princeton, NJ 08540-6650
   FEI: 2244771

An analysis of the firm's inspection history was performed over the past two years. An inspection conducted from 6/3/2014 to 6/19/2014 was classified NAI. However, this inspection was specific to the firm's drug product activity. Information will be requested from the firm to confirm the activities performed at this specific manufacturing site for the combination device.

Therefore, a device inspection may be required for this firm pending the responsibility description for this firm from the applicant.

Update (Date: 08/26/15):
An inspection is not required for this firm because this facility is not responsible for the design, manufacture and assembly of the final combination product. This facility performs drug manufacturing including the Insulin drug product for the combination product. This site was last inspected June 3, 2014 to June 19, 2014 and was classified NAI.

2. Novo Nordisk Pharmaceutical Industries Incorporated
   3612 Powhatan Rd
   Clayton, NC 27527-9217
   FEI: 1000158576

An analysis of the firm's inspection history over the past 2 years revealed that a drug inspection was performed and classified as NAI. The inspection was conducted from August 18, 2014, to August 21, 2014. A request will be sent for the firm to identify specific activities performed at this manufacturing site for the combination product.

Therefore, a device inspection may be required for this firm pending the responsibility description for this firm from the applicant.

Update (Date: 08/26/15):
An inspection is not required for this firm because this facility is not responsible for the design, manufacture and assembly of the final combination product. This is a sterile drug manufacturing facility and includes the manufacture of Insulin for the combination product. The last inspection was performed August 18 to August 21, 2014 and was classified NAI.

Update (Date: 08/26/15):
New Pre Approval Inspection Recommendation
Upon review of the firm's response, the following facility was identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

3. Novo Nordisk A/S
   Brennum Park
   DK-3400 Hillerod
   Denmark
   FEI: 3003131673

An analysis of the firm's inspection history was performed over the past two years. Novo Nordisk has indicated they have the ultimate responsibility for the final

combination product. This facility where the final assembly of the final combination product occurs was last inspected 4/3/2013 to 4/12/2013 and was classified VAI.

Therefore, a device inspection is required for this firm.

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

Novo Nordisk did not identify the name of the firm who is ultimately responsible for the overall combination product.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.20.

Update Date: 08/26/15):

The firm's response dated 08/17/15 is adequate. Novo Nordisk specified they have the ultimate responsibility for the overall combination product. In Appendix A, the firm provided a group of documents which covered management controls. They included:

- Novo Nordisk Way (017854)
- Novo Nordisk Policies (128363)
- Novo Nordisk Quality Manual (166087)
- Product Supply Quality Manual (019436)
- R & D Quality Manual (053775)
- Document Control of QBIQ Documents (100084)

These procedures document policies that ensure compliance with the quality system requirements for Management Controls. These documents control the firm's overall Management Controls including: quality policy, quality system procedures, quality planning, management review and training of personnel.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

The firm details the design and development plan of the PDS290 pen injector delivery device in the validation of device use for the container closure system of the Risk Management Conclusions final report. The formative evaluations and design modifications section captures the design control plan. Also, the validation testing

section of the Risk Management Conclusions final report details development and design control activities. Multiple studies were conducted by the firm to verify the design of the Insulin Degludec/Insulin PDS290 pen injector.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50
The firm's procedures or descriptions for purchasing controls are not provided in the submission. The firm does however identify the following firms as component manufacturers: (b) (4) .

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.50.

Update (Date: 08/26/15):
The firm's response dated 08/17/15 is adequate. The firm's procedures or descriptions for purchasing controls were provided in the submission. The firm identifies the following group of procedures that are in place for purchasing controls. The firm included Selection and Approval of Direct Spend Suppliers (103259); Re-evaluation of Suppliers – Direct Spend (103203); and Sourcing – Direct Spend (019443) and they are located in the firm's supplement in Appendix A. Also, the firm identified the following firms as component manufacturers: (b) (4)

These documents demonstrate the firm's Purchasing Controls through the maintenance of records of acceptable suppliers. Also, the firm's procedures for supplier evaluation criteria are documented to demonstrate control over its suppliers to comply with the quality system regulations for Purchasing Controls.
The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100
The firm has not provided a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System.

Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.100.

Update (Date: 08/26/15):

The firm's response dated 08/17/15 is adequate. The firm provided a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System and they are identified as CAPA system (150266) and Corrective Actions and Preventive Actions (019470). These procedures can be found in Appendix A.

These CAPA procedures demonstrate the firm's control over policies for identifying and addressing problems in order to prevent their occurrence or reoccurrence to ensure compliance with quality system regulations. The documents include procedures to investigate the cause of nonconformities; to validate corrective or preventive actions and to implement and record changes in procedures.

Therefore, the information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170
Installation is not required for this combination product.

Servicing, 21 CFR 820.200
Servicing is not required for this combination product.

MANUFACTURING
Production and Process Controls
The firm provided a summary of its process controls in section 3.2.P.3.3 Description of Manufacturing Process and Process Controls. Description of the manufacturing process for the finished combination product includes controls for the pre-treatment of primary packaging material, (b) (4), caps, (b) (4) filling as well as a description of the packaging operation.

Production Flow
The firm also provided a production flow diagram identifying the steps involved in the manufacture of the finished Insulin/Degludec/insulin combination product. See Figure 1 below.

Figure 1 Manufacturing of insulin degludec/insulin aspart 100 U/ml

Acceptance Activities
The firm does not provide information describing how it will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities.

Update (Date: 08/26/15):
The firm's response dated 08/17/15 is inadequate. The firm states the use of drug CGMPs to provide evidence of compliance with acceptance activities for the finished combination product. Specifically 21CFR 211 Subpart E – Control of Components and Drug Product Containers and Closures and Subpart F – Production and Process Controls were applied by the firm to ensure compliance of the finished combination product.

However, the firm did not provide any descriptions of the incoming, in-process, and releasing acceptance tests/activities to assure that the final combination products are manufactured within specifications.

Documentation Review Recommendation

The following deficiencies have been identified while doing the documentation review of application Insulin Degludec/Insulin PDS290 Pen injector NDA 203313 in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

1. Your firm did not provide any information on its procedure(s) for acceptance activities. Please provide a description of the incoming, in-process, and releasing acceptance tests/activities your firm performs to assure that the final combination products are manufactured within specifications.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of application NDA203313 and has the following recommendations:

The approvability of application Insulin Degludec/insulin PDS290 Pen Injector should be delayed for the following reasons:

(1) Deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review.

(2) A pre-approval inspection is recommended for the following facilities:

Novo Nordisk A/S
Brennum Park
DK-3400 Hilleroed
Denmark
FEI: 3003131673

Crystal Lewis -S

Digitally signed by Crystal Lewis -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Crystal Lewis -S, 0.9.2342.19200300.100.1.1=2000430186
Date: 2015.09.01 11:26:12 -04'00'

Crystal Lewis

Prepared: CLewis: 07/17/2015
Reviewed: VVerna: 7/22/2015; 8/4/2015; 8/12/15; 8/27/15; 8/28/2015

CTS No.: ICC1500306 - ICC1500428
NDA203313

Review Cycle Meeting Attendance:
Month/Day/Year
Month/Day/Year
Month/Day/Year

Inspectional Guidance

Firm to be inspected:

Novo Nordisk A/S
Brennum Park
DK-3400 Hillerod
Denmark
FEI: 3003131673

CDRH recommends the inspection under the applicable Medical Device Regulations of Novo Nordisk, located in Hilleroed, Denmark, USA (FEI # 3003131673).
(1) A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the Insulin Degludec/Insulin PDS290 Pen Injector (NDA203313). Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact
Crystal Lewis
CSO,
REGO
DMQ
Office of Compliance, WO66 RM 2628
Phone: 301-796-6116

Secondary Contacts (if Primary is unavailable and a timely answer is required)
Viky Verna
Chief
REGO
DMQ
Office of Compliance, WO66 RM 2628
Phone: 301-796- 2909

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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/s/

CALLIE C CAPPEL-LYNCH
09/01/2015
signing for Crystal Lewis

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 7, 2015
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 203313 (Ryzodeg) NDA 203314 (Tresiba)
Product Name and Strength:	Ryzodeg (insulin degludec and insulin aspart) injection, 100 units/mL Tresiba (insulin degludec) injection, 100 units/mL & 200 units/mL
Submission Date:	March 26, 2015
Applicant/Sponsor Name:	Novo Nordisk
OSE RCM #:	2015-725-1 & 2015-715-1
DMEPA Primary Reviewer:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD

1 PURPOSE OF MEMO

DMEP requested that we review the revised container label and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

[1] Vee S. Label and Labeling Review for Ryzodeg (NDA 203313) and Tresiba (NDA 203314). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JUL 17. 32 p. OSE RCM No.: 2015-725 & 715.

2 CONCLUSIONS

The revised container label and carton labeling are acceptable from a medication error perspective.

APPENDIX A. LABEL AND LABELING SUBMITTED ON AUGUST 3, 2015

Ryzodeg

(b) (4)

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

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/s/

SARAH K VEE
08/07/2015

YELENA L MASLOV
08/10/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 17, 2015
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 203313 (Ryzodeg) NDA 203314 (Tresiba)
Product Name and Strength:	Ryzodeg (70 % insulin degludec and 30 % insulin aspart) injection, 100 units/mL Tresiba (insulin degludec) injection, 100 units/mL & 200 units/mL
Product Type:	Combination Product (Drug + Device)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novo Nordisk
Submission Date:	March 26, 2015
OSE RCM #:	2015-725 & 2015-715
DMEPA Primary Reviewer:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

NDA 203313 and 203314 received a Complete Response (CR) on February 8, 2013 for cardiovascular safety deficiencies. Novo Nordisk submitted their response on March 26, 2015. DMEP requested that we review the associated labels and labeling from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

On June 24, 2015 we sent an information request (IR) to Novo Nordisk regarding (b) (4) In response to our IR Novo Nordisk (b) (4)

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA previously reviewed and provided comments for some of the labels and labeling for these two products (See Appendix B). Thus, the labels and labeling will need to be revised to have consistency through all the elements to ensure safe use of the product.

DMEPA also reviewed the human factors validation studies (See Appendix B) for these two products and found them acceptable.

Based on our overall evaluation of the HF study results and the proposed labels and labeling of the product, we recommend the revisions be implemented to the proposed container label, carton and insert labeling as outlined in section 4.1 prior to approval of the products.

4 CONCLUSION & RECOMMENDATIONS

The proposed container label, carton and package insert labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product, to mitigate any confusion, and to clarify information.

4.1 RECOMMENDATIONS FOR NOVO NORDISK

We recommend the following be implemented prior to approval of these NDAs:

4.1.1 Ryzodeg (NDA 203313)

A. Package Insert
   1. Revise all instances of the error prone abbreviation "U" when it appears after the concentration or insulin dose (i.e. 100 U/mL [redacted] (b) (4)) and replace them with the word "unit" or "units".

B. Container Labels
   1. Revise the fonts of the proprietary and established names so that the established name is at least one half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
   2. Revise the strength presentation adjacent to the proprietary name to read "100 units/mL (U-100)" to remove the error prone abbreviation "U."
   3. Relocate the strength statement to appear below the safety warning, "For Single Patient Use Only".
   4. The safety warning, "For Single Patient Use Only", should be placed immediately below the established name so that there is no intervening matter between the established name and the warning. This will ensure that the warning is in the same viewing angle and field as the drug name and less likely to be overlooked. We recommend using a red-shaded and bolded letters in a contrasting colored box to enhance visibility and prominence.
   5. Unbold the statement "Rx Only".

C. Carton Labeling (FlexTouch Pen)
   1. See comments B1 through B5.
   2. Revise the location and increase the prominence of the NDC number so that it appears above the proprietary name to assist healthcare providers in identifying the product.

4.1.2 Tresiba (NDA 203314)

A. Package Insert

1. Revise all instances of the error prone abbreviation "U" when it appears after the concentration or insulin dose (i.e. 100 U/mL, 200 U/mL, (b) (4)) and replace them with the word "units".

B. Container Labels

1. Revise the fonts of the proprietary and established names so that the established name is at least one half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
2. Revise the strength presentation adjacent to the proprietary name to read "100 units/mL (U-100)" or "200 units/mL (U-200)" to remove the error prone abbreviation "U."
3. Relocate the strength statement to appear below the safety warning, "For Single Patient Use Only".
4. The safety warning, "For Single Patient Use Only", should be placed immediately below the established name so that there is no intervening matter between the established name and the warning. This will ensure that the warning is in the same viewing angle and field as the drug name and less likely to be overlooked. We recommend using a red-shaded and bolded letters in a contrasting colored box to enhance visibility and prominence.
5. Unbold the statement "Rx Only".

C. Carton Labeling

1. See Comments B 1 through B 5.
2. Revise the location and increase the prominence of the NDC number so that it appears above the proprietary name to assist healthcare providers in identifying the product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Tables 2 & 3 present relevant product information for Ryzodeg and Tresiba that Novo Nordisk submitted on March 26, 2015.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Ryzodeg</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>70% insulin degludec and 30% insulin aspart</td></tr>
<tr><td>Indication</td><td>(b) (4) (b) (4) insulin analog, (b) (4) indicated to improve glycemic control in adults with diabetes mellitus</td></tr>
<tr><td>Route of Administration</td><td>subcutaneous injection</td></tr>
<tr><td>Dosage Form</td><td>solution for injection</td></tr>
<tr><td>Strength</td><td>100 units/mL</td></tr>
<tr><td>Dose and Frequency</td><td>individualized dose once or twice daily</td></tr>
<tr><td>How Supplied</td><td>
<table>
<tr><th>Ryzodeg</th><th>Total volume</th><th>Concentration</th><th>Total units available in presentation</th><th>NDC number</th><th>Max dose per injection *</th><th>Dose increment *</th></tr>
<tr><td>U-100 FlexTouch</td><td>3 mL</td><td>100 U/mL</td><td>300 U</td><td>0169-2770-15</td><td>80 U</td><td>1 U</td></tr>
<tr><td colspan="7">(b) (4)</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>
<table>
<tr><th></th><th>Not in-use (unopened)

Refrigerated (2°C - 8°C [36°F - 46°F])</th><th>Not in-use (unopened)

Room Temperature (below 30°C [86°F])</th><th>In-use (opened)

Room Temperature (below 30°C[86°F])</th></tr>
<tr><td>3 mL Ryzodeg U100 FlexTouch (b) (4)</td><td>Until expiration date</td><td>28 days
(4 weeks)</td><td>28 days
(4 weeks)
(Do not refrigerate)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th colspan="2">Table 3. Relevant Product Information for Tresiba</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>insulin degludec</td></tr>
<tr><td>Indication</td><td>[redacted] (b) (4) human insulin analog indicated to improve glycemic control in adults with diabetes mellitus</td></tr>
<tr><td>Route of Administration</td><td>Subcutaneous injection</td></tr>
<tr><td>Dosage Form</td><td>Solution for injection</td></tr>
<tr><td>Strength</td><td>100 units/mL and 200 units/mL</td></tr>
<tr><td>Dose and Frequency</td><td>Individualized dose once daily</td></tr>
<tr><td>How Supplied</td><td>
<table>
<tr><th>Tresiba</th><th>Total volume</th><th>Concentration</th><th>Total units available in presentation</th><th>NDC number</th><th>Max dose per injection*</th><th>Dose increment*</th></tr>
<tr><td>U-100 FlexTouch</td><td>3 mL</td><td>100 U/mL</td><td>300 U</td><td>0169-2660-15</td><td>80 U</td><td>1 U</td></tr>
<tr><td>U-200 FlexTouch</td><td>3 mL</td><td>200 U/mL</td><td>600 U</td><td>0169-2550-13</td><td>160 U</td><td>2 U</td></tr>
<tr><td colspan="7">[redacted] (b) (4)</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>
<table>
<tr><th></th><th>Not in-use (unopened)

Refrigerated (2°C - 8°C[36°F - 46°F])</th><th>Not in-use (unopened)

Room Temperature (below 30°C[86°F])</th><th>In-use (opened)

Room Temperature (below 30°C[86°F])</th></tr>
<tr><td>3 mL Tresiba U100 FlexTouch [redacted] (b) (4)</td><td>Until expiration date</td><td>56 days
(8 weeks)</td><td>56 days
(8 weeks)
[redacted] (b) (4)</td></tr>
<tr><td>3 mL Tresiba U200 FlexTouch</td><td>Until expiration date</td><td>56 days
(8 weeks)</td><td>56 days
(8 weeks)
[redacted] (b) (4)</td></tr>
</table>
</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 14, 2015, we searched the L:drive and AIMS using the terms, Ryzodeg and Tresiba to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 3 previous reviews, and we confirmed that some of our previous recommendations were implemented.

Information to include in the citation for previous reviews:

Abate, R. Label and Labeling Review for Tresiba and Ryzodeg. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 JUL 12. RCM No.:2011-3892.

Abate, R. Label and Labeling Review for Tresiba and Ryzodeg. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 NOV 27. RCM No.:2011-3892-1.

Abate, R. Human Factors, Labels and Labeling Review for Tresiba and Ryzodeg. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 JAN 15. RCM No.:2011-3894.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Ryzodeg and Tresiba labels and labeling submitted by Novo Nordisk on March 26, 2015.

- Container label
- Sample container label
- Carton labeling
- Sample carton labeling
- (b) (4)
- Instructions for Use

C.2 Label and Labeling Images

Ryzodeg

(b) (4)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SARAH K VEE
07/17/2015

YELENA L MASLOV
07/21/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 203313

Application Type: New NDA

Name of Drug/Dosage Form: Ryzodeg® (70% insulin degludec and 30% insulin aspart [rDNA origin] injection) solution for subcutaneous injection

Applicant: Novo Nordisk

Receipt Date: 3/26/15

Goal Date: 9/26/15

1. Regulatory History and Applicant's Main Proposals

On September 29, 2011, Novo Nordisk submitted New Drug Applications for insulin degludec (conditionally accepted proprietary name: TRESIBA) and a fixed-dose combination of insulin degludec and insulin aspart (conditionally accepted proprietary name: RYZODEG). Insulin degludec (IDeg) is a long-acting (basal) insulin analog available as IDeg U100 and IDeg U200. Ryzodeg is a fixed-dose combination of insulin degludec and insulin aspart (IAsp), a short– acting insulin analog. Insulin aspart was approved on June 7, 2000, under the proprietary name NovoLog (NDA 020986). Ryzodeg is composed of 70% IDeg and 30% IAsp (U100). Both Ryzodeg and Tresiba are intended for once daily subcutaneous use in adults with type-1 and type-2 diabetes mellitus. The dosage of both drugs is to be individualized based on glycemic response, with no upper dosage-limit.

On May 16, 2012, Novo Nordisk submitted a major amendment which resulted in extending the review goal date to October 29, 2012. An advisory committee meeting was held on November 8, 2012, to discuss the safety and efficacy of both products. On February 8, 2013, a Complete Response Letter was issued for both NDAs.

On March 26, 2015, Novo Nordisk submitted a complete class 2 resubmission for both NDAs.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by April 29, 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *Highlight section is longer than 1/2 page*

NO 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *Horizontal lines are not present*

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *White space is not present before major headings.*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Selected Requirements of Prescribing Information

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: *Drug product is not in upper case letters.*

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *All subsections are not in title case*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *All subsections are not presented in title case.*

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

NO 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *Does not includes types of FDA approved patient labeling*

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

CALLIE C CAPPEL-LYNCH
04/08/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 203314

Application Type: New NDA

Name of Drug/Dosage Form: Tresiba® (insulin degludec [rDNA origin] injection) solution for subcutaneous injection

Applicant: Novo Nordisk

Receipt Date: 3/26/15

Goal Date: 9/26/15

1. Regulatory History and Applicant's Main Proposals

On September 29, 2011, Novo Nordisk submitted New Drug Applications for insulin degludec (conditionally accepted proprietary name: TRESIBA) and a fixed-dose combination of insulin degludec and insulin aspart (conditionally accepted proprietary name: RYZODEG). Insulin degludec (IDeg) is a long-acting (basal) insulin analog available as IDeg U100 and IDeg U200. Ryzodeg is a fixed-dose combination of insulin degludec and insulin aspart (IAsp), a short– acting insulin analog. Insulin aspart was approved on June 7, 2000, under the proprietary name NovoLog (NDA 020986). Ryzodeg is composed of 70% IDeg and 30% IAsp (U100). Both Ryzodeg and Tresiba are intended for once daily subcutaneous use in adults with type-1 and type-2 diabetes mellitus. The dosage of both drugs is to be individualized based on glycemic response, with no upper dosage-limit.

On May 16, 2012, Novo Nordisk submitted a major amendment which resulted in extending the review goal date to October 29, 2012. An advisory committee meeting was held on November 8, 2012, to discuss the safety and efficacy of both products. On February 8, 2013, a Complete Response Letter was issued for both NDAs.

On March 26, 2015, Novo Nordisk submitted a complete class 2 resubmission for both NDAs.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by April 29, 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *Highlight section is longer than 1/2 page*

NO 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *Horizontal line is not present betweel TOC and FPI*

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *White space is not present before major headings.*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Selected Requirements of Prescribing Information

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: *Drug product is not in upper case letters.*

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *All subsections are not in title case*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *All subsections are not presented in title case.*

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

NO 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *Does not includes types of FDA approved patient labeling*

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

CALLIE C CAPPEL-LYNCH
04/08/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	**February 11, 2013**
To:	Mary Parks, MD Director **Division of Metabolic and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	RYZODEG (insulin degludec/insulin aspart [rDNA origin])
Dosage Form and Route:	Solution for Injection
Application Type/Number:	NDA 203-313
Applicant:	Novo Nordisk Inc.

1 INTRODUCTION

On September 29, 2011, Novo Nordisk Inc. submitted for the Agency's review a New Drug Application (NDA 203-313) for RYZODEG (insulin degludec/insulin aspart [rDNA origin]) indicated for the treatment of adults with diabetes mellitus (b) (4) . On October 19, 2011, the Division of Metabolic and Endocrinology Products (DMEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for RYZODEG (insulin degludec/insulin aspart [rDNA origin]).

This memorandum documents the DMPP review deferral of the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for RYZODEG (insulin degludec/insulin aspart [rDNA origin]).

2 CONCLUSIONS

Due to outstanding clinical, manufacturing, and safety deficiencies, DMEP issued a Complete Response (CR) letter on February 08, 2013. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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

/s/

SHAWNA L HUTCHINS
02/11/2013

MELISSA I HULETT
02/11/2013

LASHAWN M GRIFFITHS
02/13/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	**February 11, 2013**
To:	Mary Parks, MD Director **Division of Metabolic and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	TRESIBA (insulin degludec [rDNA origin])
Dosage Form and Route:	Solution for Injection
Application Type/Number:	NDA 203-314
Applicant:	Novo Nordisk Inc.

1 INTRODUCTION

On September 29, 2011, Novo Nordisk Inc. submitted for the Agency's review a New Drug Application (NDA 203-314) for TRESIBA (insulin degludec [rDNA origin]) indicated for the treatment of adults with diabetes mellitus (b) (4) . On October 19, 2011, the Division of Metabolic and Endocrinology Products (DMEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TRESIBA (insulin degludec [rDNA origin]).

This memorandum documents the DMPP review deferral of the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TRESIBA (insulin degludec [rDNA origin]).

2 CONCLUSIONS

Due to outstanding clinical, manufacturing, and safety deficiencies, DMEP issued a Complete Response (CR) letter on February 08, 2013. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SHAWNA L HUTCHINS
02/11/2013

MELISSA I HULETT
02/12/2013

LASHAWN M GRIFFITHS
02/13/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

DMEPA Review of Human Factors Study Report

Date:	February 8, 2013
Reviewer(s):	Richard Abate, RPh, MS, Safety Evaluator Division of Medication Error Prevention and Analysis
Deputy Director	Kellie Taylor, PharmD., MPH Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh, Division of Medication Error Prevention and Analysis
Drug Name(s):	Tresiba (Insulin Degludec [rDNA origin]) Injection FlexTouch 100 units/mL and 200 units/mL pen injectors Ryzodeg (70% Insulin Degludec and 30% Insulin Aspart [rDNA origin]) Injection FlexTouch 100 units/mL pen injector
Application Type/Number:	NDA 203313 (Ryzodeg) NDA 203314 (Tresiba)
Applicant:	Novo Nordisk, Inc
OSE RCM #:	2012-2962

TABLE OF CONTENTS

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA's) evaluation of the supplemental summative usability test report (UT103) submitted by Novo Nordisk to support the approval of NDAs 203313, Ryzodeg (70% insulin degludec and 30% insulin aspart) and 203314, Tresiba (insulin degludec) which include a presentation of these insulins in the PDS290 pen injector device. The Division of Metabolism and Endocrinology Products (DMEP) requested DMEPA review the report of this supplement study to further evaluate the risk of dosing errors related to the novel strength presentation for Tresiba (insulin degludec), 200 units/mL, which DMEPA identified as a concern for Tresiba in our evaluation of the prior supplemental summative test (UT86) in OSE review 2012-1040. DMEPA found that the PDS290 to be acceptable from a medication error perspective for use with the 100 units/mL strength presentations of Ryzodeg and Tresiba.

1.1 REGULATORY HISTORY

Novo Nordisk submitted the protocol for the supplemental summative usability test UT103 August 10, 2012 as part of a Type A meeting package. This submission was in response to a July 9, 2012 Discipline Review letter from DMEPA and the Center for Device and Radiologic Health (CDRH) Human Factors team which noted deficiencies with the PDS290 for the NDAs 203313 and 203314. DMEP, DMEPA and CDRH Human Factors team met with Novo Nordisk on October 3, 2012 in a teleconference to discuss the protocol and came to agreement as to what would be included in the supplemental study (UT103).

2 REVIEW METHODS AND MATERIALS

DMEPA evaluated the following submissions for this review:

- The protocol for the Focused and Supplemental Summative Usability Test on Tresiba® 200 U/mL pen-injector handling including patients with diabetes and in-patient nurses (UT103) submitted December 17, 2012.
- Supplemental Summative Usabilty Test Report for UT103 submitted December 17, 2012.
- Novo Nordisk's Risk Management Conclusions Final Report for UT103 submitted December 17, 2012.
- Novo Nordisk's Risk Management Analysis Input to Usability Test (UT103): Addendum submitted December 17, 2012.

3 REVIEW RESULTS

The following sections describe DMEPA's resulting evaluation of the Supplemental Usability Test Report relative to the dosing errors.

3.1 STUDY DESIGN

The study design of UT103 was evaluated and agreed to with the Applicant at the teleconference on October 3, 2012. (Appendix A)

3.2 STUDY RESULTS FOR DOSING ERRORS RELATED TO THE 200 UNITS/mL STRENGTH

The reported use errors and close calls committed by the participants in this study are summarized in Appendix B and C.

The issue of concern for DMEPA remains the extent of confusion leading to medication errors that the novel insulin strength presentation of Tresiba (200 units/mL) in a pen injector may create for users. In the UT103 study report, no participants attempted to convert the dose based on the insulin concentration or set the dose incorrectly on the pen injector because of the insulin concentration. However, one reported close call involved an untrained nurse participant (N14) who noted some confusion created by the strength of the Tresiba when he set the dose incorrectly to 4 units rather than 80 units as indicated on the task card and administered it. The nurse did not describe if or how the difference in strength contributed to this error.

Additionally, two participants made simulated phone calls to Novo Nordisk related to either the strength of the Tresiba (200 units/mL) or the presentation of dose dialed for the Tresiba 200 units/mL Flex Touch pen. One trained patient participant (A27) noted that he was unsure how the U200 pen injector differs from setting the dose from his current U100 pen injector since his usual dose was 11 units of insulin and he noted that this dose did not appear on the dial. He further voiced concern that the concentration difference may cause him to inadvertently administer an incorrect dose of insulin. The section of the IFU content related to the concentrations of Tresiba was read to the patient who notes that the dose set on the dial is the dose delivered by the PDS290. The participant was able to set the dose on the pen injector to 30 units and administer the dose.

The other trained patient participant (A35) made simulated phone calls to Novo Nordisk because the dose on the task card was 30 units and the dial appeared to go from "28, 29, then the next one is 32. How do I do 30 units?" It was explained that the dial on the Tresiba 200 units/mL Flex Touch Pen is set to deliver only even number doses of insulin. The patient noted that the notch between 28 and 32 units was 30 units. The participant then set and administered the correct dose.

3.2.1 Other Use Errors Related to Dose

One untrained patient participant (A28) set the dose incorrectly during the blocked needle task. After identifying that the needle was defective and changing it, she set the dose to 26 units on the PDS290 rather than 30 units. However, this participant chose not to remove her glasses to see the numbers on the dial which she stated she normally does at home to set the dose on her pen injector.

Two untrained patient participants (A22 and E5) set the dose incorrectly on the device during the normal injection task. However, neither of these errors is attributed to the concentration of the product or confusion caused by the novel concentration. Rather, the causes were attributed to test artefact as both untrained participants set the PDS290 to

their usual insulin doses (i.e., "12-14 units" and 70 units, respectively) instead of the dose listed on the task card. We noted that neither of these events appears in the summary of use errors of the report.

3.2.2 Close Calls Related to Dose

The remaining close call involved the trained patient participant who initially dialed the dose to 82 units rather than the 80 units on the task card. However, the participant (E12) noted that dose was incorrect when the test administrator returned the device to the participant after noting the initial dose dialed. The patient "checked to see if it was the same pen," realized the dose was incorrect, and then corrected the dose to 80 units prior to administration.

3.2.3 DMEPA's Comments on Study Results

The reported dosing errors appear to be independent of the strength of the Tresiba used in the study and not caused by any confusion that the novel strength (200 units/mL) may create. However, two participants (one trained patient and one untrained nurse) noted the strength difference as a potential source of confusion. The one trained patient participant noted that the dial of the 200 units/mL Flex Touch pen differs in presentation (each mark representing two units rather than one unit of insulin) from a U100 pen injector which was noted as a source of confusion. Further, when confusion was identified by the patient participants, each requested clarification prior to proceeding with the task. The clarifying information addressed the identified confusion. Although the untrained nurse participant noted the difference in insulin strength, he described his prior insulin administration experience as administering low doses of insulin using a vial and syringe. He may not have recognized the fact that doses of 80 units of insulin were prescribed because once he realized the pen injector could be set to the 80 units dose on the task card, he "started over" and set the dose to 80 units resulting in a total of 84 units insulin being administered.

4 DISCUSSION

Overall the number of dosing errors in UT103 was few. The identified causes for these dose errors were 1) recall bias as two patients set their usual insulin doses on the first task and 2) the patient's visual impairment as the patient was unable to read the dose on the dial without removing her glasses.

We acknowledge that UT103 addressed our concerns in study design. The untrained participants were provided materials for the tasks and provided time, if needed, to familiarize themselves with the PDS290 prior to starting the tasks rather than required to read the Instructions for Use. In addition. the participants included sufficient numbers of insulin resistant patients and inpatient nurses both trained and untrained in each group. Finally, as agreed at the October 3, 2012 teleconference, half of the untrained participants were informed that the strength of the Tresiba was 200 units/mL but told nothing about dosing with the pen injector while the other half were provided no information about strength or dose.

4.1 PRESENTATION OF A CONCENTRATED INSULIN (200 UNITS/ML) IN A PEN INJECTOR

DMEPA expects that the introduction of a new strength presentation for insulin (200 units/mL) to the marketplace provides a source of confusion because insulin products in pen injectors have only been marketed as the 100 units/mL (U-100) concentration. DMEPA previously acknowledged that the design of the PDS290 or FlexTouch Pen is intended to address some of this confusion due to the fact that the dose dialed on the device is the dose delivered regardless of the concentration of Tresiba. In OSE 2012-1040, we expressed concern that the human factors assessment in UT86 of the introduction of the 200 units/mL product to insulin resistant patients was inadequate to demonstrate the safety of the proposed product. In addition, the results of UT103 provide data that confusion based on the concentration of Tresiba 200 units/mL is likely to occur with some users. However, UT103 provides an adequate number and type of participants to demonstrate that the risk to users who would be confused enough by the strength and attempt to manipulate doses based on the novel strength may be mitigated by the label, labeling, design of the Flex Touch pen, and the availability of a 1-800 support telephone number. Furthermore, the dose errors that occurred in UT103 seem to be user related (recall bias and visual impairment) rather than product related.

5 CONCLUSIONS

The use errors and close calls related to setting the dose in UT103 were few and distributed between both the trained and untrained participants using the PDS290 with the Tresiba 200 units/mL presentation. We conclude based on the data provided from UT103 that the labeling, product design, and 1-800 support line minimize the risk of confusion from the Tresiba FlexTouch pen in the 200 units/mL concentration would result in medication error. Overall, DMEPA finds from a medication error perspective that the summative study adequately demonstrates patients and healthcare providers can safely use the PDS290 to administer Tresiba FlexTouch 200 units/mL presentation at this time and thus is suitable for approval.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

6 REFERENCES

OSE review 2012-1040; DMEPA Review of Human Factors Study report for UT86, June 26, 2012, Abate, R.

APPENDICES

Appendix A: Study Design of UT 103

Participants:

15 trained people (adults and elderly patients) with insulin-dependent diabetes who are "insulin resistant"

> *("Insulin resistant" individuals who administer > 50 units of basal insulin per day. The definition was agreed to at the October 3, 2012 teleconference)*

15 untrained people (adults and elderly patients) with insulin-dependent diabetes who are "insulin resistant"

15 trained people (adults and elderly patients) with insulin-dependent diabetes who are "insulin sensitive"

> *("Insulin sensitive" individuals who administer ≤ 50 units of basal and/or mixed insulin per day. The definition was agreed to at the October 3, 2012 teleconference.)*

15 untrained people (adults and elderly patients) with insulin-dependent diabetes who are "insulin sensitive"

15 trained inpatient nurses

15 untrained inpatient nurses

Training:
The training included a product orientation session during which trained participants (1) received 15-30 minutes of one-on-one, hands-on training by one of two independent Certified Diabetes Educators (CDEs), (b) (4). Subsequently, the CDE assessed each trainee's preparedness to use the PDS290 pen-injector. They made the assessments by judging trainees' newly acquired skills and documenting their competency using the pre-defined training records. The participants then returned 2–36 hours later to participate in a test session lasting up to an hour.

Introduction to test materials:

Prior to administering the hands-on tasks, the test administrator gave each test participant, both trained and untrained, the option to handle the Tresiba® 200 U/mL pen-injector. All trained participants were informed at this point that the concentration of the insulin is 200 U/mL and that no dose conversion is needed. Half of the untrained participants were informed that the concentration of the insulin is 200 U/mL (but were not told that no dose conversion is needed) and the remaining half of the untrained participants did not receive any information about the insulin's concentration. During this introductory period, all participants had access to the IFU (folded as it would come in the pen-injector carton), one pen-injector, an empty pen-injector carton, a box of needles, (b) (4). Participants also had access to the telephone.

Task 1 (normal injection): Deliver [30 or 80] units of insulin using the pen-injector containingTresiba® 200 U/mL.

Note: All participants completed this task. (patients and nurses)
Task 2 (blocked needle): Deliver [30 or 80] units of insulin using the pen-injector containing Tresiba® 200 U/mL.

Note: Only patient participants performed this task.

(b) (4) presented task instructions to administer the following doses:
High-dose diabetes patients and inpatient nurses: 80 units
Low-dose diabetes patients: 30 units

Appendix B: Summary of reported use errors from UT103.

Table 4: Summary of use errors committed by trained participants

	Number of:			
Use error description	Participants who committed the use error	Use errors	Opportunities to commit the use error [5]	Use error rate
Pen is not primed before first injection	1 / 50, (2.0%) Patients: 1 Nurses: 0	1 Patients: 1 Nurses: 0	52 Patients: 34 Nurses: 18	1 / 52, (1.9 %) Patients: 1 / 34, (2.9 %) Nurses: 0 / 18, (0%)
Needle stick injury	1 / 50, (2.0%) Patients: 1 Nurses: 0	1 Patients: 1 Nurses: 0	N/A	N/A

Table 5: Summary of use errors committed by untrained participants

	Number of:			
Use error description	Participants who committed the use error	Use errors	Opportunities to commit the use error [6]	Use error rate
Pen is not primed before first injection	16 / 48, (33.3%) Patients: 13 Nurses: 3	18 Patients: 15 Nurses: 3	50 Patients: 35 Nurses: 15	18 / 50, (36.0%) Patients: 15 / 35, (42.9%) Nurses: 3 / 15, (20.0%)
Dose not set correctly	1 / 48, (2.1%) Patients: 1 Nurses: 0	1 Patients: 1 Nurses: 0	97 Patients: 81 Nurses: 16	1 / 97, (1.0%) Patients: 1 / 81, (1.2%) Nurses: 0 / 16, (0%)
Misinterpreted the dose delivered after detecting blocked needle	9 / 30, (30.0%) Patients: 9 Nurses: N/A	9 Patients: 9 Nurses: N/A	30 Patients: 30 Nurses: N/A	9 / 30, (30.0%) Patients: 9 / 30, (30.0%) Nurses: N/A
Needle is not fully inserted prior to injection start	1 / 48, (2.1%) Patients: 0 Nurses: 1	1 Patients: 0 Nurses: 1	100 Patients: 84 Nurses: 16	1 / 100, (1.0%) Patients: 0 / 84, (0%) Nurses: 1 / 16, (6.3%)
Blocked needle is not detected	3 / 33, (9.1%) Patients: 3 Nurses: N/A	3 Patients: 3 Nurses: N/A	33 Patients: 33 Nurses: N/A	3 / 33, (9.1%) Patients: 3 / 33, (9.1%) Nurses: N/A
Needle is not removed after injection	1 / 48, (2.1%) Patients: 1 Nurses: 0	1 Patients: 1 Nurses: 0	100 Patients: 84 Nurses: 16	1 / 100, (1.0%) Patients: 1 / 84, (1.2%) Nurses: 0 / 16 (0%)
Pen-injector cap is not mounted after use	1 / 48, (2.1%) Patients: 1 Nurses: 0	1 Patients: 1 Nurses: 0	81 Patients: 66 Nurses: 15	1 / 81, (1.2%) Patients: 1 / 66 (1.5%) Nurses: 0 / 15, (0%)
Needle stick injury	1 / 48, (2.1%) Patients: 1 Nurses: 0	1 Patients: 1 Nurses: 0	N/A	N/A

Appendix C: Summary of reported close calls from UT103.

Table 17: Summary of close calls encountered by trained participants.

	Number of:			
Close call description (i.e., description of the use error that almost occurred)	**Participants who encountered the close call**	**Close calls**	**Opportunities to encounter close call**	**Close call rate**
Pen is not primed before first injection	2 / 50, (4.0%) Patients: 1 Nurses: 1	2 Patients: 1 Nurses: 1	52 Patients: 34 Nurses: 18	2 / 52, (3.8%) Patients: 1 / 34, (2.9%) Nurses: 1 / 18, (5.6%)
Dose not set correctly	1 / 50, (2.0%) Patients: 1 Nurses: 0	1 Patients: 1 Nurses: 0	87 Patients: 69 Nurses: 18	1 / 87, (1.1%) Patients: 1 / 69, (1.4%) Nurses: 0 / 18, (0%)

Table 18: Summary of close calls encountered by untrained participants.

	Number of:			
Close call description (i.e., description of the use error that almost occurred)	**Participants who encountered the close call**	**Close calls**	**Opportunities to encounter close call**	**Close call rate**
Pen is not primed before first injection	1 / 48, (2.1%) Patients: 1 Nurses: 0	1 Patients: 1 Nurses: 0	50 Patients: 35 Nurses: 15	1 / 50, (2.0%) Patients: 1 / 35, (2.9%) Nurses: 0 / 15, (0%)
Needle is attached after dose is set and dose is altered	2 / 48, (4.2%) Patients: 1 Nurses: 1	2 Patients: 1 Nurses: 1	79 Patients: 63 Nurses: 16	2 / 79, (2.5%) Patients: 1 / 63, (1.6%) Nurses: 1 / 16, (6.3%)
Dose not set correctly	1 / 48, (2.1%) Patients: 0 Nurses: 1	1 Patients: 0 Nurses: 1	97 Patients: 81 Nurses: 16	1 / 97, (1.0%) Patients: 0 / 81, (0%) Nurses: 1 / 16 (6.3%)
Needle is not removed after injection	1 / 48, (2.1%) Patients: 1 Nurses: 0	1 Patients: 1 Nurses: 0	100 Patients: 84 Nurses: 16	1 / 100, (1.0%) Patients: 1 / 84, (1.2%) Nurses: 0 / 16, (0%)
Pen-injector cap is not mounted after use	1 / 48, (2.1%) Patients: 0 Nurses: 1	1 Patients: 0 Nurses: 1	81 Patients: 66 Nurses: 15	1 / 81, (1.2%) Patients: 0 / 66, (0%) Nurses: 1 / 15, (6.7%)

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

/s/

RICHARD A ABATE
02/08/2013

KELLIE A TAYLOR
02/08/2013

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST
02/08/2013

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:
--Originating Center: When the consult request is initiated.
--Consulting Center: When the consult is completed.
Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm.

For Consulting Center Use Only:
Date Received: 5/1/2012
Assigned to: QuynhNhu Nguyen
Date Assigned:
Assigned by:
Completed date: 6/18/2012
Reviewer Initials: QNN8
Supervisory Concurrence: Molly Story for Rachel Hartford

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: ODE/DAGID
Mail Code: HF
Consulting Reviewer Name: QuynhNhu Nguyen
Building/Room #: WO66, Rm2531
Phone #: 301-796-6273
Fax #:
Email Address: quynht.nguyen@fda.hhs.gov
RPM/CSO Name and Mail Code: QuynhNhu Nguyen

From (Originating Center):
Center: CDER
Division: DMEP
Mail Code: HF-510
Requesting Reviewer Name:
Building/Room #:
Phone#:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Rachel Hartford x60331
Requesting Reviewer's Concurring Supervisor's Name:

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 1May12
Requested Completion Date: 15Jun12

Submission/Application Number: NDA 203314 (Not Barcode Number)
Submission Type: NDA (510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☑ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: 24Apr12
Official Submission Due Date:

Name of Product: Ryzodeg (70% insulin degludec / (b) (4)% insulin aspart)
Name of Firm: Novo Nordisk

Intended Use: (375 characters max) treatment of diabetes

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
(525 characters max) Focused Summative Usability Test PDS290-UT86-2012

Documents to be returned to Requesting Reviewer? ☐ Yes ☑ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☑ Consultative Review ☐ Collaborative Review

(940 characters max -- use additional sheet if necessary) Please review the Focused Summative Usability Test PDS290-UT86-2012.
EDR Location: \\CDSESUB1\EVSPROD\NDA203314\203314.enx
Supporting Document Number: 17
eCTD Sequence Number: 0016
Letter Date: 04/24/2012
Stamp Date: 4/24/2012

GEN1200361 ; GEN128317

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

/s/

RACHEL E HARTFORD
05/01/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: June 15, 2012

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID

THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID

CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID

TO: Rachel Hartford, Senior Regulatory Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: **NDA 203313/203314**
Applicant: Novo Nordisk
Device Constituent: Ryzodeg and Tresiba PDS290 Pen Injector
Intended Treatment: Diabetes

QuynhNhu Nguyen, Combination Products Human Factors Specialist — 6/18/2012 Date

Molly F. Story, for Ron Kaye

Ron Kaye, Human Factors and Device Use-Safety Team Leader — 6/18/12 Date

Review Memo – Table of Content

CDRH Human Factors Review

Overview

The Division of Metabolism and Endocrinology requested a Human Factors consultative review of the NDAs 203313 and 203314 submitted by Novo Nordisk. This review provides CDRH's review and recommendations on the Human Factors related information contained in both of the NDAs.

This review is conducted on the Human Factors/usability re-validation study (UT86) that Novo Nordisk submitted under the NDAs. Previously, CDRH Human Factors team has reviewed the Human Factors/usability validation study (UT54) and did not find adequate evidence to support safe and effective use. The Agency issued an advice letter dated December 23, 2012 requesting Novo Nordisk to address the issues identified from the 1st study. Novo Nordisk then submitted their response to the information request, made changes to the Instructions for Use, and provided a supplemental Human Factors/usability validation study protocol based on the IFU changes. The Agency then issued another advice letter dated May 3, 2012 requesting for a rationale or evidence that the proposed IFU changes will adequately address the use-related issues observed in the previous study. However, Novo Nordisk seemed to have conducted the revalidation study prior to incorporating the comments/advice that the Agency issued on May 3, 2012.

Please see the recommendation section (page 7-9) for questions to be transmitted to Novo Nordisk.

Review Materials

EDR Location: \\CDSESUB1\EVSPROD\NDA203313\203313.enx
Supporting Document Number: 17
eCTD Sequence Number: 0016
Letter Date: 04/24/2012
Stamp Date: 4/24/2012

EDR Location: \\CDSESUB1\EVSPROD\NDA203314\203314.enx
Supporting Document Number: 17
eCTD Sequence Number: 0016
Letter Date: 04/24/2012
Stamp Date: 4/24/2012

CDRH Human Factors Review

Combination Product Device Information

Submission Number: NDAs 203313 and 203314
Applicant: Novo Nordisk
Drug Constituent: Insulin degludec
Device Constituent: PDS290 pen injectors

Intended treatment: Diabetes

CDRH Human Factors Involvement History

- 8-DEC-2012: CDRH HF provided a review of the Human Factors report contained in the NDA (See Appendix 1) – A General Advice letter was issued on 23-DEC-2012.
- 19-JAN-2012: CDRH HF was requested to provide a review on the Applicant's response to Human Factors request, and on a supplemental validation protocol – A General Advice letter was issued on 3-MAY-2012
- 1-MAY-2012: CDRH HF was requested to provide a review of the results of the supplemental validation protocol

Review of Human Factors Related Information

The re-validation study was conducted with 51 participants (17 adult users, 18 elderly users, and 16 child users). Novo Nordisk indicated that based on the FDA feedback received on 23 December 2011, the following use errors were identified as requiring further mitigation:

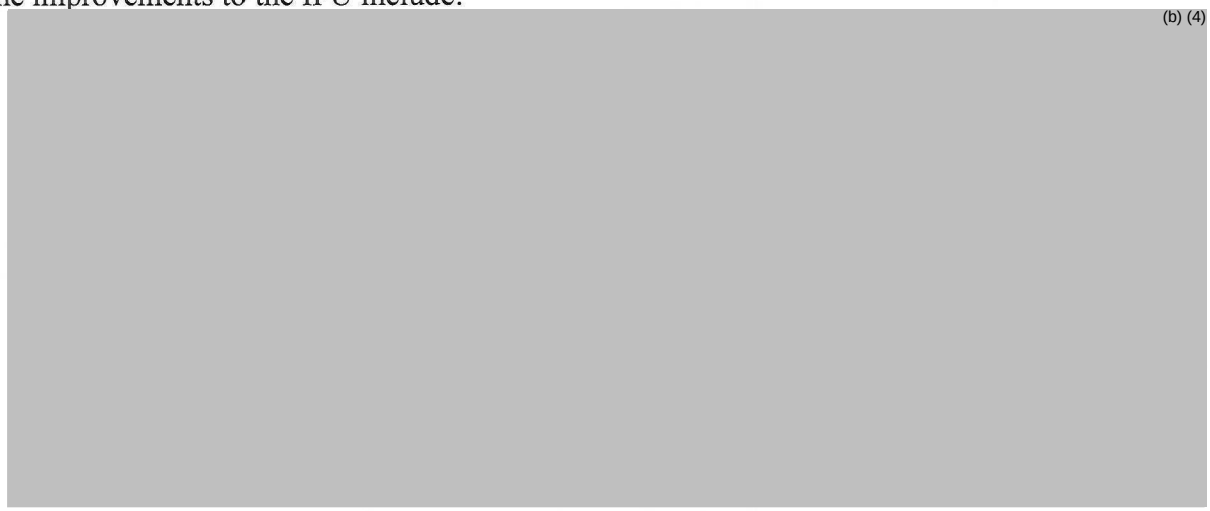
- Dose not set correctly
- Miscalculating the second dose when splitting the intended dose between two pens
- Dose button is not held down until dose counter is back to "0"
- Needle not held in skin for appropriate amount of time
- Needle stick injuries
- Remove the needle/Reuse of needle
- Not detecting a blocked needle

Novo Nordisk performed further human factors/usability evaluation that determined the following mitigations should be implemented before the UT86 handling test to address the specific use errors cited by the FDA:

- Improvements to the IFU
- Improvements to the training – ancillary instructional video available to the users

The improvements to the IFU include:

(b) (4)



Of the 51 participants, 36 participants received training and 16 did not receive training. Training sessions for the "trained" participant group included the following modules:

- Describing the basics of pen-injector use
- Reviewing in detail each step and warning presented in the IFU and explaining the importance of each step
- Demonstrating proper PDS290 pen-injector use
- Showing the ancillary instructional video

Hands-on practice period

- Administering a "question and answer" period and answering any participant questions
- Delivering supplemental training as needed past the pre-planned 30 minutes
- Test participants participated in training sessions during which they (1) received 15–30 minutes of one-on-one, hands-on training by a diabetes educator, and (2) watched the ancillary instructional video. A delay period between training and the actual test (2–32 hours) was also incorporated.

The study results are summarized in the following table:

		Number of:			
Use error description	Potential medical impact of the observed use errors	Participants who committed the use error	Use errors	Opportunities to commit the use error	Use error rate**
Pen is not primed before first injection (U200)	Minor transient hyperglycaemia	1 / 10* (10.0%)	1 Trained: 0 Untrained: 1	25 Trained: 14 Untrained: 11	1 / 25 (4.0%) Trained: (0%) Untrained: (9.1%)
Initially misinterpreted priming instructions	Minor transient hyperglycaemia	1 / 51 (2.0%)	1 Trained: 0 Untrained: 1	N/A	N/A
Dose not set correctly	Minor transient hyperglycaemia	1 / 51 (2.0%)	2 Trained: 0 Untrained: 2	281 Trained: 184 Untrained: 97	2 / 281 (0.7%) Trained: (0%) Untrained: (2.1%)
Misinterprets the dose delivered after detecting blocked needle	Minor transient hyperglycaemia	1 / 51 (2.0%)	1 Trained: 0 Untrained: 1	51 Trained: 35 Untrained: 16	1 / 51 (2.0%) Trained: (0%) Untrained: (6.3%)
Needle is not held in the skin at least 1 second after the scale is back to "0"	Minor transient hyperglycaemia	2 / 51 (3.9%)	2 Trained: 1 Untrained: 1	281 Trained: 184 Untrained: 97	2 / 281 (0.7%) Trained: (0.5%) Untrained: (0.5%)
Needle stick injury	Transient minor pain	1 / 51 (2.0%)	1 Trained: 1 Untrained: 0	N/A	N/A

*Per the protocol, approximately one third of the adult and elderly test participants used a pen-injector labelled as one of the three insulin types: Tresiba® 100 U/ml, Tresiba® 200 U/ml, and Ryzodeg® 100 U/ml. 10 (10) out of the 35 adult and elderly participants used a Tresiba® 200 U/ml pen-injector

The study results showed that the use error rates have been reduced. However, based on the analysis provided by Novo Nordisk on all use errors, this reviewer remains concerned with the following use errors:

- 1 participant did not set dose correctly

  This participant was an elderly, pen-experienced, and untrained participant. The participant was on basal–bolus insulin therapy with Lantus® vial and syringe as basal insulin and NovoLog® FlexPen® as bolus insulin. It should be noted that the Novolog® FlexPen® delivers 1 unit increments of insulin when dialled. When using his vial and syringe, he has to convert number of units to the correct volume.

  He was tested with a PDS290 pen-injector for insulin degludec 200 U/ml, for which the dose is dialled in 2-unit increments. Despite the different concentrations, all the user had to do was to set PDS290 to the correct units to be deliver, which is shown on the dose counter, and the pen-injection delivers the exact amount of units indicated by the dose counter without performing any dose conversion. However, in this case, the participant dialled and administered an incorrect dose during two different tasks during normal injection and during end-of content/split dose between two pens. The medical consequence would be underdosing.

  Novo Nordisk also reported that one participant experienced close call with this step. Because this type of use error can result incorrect dosing in actual use and while Novo Nordisk has taken helpful measures to reduce the potential of use errors, they do not directly address the potential of users converting the number of units required based on the prescribed dose. The reviewer recommends that Novo Nordisk implement further mitigation via modifying the IFU to inform the users that regardless of the concentration of insulin used, the PDS290 pen-injectors are designed to deliver the specified number of insulin units as prescribed, and that the users do not need to perform any dose conversion.

- 1 participant misinterpret the dose delivered after detecting blocked needle

  This participant was an elderly, pen-experienced and untrained participant. The participant set the dose correctly (instructed dose - 36 units of 200 U/ml Tresiba®) and attempted to administer the injection. The participant removed the needle from the cushion and noticed that the dose counter showed "26", thereby providing visual feedback that the dose counter did not return to zero and that the intended dose was not delivered. The participant incorrectly concluded that he had delivered 10 units, and that he needed to deliver 26 additional units to administer the full 36 unit dose. The participant replaced the needle on the pen-injector and administered 26 units, rather than 36 units.

  Novo Nordisk also reported that two participants experienced close call with this step. Because this type of use error can result incorrect dosing in actual use and while Novo Nordisk has taken helpful measures to reduce the potential of use errors, they do not directly address the potential of users misinterpreting that some insulin has been delivered when in actuality, no insulin has been delivered. As discussed in previous review memo, this finding indicated that users were not aware of the potential for dose

counter malfunction associated with blocked needles i.e. the device dose counter may wrongly report that up to a maximum of 7 units have been delivered. This could result in clinically significant dosing errors after the user discovers that the needle on the device is blocked.

This reviewer believes that the dose counter, which serves as a visual feedback to the users, is not optimally designed as it can mislead users and cause confusion with regards to dosing after the device problem (i.e. blocked needle) is discovered. If there are no design alternatives to reduce this risk further, the reviewer recommends that Novo Nordisk implement further mitigation via modifying the IFU to inform the users that in case of a blocked needle, the dose counter will display a value that is different from the original dose that the user has set. In addition, the IFU should provide specific instructions for use to resolve a blocked needle situation.

- 2 participants did not hold the needle at the injection site for the specified time

One participant was an elderly, pen-experienced and trained participant committed one use error during her fifth task (blocked needle). The other participant was an adult, pen-naïve and untrained participant committed one use error during the first task (normal injection). The participants both set the dose correctly and administered the injection, but held the needle in the cushion for less than one second after the dose counter had returned to"0".

Novo Nordisk stated that the IFU that the needle should be held in the skin for 6 seconds, yet dose accuracy testing has demonstrated that a full dose can be delivered after 1 second after the dose counter returns to "0". As previously communicated, the reviewer is not clear about instructing patients to hold the needle for 6 seconds, and then defining that it is only a use error if the participant did not keep the needle in the skin for at least 1 second after the dose counter returns to "0." If proper injection is defined as holding the needle for 6 seconds, then the study should demonstrate that users can hold the device for 6 seconds.

Novo Nordisk also reported that one participant experienced close call with this step. Because this type of use error can result wet injection and/or incorrect dosing in actual use and while Novo Nordisk has taken helpful measures to reduce the potential of use errors, they do not directly address the potential of users pulling the needle out within the specified time.

CDRH Human Factors Review Recommendations

The reviewer recommends that Novo Nordisk address the use errors identified in the UT86 report. Please transmit the following questions to Novo Nordisk.

The UT86 report, while demonstrating that through improving IFU and training materials, the use errors can be reduced, we are concerned with the results of the study continue to show use

errors that can result in incorrect dosing that require further mitigations. We are most concerned with the following findings:

- 1 participant did not set dose correctly and committed use error

  You reported that this participant was an elderly, pen-experienced, and untrained participant. The participant was on basal–bolus insulin therapy with Lantus® vial and syringe as basal insulin and NovoLog® FlexPen® as bolus insulin. It should be noted that the Novolog® FlexPen® delivers 1 unit increments of insulin when dialled. When using his vial and syringe, he has to convert number of units to the correct volume. The test reslts reported that this participant dialled and administered an incorrect dose during two different tasks during normal injection and during end-of content/split dose between two pens. You also reported that one participant experienced close call with this step. Because this type of use error can result incorrect dosing in actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential of risk of users converting the number of units required based on the prescribed dose. We recommends that you implement further mitigation via modifying the IFU to inform the users that regardless of the concentration of insulin used, the PDS290 pen-injectors are designed to deliver the specified number of insulin units as prescribed, and that the users do not need to perform any dose conversion.

- 1 participant misinterpret the dose delivered after detecting blocked needle

  You reported that this participant was an elderly, pen-experienced and untrained participant. The participant set the dose correctly (instructed dose - 36 units of 200 U/ml Tresiba®) and attempted to administer the injection. However, due the block needle scenario, the participant incorrectly concluded that he had delivered 10 units, and that he needed to deliver 26 additional units to administer the full 36 unit dose. The participant replaced the needle on the pen-injector and administered 26 units, rather than 36 units. Because this type of use error can result incorrect dosing in actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential of risk of users misinterpreting that some insulin has been delivered when in actuality, no insulin has been delivered in situation where the needle is blocked. You also reported that tww participants experienced close call with this step. As previously communicated in our General Advice letter dated May 3, 2012, this finding indicated that user might not be aware of the potential for dose counter malfunction associated with blocked needles i.e. the device dose counter may wrongly report that up to a maximum of 7 units have been delivered. This could result in clinically significant dosing errors after the user discovers that the needle on the device is blocked. We conclude that the dose counter, which serves as a visual feedback to the users, is not optimally designed as it can mislead users and cause confusion with regards to dosing after the device problem (i.e. blocked needle) is discovered. If there are no design alternatives to reduce this risk further, we recommend that you implement further mitigation via modifying the IFU to inform the users that in case of a blocked needle, the dose counter will display a value that is different from the original dose that the user has set. In addition, the IFU should provide specific instructions for use to resolve a blocked needle situation.

- 2 participants did not hold the needle at the injection site for the specified time

You reported that one participant was an elderly, pen-experienced and trained participant committed one use error during her fifth task (blocked needle). The other participant was an adult, pen-naïve and untrained participant committed one use error during the first task (normal injection). The participants both set the dose correctly and administered the injection, but held the needle in the cushion for less than one second after the dose counter had returned to"0". You also reported that one participant experienced close call with this step. As previously communicated in our General Advice letter dated May 3, 2012, we are concerned that you instruct patients to hold the needle for 6 seconds. However, in the study, you defined that it is only a use error if the participant did not keep the needle in the skin for at least 1 second after the dose counter returns to "0." If proper injection is defined as holding the needle for 6 seconds, then the study should demonstrate that users can hold the device for 6 seconds.

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/s/

RACHEL E HARTFORD

06/21/2012

On behalf of
QuynhNhu Nguyen
Biomedical Engineer/Human Factors Reviewer CDRH/ODE/DAGID

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: February 1, 2012

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID

THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID

CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID

TO: Rachel Hartford, Senior Regulatory Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: **NDA 203313/203314**
Applicant: Novo Nordisk
Device Constituent:
Ryzodeg (100 U/mL) PDS290 Pen Injector
Tresiba (100 U/mL and 200 U/mL) PDS290 Pen Injector
Intended Treatment: Diabetes

QuynhNhu Nguyen, Combination Products Human Factors Specialist — 2/4/2013 Date

Ron Kaye, Human Factors and Device Use-Safety Team Leader — 2/4/13 Date

Contents

CDRH Human Factors Review

Overview

The Division of Metabolism and Endocrinology requested a Human Factors consultative review of the NDAs 203313 and 203314 submitted by Novo Nordisk. This review provides CDRH's review on the Human Factors related information contained in both of the NDAs.

This review is conducted on the Human Factors/usability supplemental study (UT103) with the Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL) that Novo Nordisk submitted under the NDAs. Previously, CDRH Human Factors team has reviewed the Human Factors/usability validation study (UT86) and had several outstanding concerns with the use of the Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL) pen injector . As a result, Novo Nordisk made additional changes to the Instructions for Use and ancillary instructional video to address the following specific concerns received in the FDA´s Discipline Review letter of July 09, 2012:

- Not setting the dose correctly for the Tresiba® 200 U/mL due to dose conversion
- Misinterpreted the dose delivered after detecting blocked needle
- Needle not held in skin for appropriate amount of time
- Validation of the PDS290 pen-injector by inpatient nurses

No new use errors were introduced as a result of the mitigations that were implemented in the IFU before the current summative test (UT103). The reviewer finds Novo Nordisk's response acceptable, and has no further questions regarding Human Factors/usability test UT103.

Review Materials

EDR Location: \\CDSESUB1\EVSPROD\NDA203313\203313.enx
Supporting Document Number: 38 eCTD Sequence Number: 0036

EDR Location: \\CDSESUB1\EVSPROD\NDA203314\203314.enx
Supporting Document Number: 42 eCTD Sequence Number: 0040

CDRH Human Factors Review

Combination Product Device Information

Submission Number: NDAs 203313 and 203314
Applicant: Novo Nordisk
Drug Constituent: Insulin degludec
Device Constituent: PDS290 pen injectors
Intended treatment: Diabetes

CDRH Human Factors Involvement History

- 8-DEC-2012: CDRH HF provided a review of the Human Factors report contained in the NDA (See Appendix 1) – A General Advice letter was issued on 23-DEC-2012.

- 19-JAN-2012: CDRH HF was requested to provide a review on the Applicant's response to Human Factors request, and on a supplemental validation protocol (UT86)
- 1-MAY-2012: CDRH HF was requested to provide a review of a supplemental validation protocol (UT103)
- 19-DEC-2012: CDRH HF was requested to provide a review of the results of the UT103 supplemental validation study

Review of Human Factors Related Information

The supplemental validation study (UT103) was conducted with 98 participants or the Tresiba® 200 U/mL pen-injector. The test included a normal injection and an artificially blocked needle task. The participants were divided into two groups where one received training prior to participating in the usability test session and one group did not. Novo Nordisk indicated that based on the FDA feedback received on July 9, 2012, the following use errors were identified as requiring further mitigation:

- Not setting the dose correctly for the Tresiba® 200 U/mL due to dose conversion
- Misinterpreted the dose delivered after detecting blocked needle
- Needle not held in skin for appropriate amount of time
- Validation of the PDS290 pen-injector by inpatient nurses

Novo Nordisk performed further human factors/usability evaluation that determined the following mitigations should be implemented before the UT103 handling test to address the specific use errors cited by the FDA. The results of the 50 participants, who received representative training, which is expected for the use of this product, showed they were able to successfully perform all injection tasks without coming use errors/task failures. In addition, they understood correctly the IFU excerpts included in the IFU Evaluation exercise. Accordingly, they understood the following important instructions:

- Do not convert the dose when using Tresiba® 200 U/mL (i.e. dial the prescribed dose in
- units)
- Replace the blocked needle with a new needle and dial the original, full dose
- How to identify and handle a blocked needle and successfully deliver the correct dose
- Hold the needle in the skin and count slowly to six after the dose counter returns to zero

While there were two task failures observed, the failures were determined to not have significant clinical impact. No new use errors were introduced as a result of the mitigations that were implemented in the IFU before the current summative test (UT103). **The reviewer finds Novo Nordisk's response acceptable, and has no further questions regarding Human Factors/usability test UT103.**

Appendix A: Review of Applicant's Evaluation of Prior Human Factors Report (Dated June 29, 2011

Overview

The Division of Metabolism and Endocrinology requested a Human Factors consultative review of the NDAs 203313 and 203314 submitted by Novo Nordisk. This review provides CDRH's review and recommendations on the Human Factors related information contained in both of the NDAs.

This review is conducted on the Human Factors/usability re-validation study (UT86) that Novo Nordisk submitted under the NDAs. Previously, CDRH Human Factors team has reviewed the Human Factors/usability validation study (UT54) and did not find adequate evidence to support safe and effective use. The Agency issued an advice letter dated December 23, 2012 requesting Novo Nordisk to address the issues identified from the 1st study. Novo Nordisk then submitted their response to the information request, made changes to the Instructions for Use, and provided a supplemental Human Factors/usability validation study protocol based on the IFU changes. The Agency then issued another advice letter dated May 3, 2012 requesting for a rationale or evidence that the proposed IFU changes will adequately address the use-related issues observed in the previous study. However, Novo Nordisk seemed to have conducted the revalidation study prior to incorporating the comments/advice that the Agency issued on May 3, 2012.

Please see the recommendation section (page 7-9) for questions to be transmitted to Novo Nordisk.

Review Materials

EDR Location: \\CDSESUB1\EVSPROD\NDA203313\203313.enx
Supporting Document Number: 17
eCTD Sequence Number: 0016
Letter Date: 04/24/2012
Stamp Date: 4/24/2012

EDR Location: \\CDSESUB1\EVSPROD\NDA203314\203314.enx
Supporting Document Number: 17
eCTD Sequence Number: 0016
Letter Date: 04/24/2012
Stamp Date: 4/24/2012

CDRH Human Factors Review

Combination Product Device Information

Submission Number: NDAs 203313 and 203314
Applicant: Novo Nordisk
Drug Constituent: Insulin degludec

Device Constituent: PDS290 pen injectors
Intended treatment: Diabetes

CDRH Human Factors Involvement History

- 8-DEC-2012: CDRH HF provided a review of the Human Factors report contained in the NDA (See Appendix 1) – A General Advice letter was issued on 23-DEC-2012.
- 19-JAN-2012: CDRH HF was requested to provide a review on the Applicant's response to Human Factors request, and on a supplemental validation protocol – A General Advice letter was issued on 3-MAY-2012
- 1-MAY-2012: CDRH HF was requested to provide a review of the results of the supplemental validation protocol

Review of Human Factors Related Information

The re-validation study was conducted with 51 participants (17 adult users, 18 elderly users, and 16 child users). Novo Nordisk indicated that based on the FDA feedback received on 23 December 2011, the following use errors were identified as requiring further mitigation:

- Dose not set correctly
- Miscalculating the second dose when splitting the intended dose between two pens
- Dose button is not held down until dose counter is back to "0"
- Needle not held in skin for appropriate amount of time
- Needle stick injuries
- Remove the needle/Reuse of needle
- Not detecting a blocked needle

Novo Nordisk performed further human factors/usability evaluation that determined the following mitigations should be implemented before the UT86 handling test to address the specific use errors cited by the FDA:

- Improvements to the IFU
- Improvements to the training – ancillary instructional video available to the users

The improvements to the IFU include:

(b) (4)

Of the 51 participants, 36 participants received training and 16 did not receive training. Training sessions for the "trained" participant group included the following modules:

- Describing the basics of pen-injector use
- Reviewing in detail each step and warning presented in the IFU and explaining the importance of each step
- Demonstrating proper PDS290 pen-injector use
- Showing the ancillary instructional video

Hands-on practice period

- Administering a "question and answer" period and answering any participant questions
- Delivering supplemental training as needed past the pre-planned 30 minutes
- Test participants participated in training sessions during which they (1) received 15–30 minutes of one-on-one, hands-on training by a diabetes educator, and (2) watched the ancillary instructional video. A delay period between training and the actual test (2–32 hours) was also incorporated.

The study results are summarized in the following table:

		Number of:			
Use error description	**Potential medical impact of the observed use errors**	**Participants who committed the use error**	**Use errors**	**Opportunities to commit the use error**	**Use error rate****
Pen is not primed before first injection (U200)	Minor transient hyperglycaemia	1 / 10* (10.0%)	1 Trained: 0 Untrained: 1	25 Trained: 14 Untrained: 11	1 / 25 (4.0%) Trained: (0%) Untrained: (9.1%)
Initially misinterpreted priming instructions	Minor transient hyperglycaemia	1 / 51 (2.0%)	1 Trained: 0 Untrained: 1	N/A	N/A
Dose not set correctly	Minor transient hyperglycaemia	1 / 51 (2.0%)	2 Trained: 0 Untrained: 2	281 Trained: 184 Untrained: 97	2 / 281 (0.7%) Trained: (0%) Untrained: (2.1%)
Misinterprets the dose delivered after detecting blocked needle	Minor transient hyperglycaemia	1 / 51 (2.0%)	1 Trained: 0 Untrained: 1	51 Trained: 35 Untrained: 16	1 / 51 (2.0%) Trained: (0%) Untrained: (6.3%)
Needle is not held in the skin at least 1 second after the scale is back to "0"	Minor transient hyperglycaemia	2 / 51 (3.9%)	2 Trained: 1 Untrained: 1	281 Trained: 184 Untrained: 97	2 / 281 (0.7%) Trained: (0.5%) Untrained: (0.5%)
Needle stick injury	Transient minor pain	1 / 51 (2.0%)	1 Trained: 1 Untrained: 0	N/A	N/A

*Per the protocol, approximately one third of the adult and elderly test participants used a pen-injector labelled as one of the three insulin types: Tresiba® 100 U/ml, Tresiba® 200 U/ml, and Ryzodeg® 100 U/ml. 10 (10) out of the 35 adult and elderly participants used a Tresiba® 200 U/ml pen-injector

The study results showed that the use error rates have been reduced. However, based on the analysis provided by Novo Nordisk on all use errors, this reviewer remains concerned with the following use errors:

- 1 participant did not set dose correctly

This participant was an elderly, pen-experienced, and untrained participant. The participant was on basal–bolus insulin therapy with Lantus® vial and syringe as basal insulin and NovoLog® FlexPen® as bolus insulin. It should be noted that the Novolog® FlexPen® delivers 1 unit increments of insulin when dialled. When using his vial and syringe, he has to convert number of units to the correct volume.

He was tested with a PDS290 pen-injector for insulin degludec 200 U/ml, for which the dose is dialled in 2-unit increments. Despite the different concentrations, all the user had to do was to set PDS290 to the correct units to be deliver, which is shown on the dose counter, and the pen-injection delivers the exact amount of units indicated by the dose counter without performing any dose conversion. However, in this case, the participant dialled and administered an incorrect dose during two different tasks during normal injection and during end-of content/split dose between two pens. The medical consequence would be underdosing.

Novo Nordisk also reported that one participant experienced close call with this step. Because this type of use error can result incorrect dosing in actual use and while Novo Nordisk has taken helpful measures to reduce the potential of use errors, they do not directly address the potential of users converting the number of units required based on the prescribed dose. The reviewer recommends that Novo Nordisk implement further mitigation via modifying the IFU to inform the users that regardless of the concentration of insulin used, the PDS290 pen-injectors are designed to deliver the specified number of insulin units as prescribed, and that the users do not need to perform any dose conversion.

- 1 participant misinterpret the dose delivered after detecting blocked needle

  This participant was an elderly, pen-experienced and untrained participant. The participant set the dose correctly (instructed dose - 36 units of 200 U/ml Tresiba®) and attempted to administer the injection. The participant removed the needle from the cushion and noticed that the dose counter showed “26”, thereby providing visual feedback that the dose counter did not return to zero and that the intended dose was not delivered. The participant incorrectly concluded that he had delivered 10 units, and that he needed to deliver 26 additional units to administer the full 36 unit dose. The participant replaced the needle on the pen-injector and administered 26 units, rather than 36 units.

  Novo Nordisk also reported that two participants experienced close call with this step. Because this type of use error can result incorrect dosing in actual use and while Novo Nordisk has taken helpful measures to reduce the potential of use errors, they do not directly address the potential of users misinterpreting that some insulin has been delivered when in actuality, no insulin has been delivered. As discussed in previous review memo, this finding indicated that users were not aware of the potential for dose counter malfunction associated with blocked needles i.e. the device dose counter may wrongly report that up to a maximum of 7 units have been delivered. This could result in clinically significant dosing errors after the user discovers that the needle on the device is blocked.

This reviewer believes that the dose counter, which serves as a visual feedback to the users, is not optimally designed as it can mislead users and cause confusion with regards to dosing after the device problem (i.e. blocked needle) is discovered. If there are no design alternatives to reduce this risk further, the reviewer recommends that Novo Nordisk implement further mitigation via modifying the IFU to inform the users that in case of a blocked needle, the dose counter will display a value that is different from the original dose that the user has set. In addition, the IFU should provide specific instructions for use to resolve a blocked needle situation.

- 2 participants did not hold the needle at the injection site for the specified time

One participant was an elderly, pen-experienced and trained participant committed one use error during her fifth task (blocked needle). The other participant was an adult, pen-naïve and untrained participant committed one use error during the first task (normal injection). The participants both set the dose correctly and administered the injection, but held the needle in the cushion for less than one second after the dose counter had returned to"0".

Novo Nordisk stated that the IFU that the needle should be held in the skin for 6 seconds, yet dose accuracy testing has demonstrated that a full dose can be delivered after 1 second after the dose counter returns to "0". As previously communicated, the reviewer is not clear about instructing patients to hold the needle for 6 seconds, and then defining that it is only a use error if the participant did not keep the needle in the skin for at least 1 second after the dose counter returns to "0." If proper injection is defined as holding the needle for 6 seconds, then the study should demonstrate that users can hold the device for 6 seconds.

Novo Nordisk also reported that one participant experienced close call with this step. Because this type of use error can result wet injection and/or incorrect dosing in actual use and while Novo Nordisk has taken helpful measures to reduce the potential of use errors, they do not directly address the potential of users pulling the needle out within the specified time.

CDRH Human Factors Review Recommendations

The reviewer recommends that Novo Nordisk address the use errors identified in the UT86 report. Please transmit the following questions to Novo Nordisk.

The UT86 report, while demonstrating that through improving IFU and training materials, the use errors can be reduced, we are concerned with the results of the study continue to show use errors that can result in incorrect dosing that require further mitigations. We are most concerned with the following findings:

- 1 participant did not set dose correctly and committed use error

You reported that this participant was an elderly, pen-experienced, and untrained participant. The participant was on basal–bolus insulin therapy with Lantus® vial and syringe as basal insulin and NovoLog® FlexPen® as bolus insulin. It should be noted that the Novolog® FlexPen® delivers 1 unit increments of insulin when dialled. When using his vial and syringe, he has to convert number of units to the correct volume. The test reslts reported that this participant dialled and administered an incorrect dose during two different tasks during normal injection and during end-of content/split dose between two pens. You also reported that one participant experienced close call with this step. Because this type of use error can result incorrect dosing in actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential of risk of users converting the number of units required based on the prescribed dose. We recommends that you implement further mitigation via modifying the IFU to inform the users that regardless of the concentration of insulin used, the PDS290 pen-injectors are designed to deliver the specified number of insulin units as prescribed, and that the users do not need to perform any dose conversion.

- 1 participant misinterpret the dose delivered after detecting blocked needle

You reported that this participant was an elderly, pen-experienced and untrained participant. The participant set the dose correctly (instructed dose - 36 units of 200 U/ml Tresiba®) and attempted to administer the injection. However, due the block needle scenario, the participant incorrectly concluded that he had delivered 10 units, and that he needed to deliver 26 additional units to administer the full 36 unit dose. The participant replaced the needle on the pen-injector and administered 26 units, rather than 36 units. Because this type of use error can result incorrect dosing in actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential of risk of users misinterpreting that some insulin has been delivered when in actuality, no insulin has been delivered in situation where the needle is blocked. You also reported that tww participants experienced close call with this step. As previously communicated in our General Advice letter dated May 3, 2012, this finding indicated that user might not be aware of the potential for dose counter malfunction associated with blocked needles i.e. the device dose counter may wrongly report that up to a maximum of 7 units have been delivered. This could result in clinically significant dosing errors after the user discovers that the needle on the device is blocked. We conclude that the dose counter, which serves as a visual feedback to the users, is not optimally designed as it can mislead users and cause confusion with regards to dosing after the device problem (i.e. blocked needle) is discovered. If there are no design alternatives to reduce this risk further, we recommend that you implement further mitigation via modifying the IFU to inform the users that in case of a blocked needle, the dose counter will display a value that is different from the original dose that the user has set. In addition, the IFU should provide specific instructions for use to resolve a blocked needle situation.

- 2 participants did not hold the needle at the injection site for the specified time

You reported that one participant was an elderly, pen-experienced and trained participant committed one use error during her fifth task (blocked needle). The other participant was

an adult, pen-naïve and untrained participant committed one use error during the first task (normal injection). The participants both set the dose correctly and administered the injection, but held the needle in the cushion for less than one second after the dose counter had returned to“0”. You also reported that one participant experienced close call with this step. As previously communicated in our General Advice letter dated May 3, 2012, we are concerned that you instruct patients to hold the needle for 6 seconds. However, in the study, you defined that it is only a use error if the participant did not keep the needle in the skin for at least 1 second after the dose counter returns to "0." If proper injection is defined as holding the needle for 6 seconds, then the study should demonstrate that users can hold the device for 6 seconds.

Appendix B: Review of Applicant's Evaluation of Prior Human Factors Report (Dated April 24, 2012)

Overview

The Division of Metabolism and Endocrinology requested a Human Factors consultative review of the NDAs 203313 and 203314 submitted by Novo Nordisk. This review provides CDRH's review and recommendations on the Human Factors related information contained in both of the NDAs.

The reviewer believes based on the significant proportion of the use errors and the nature of the use errors, and the additional analysis provided by Novo Nordisk, in particular those associated with the dose counter mechanism, as well as other issues, the design of the device as well as training in addition to the proposed changes to IFU, should also be considered and should be further optimized. Novo Nordisk did not provide a rationale of why they believe the IFU changes and the proposed supplemental study will be adequate in addressing use-related issues identified in the prior study.

Furthermore, the reviewer notes that the methodology of proposed study does not represent realistic use i.e. participants (b) (4), and selected participants will receive training. Furthermore, the (b) (4) does not represent realistic way users would normally behave. This methodology was also employed in the prior study. The reviewer believes that these studies are more exploratory in nature (b) (4). In the Human Factors/usability validation study, the participants should use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, Novo Nordisk should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete. In addition the extent and level of training should be identical to the training that actual users will receive. Lastly, the validation study requires that users across all users group be represented, (b) (4) while performing simulated use.

Please note that the device platform used in this combination product is identical the device under NDAs 20986 and 21536, Novolog and Levemir injector. The Human Factors testing for those two NDAs illustrated major concerns regarding human factors/use-safety for which we issued an Information Request letter. For both sets of NDAs, the Human Factors testing showed use errors/failures continue to occur and therefore, findings regarding human factors/use safety concerns have not fully addressed.

Please see the recommendation section (page 16-18) for questions to be transmitted to Novo Nordisk.

Review Materials

NDA 203313
EDR Location: \\CDSESUB1\EVSPROD\NDA203313\203313.enx

eCTD Sequence Number: 0008

NDA 203314
EDR Location: \\CDSESUB1\EVSPROD\NDA203314\203314.enx
eCTD Sequence Number: 0008

The protocol is identical because both NDAs have the same device platform, which is the PDS290.


NDA 203313.pdf (6 MB)

CDRH Human Factors Review

Combination Product Device Information

Submission Number: NDAs 203313 and 203314
Applicant: Novo Nordisk
Drug Constituent: Insulin degludec
Device Constituent: PDS290 pen injectors
Intended treatment: Diabetes

CDRH Human Factors Involvement History

- 8-DEC-2012: CDRH HF provided a review of the Human Factors report contained in the NDA (See Appendix 1)
- 19-JAN-2012: CDRH HF was requested to provide a review on the Applicant's response to Human Factors request, and on a supplemental validation protocol

Review of Human Factors Related Information

This review is organized into three major sections:

- Evaluation of Novo Nordisk to deficiencies identified during the Dec 8, 2011 review
- Evaluation of proposed Supplemental Human Factors study protocol to validate IFU changes
- Preliminary Response to Novo Nordisk's letter dated January 10, 2012, Proposed Questions to FDA (page 4 of 4)

Evaluation of Novo Nordisk To Deficiencies Identified During The Dec 8, 2011 Review

Regarding FDA's question for training requirements, question # 1, for the adult subgroup, Novo Nordisk clarified that there were no untrained participants in the differentiation evaluation as a patient will never select their insulin type and device from a shelf at the pharmacy as it is a prescription product. For the HCPs (including pharmacists) subgroup, Novo Nordisk would like to clarify that there were no trained participants in the differentiation evaluation as it is likely that they will prescribe and/or give patients different insulin products and devices without having received prior introduction to the specific products. As HCPs are the first preventative measure

against mix-up of insulin products, the HCP subgroup was tested in a worst case scenario; i.e., not being trained. This response was found acceptable.

Regarding FDA's question pertaining to the breakdown of participants in the studies, question # 2a, Novo Nordisk provided two tables showing a breakdown of number of participants within each user group that were trained, untrained, who reported any degree of visual impairment, experienced simulated visual impairment, who reported any degree of dexterity impairment, experienced simulated dexterity impairment, and who reported any degree of hearing impairment. Both tables showed adequate representation of the intended users population. This response was found acceptable.

Regarding FDA's question pertaining to A rationale for determining who should be receiving training, and who should not among the intended users, question # 2b, Novo Nordisk provided the following:

- UT59 (differentiation test)

The rationale for training all participants in the children, adult, elderly and caregiver groups in how to identify the PDS290 pen-injector and carton before participating in the test was based on the fact that these groups will always get some level of introduction to a product, when the insulin type and device is prescribed. Mix-up at the patient level can occur if several members in the household are using different insulin types or if individual patients use more than one type of insulin e.g. bolus and basal insulin. In case of several insulin users in a household, each user will prior to the prescription receive comprehensive training and get introduction to each of the specific insulin types prescribed and therefore these patients will know their own insulin types and device.
The rationale for not introducing HCPs (including pharmacists) to the products in UT59 is that it is likely that they will prescribe and/or give patients different insulin types and devices without having received prior introduction. As HCPs are the first preventative measure against mix-up of insulin types, the HCP group was tested in a worst case scenario; i.e., not being introduced.

- UT54 (handling test)

Participants in UT54 comprised both trained and untrained users. The rationale for training all participants in the children group was based on a general experience that children will not be self-injecting without prior comprehensive training in correct handling of their pen-injector. The rationale for having both trained and untrained participants in the adult, elderly, caregiver and HCP groups was to reflect that the level of training will vary in real life and by having both trained and untrained participants from these groups, the possible realistic scenarios would be tested.

Regarding FDA's question pertaining to a rationale for why (b) (4) , question # 2c, is an approach that represents realistic use, Novo Nordisk reported tha (b) (4) . As training and the IFU are important elements in the overall assessment of the test results, Novo Nordisk decided to use this

relatively comprehensive approach. The reviewer notes that this approach does not reflect realistic use of the IFU.

Regarding FDA's question pertaining to adequate representation of diabetic patients having medical conditions such as retinopathy and neuropathy, question # 3, Novo Nordisk stated that:

- In UT59, four participants (2 elderly, 2 adult) recruited had self reported visual impairments, including cataracts (1 elderly, 1 adult), retinopathy (1 adult), colour blindness (1 adult), and loss of sight in one eye (1 elderly). The number of participants with visual impairment including participants using glasses or lenses was 34 out of the 57 participants, and in the elderly and adult segment, 75% used glasses or lenses. In addition, to ensure diversity pertaining to visual impairment, 20 participants (10 adults and 10 elderly) performed some differentiation tasks while visually impaired "artificially" using glasses to simulate diabetic retinopathy. In addition, one elderly participant had tendonitis and arthritis in her hands, limiting her hand dexterity.
- In UT54, no visual impairments were reported. However, 32 of the 61 participants with diabetes used glasses or lenses, and in the elderly segment 17 out of 21 used glasses or lenses. The elderly group included participants with up to 30 years of insulin use. In addition, to ensure diversity pertaining to visual impairment, 16 participants (8 adults and 8 elderly) performed some handling tasks while visually impaired "artificially" using glasses to simulate diabetic retinopathy. In addition, five participants recruited had at least one form of self-reported dexterity impairment including arthritis in fingers, poor rotational ability in right hand, missing finger, and mild diabetic neuropathy. In addition, to ensure diversity pertaining to dexterity impairment, 8 participants (3 adults and 5 elderly) performed some handling tasks while dexterity was impaired "artificially" using sensation and movement limiting gloves to simulate diabetic neuropathy.

Additional provided by Novo Nordisk showed that adequate representation of the intended users population including those with medical conditions such as retinopathy and neuropathy. This response was found acceptable.

Regarding FDA's question on the User Differential Study, UT59, question # 4, Novo Nordisk clarified that during the carton retrieval task, three participants committed use errors, two participants each committed a use error and one did not fulfil the task. Further investigation reveals that:

- During the exit interview the participant, A13, was made aware that he had retrieved the wrong carton and pen-injector throughout the tasks, since he retrieved (b) (4) and not (b) (4) as stated on the task card. A13 explained that he believed that (b) (4) was the name of the company producing the product and not of the insulin type itself. The participant stressed that he had misinterpreted the task as it would have been no problem for him to retrieve the carton with (b) (4). He explained that he saw the blue colour of the (b) (4) carton in the refrigerator every time he moved it in order to get to the (b) (4) carton. He also said that all cartons were easily identifiable. As a result, Novo Nordisk concluded that the main root cause behind the error was due to the test subject misunderstanding the task.
- Another participant's, A15, subjective feedback indicated that they saw NovoLog® and selected that carton because it is the product that they are currently using, which was a mistake. The participant opened the refrigerator again and retrieved the correct carton

with [redacted](b) (4), and completed the remaining five tasks successfully. Novo Nordisk concluded that the error in the first task was due to a misunderstanding of the task and that he was able to clearly identify the correct carton and peninjector.

- Another participant's, E3, subjective feedback showed that they did not select a carton because they was not able to differentiate the different cartons. Novo Nordisk concluded that the participant made the correct choice by not selecting a carton in situation where dim light minimize his ability to differentiate.

Based on the above clarification, the response was found acceptable. It appears that the use errors were caused by testing artifacts.

Regarding FDA's question on the User Handling Study, UT54, question # 5, Novo Nordisk reported that current pen-users performed two baseline injection tasks with a pen injector matching the same type of pen injector they currently use (either Novo Nordisk FlexPen®, Sanofi Aventis SoloStar® or Eli Lilly KwikPen®). For the actual test, only the PDS290 pen-injector, representing the intended commercial product, was used while performing the tasks. In conclusion, all handling tasks in UT54 were performed using PDS290 pen-injectors represented by the commercial product [redacted](b) (4) This clarification was found acceptable.

Regarding FDA's question on the Validation of Deivce use (UT59 and UT54 NN Report, Dated June 29, 2011), question # 6, which reported 94 of 105 participants committed 226 errors across tasks associated with delivering an injection and some of the errors resulted in needlestick injuries, question # 6, Novo Nordisk provided the following additional information:

- 11 participants did not set the dose correctly for their injection:

Of these participants, 9 participants experienced issues associated with device feedback with the dose counter. For example, the participant might have dialed the dose correctly i.e. 36 units but when attempting to inject the dose not realizing that there is a blocked needle, the dose counter did not show "0" but showed "28". Novo Nordisk reported that with the blocked needle condition, the dose counter may decrease up to a maximum 7 units due to internal compression inherent with pen injectors and cartridges. These were not aware of the block needle and how the dose counter behaves. The reviewer is concerned that the dose counter, which serves as a visual feedback to the users, can decrease up to a maximum of 7 units when the needle is blocked. In this case, the users were not aware and therefore misinterpreted that some insulin has been delivered because the number on the dose counter is less than what they originally set. However, in fact, no insulin was delivered. As a result, when users then tried to deliver what they think was the remaining amount, 28 units, which in fact it should have been 36, this could result underdosing, which could be clinically significant. While Novo Nordisk believes that the dose counter works properly i.e. it shows only set dose, and it is designed to return to "0" when a full dose has been delivered, the reviewer believes that these test findings demonstrated that the design of the dose counter as designed can be misleading and confusion. If no insulin is delivered, the dose counter display should show the originally set amount of insulin units. However, there appears to be some mechanical related issue that impacts the dose counter display that activates the dose counter to lead it to display a lower amount of insulin. The reviewer believes that since the dose counter serves as a useful feedback the users, the dose counter should be designed so

that it provides the correct number of units of insulin pre- and post-deliver taken into account block needle or other problems.
Of these participants, 1 participant did not know how to change the dose from 41 to 27 units because they did not know that it was possible to reverse dose. This would have resulted in an overdosing. This test finding demonstrated that training and/or instructions for use did not provide adequate mitigations to prevent these types of use errors.
Of these participants, 1 participant was confused by the instructions and delivered 2 units more than prescribed. The participant indicted that they read the instructions for priming the device and interpreted to mean that they should inject 2 units. This testing finding demonstrated that the instructions for use might have been confusing for this particular user, which resulted in an overdosing.
Of these participants, 1 participant inserted the needle with out setting a dose. It was unclear if this user received training and/or did review the IFU before use.
Of these participants, 1 participant delivered 48 units less than prescribed because there was the current pen was nearly empty. They did not know how to resolve this type of situation i.e. use a new pen to deliver a full dose, or use both pens to deliver a full dose (2 units from one pen and 48 units from another pen). This issue is discussed further in the immediate section below.
Overall, these test findings demonstrate that the device design, instructions for use, and training have not been optimized for the use of the product. The reviewer notes that Novo Nordisk proposed to make revisions to IFU. However, the reviewer believes that both the IFU and device design as well as training should be further optimized to address these issues, and that any additional mitigation will require validation.

- 9 participants miscalculated the second dose when using two pens

Of these participants, 1 child user did not know how to carry out the split dose task between two pens. Novo Nordisk reported that this participant was in-experienced and they were forced to perform a task which they had not performed before, where they would have received assistance. As a result the test administrator provided assistance, and a correct dose was delivered. Novo Nordisk argued that the test set up reflect actual use where when assistance was provided to a child user, the child was able to perform self-injection. The reviewer disagrees with this assessment. First, the test conditions and set up did not reflect actual use i.e. pairing of a child user and a parent/caregiver. Second, if child users are not expected to self-inject, they should not be asked to self-inject. The test set-up let the child user to first self-inject, and then noted that they had issues, where moderator's assistance was then provided to correct the issues. If children are not expected to self-inject, they should not self-inject, and this information should be made clear in both the device labeling/instructions for use as well as in communications to prescribing physicians.
Of these participants, 9 participants did not calculate correctly the proper dose for each of the two pens resulting in mis-dosing. Of these 9 participants, the majority did not realize that they mis-calculated and delivered incorrect dose.
Overall, these test findings demonstrate that many users can not perform the split dose calculations between two pens. The reviewer notes that Novo Nordisk proposed to make revisions to IFU.The reviewer believes that both the IFU and device design as well as training should be further optimized to address these issues, and that any additional mitigation will require validation.

- 2 participants did not hold the dose button down until it scales back to the 0 position

Novo Nordisk argued that there are existing mitigations such as visual (dose counter), audible (clicking sound), tactile (tapping sensation), and instructions for use, to minimize the occurrence of use errors. However, one participant misunderstood the dosing task three times, and did not hold the dose button down until the scale was back to "0". The reviewer notes that Novo Nordisk proposed to make revisions to IFU. However, the reviewer believes that both the IFU and device design as well as training should be further optimized to address these issues, and that any additional mitigation will require validation.

- 47 participants did not hold the needle in the skin for an appropriate amount of time (6 seconds)

In addition to waiting for the dose counter to scale back to "0", Novo Nordisk recommended that the needle should be held in the skin for 6 seconds to ensure that a full dose has been delivered. Novo Nordisk indicated that the 6 seconds hold time can be regarded as a safety precaution. Novo Nordisk also provided summarized data from dose accuracy testing, which did not clearly provide the necessary information in that it should show the amount of insulin delivered between 0-1 seconds, 1-2 seconds, 2-3 seconds, 3-4 seconds, 5-6 seconds, and >6 seconds. The reviewer believes that Novo Nordisk needs to decide whether the 6 second hold time is clinically relevant, and whether the high proportion of use errors reported should be of concerned. The reviewer notes that Novo Nordisk proposed to make revisions to IFU. However, if these user errors are clinically significant, Novo Nordisk will need to further optimize the design and/or IFU and training to address these issues, and that any additional mitigation will require validation.

- 8 participants experienced needlestick injuries

Novo Nordisk reported that in order to alert the user and make the user handle the pen-injector and needle in the most safe way possible to avoid needle sticks, statements and instructions are made in the IFU to mitigate this use error. However, participants continue to commit use errors that resulted in needlestick injuries. These test findings demonstrate that the either the Instructions for Use or the design of the device could be further optimized. he reviewer notes that Novo Nordisk proposed to make revisions to IFU only.

- 7 participants either did not remove the needle or reused the needle

Novo Nordisk reported that to mitigate these use errors, the IFU states to always use a new needle, and to always remove the used needle. If the user omits to change the needle and omits performing the required priming step, the user may be alerted that the needle is blocked, when attempting to inject the insulin dose, as the dose counter will not return to "0". Consequently, a series of mitigation steps have to be disregarded in order to not detect a blocked needle. However, participants continue to commit use errors. At this time the reviewer believes that in addition to Novo Nordisk's proposal to improve the IFU, the training program can be further optimized to educate users on the consequences of not removing the needle or reusing needles.

- 4 participants did not put the cap back on after use

Novo Nordisk reported that based on the results of forced degradation study, short term light exposure has no clinical relevant impact on the insulin. This response was found acceptable.

- 3 participants did not detect a blocked needle

Novo Nordisk reported that a blocked needle will be very unlikely to occur for a user, who uses a new needle for each injection and carefully attaches the needle as recommended in the training material. However, as previously discussed in relation to the dose setting task, the dose counter is not designed to account for the decrease up to a maximum of 7 units when the needle is blocked. The reviewer notes that Novo Nordisk proposed to make revisions to IFU. However, Novo Nordisk will need to further optimize the design and/or IFU and training to address these issues, and that any additional mitigation will require validation

- Close calls/Deviations

Regarding the close calls on participants did not hold dose button until scale was back to "0", and the close calls on blocked needle Novo Nordisk stated that the dose counter stops if the dosing is interrupted. This may aid the user in seeing the amount of missing units. It should be noted that the amount of unit displayed can be less than the set dose but that does not mean that the difference is the amount of the units have been delivered. It was noted that there was no subjective data provided from the perspective of the participants on how they perceived the close calls, and were able to correct themselves. The discussion focused on Novo Nordisk's assessment of those close calls.

Regarding FDA's question on its expectation and review of a validation report, question # 7, Novo Nordisk indicated that they will be making changes to the IFU to address the use errors. However, the reviewer believes based on the significant proportion of the use errors and the nature of the use errors, and the additional analysis provided by Novo Nordisk, in particular those associated with the dose counter mechanism, as well as other issues, the design of the device as well as training in addition to the proposed changes to IFU, would also need to be further optimized.

Evaluation of proposed Supplemental Human Factors study protocol to validate IFU changes

This section of the memo provides a review of Novo Nordisk's proposed supplemental Human Factors study protocol to validate IFU changes. In this study, Novo Nordisk seeks evidence that mitigations that have been implemented to the Degludec PDS290 pen-injector's instructions for use (IFU) reduce use errors and demonstrate that the PDS290 pen-injector is reasonably safe and effective for the intended users, uses, and use conditions. Such evidence, if found, is intended to address concerns stated in the FDA's December 23, 2011 response regarding use errors that occurred during a preceding usability test (PDS290-UT54-2011). Based on the FDA feedback, a human factors/usability evaluation was performed for the PDS290 pen-injector, IFU, carton label, and container label. It was determined that the PDS290 IFU should be updated within specific areas in order to mitigate specific use errors with the PDS290 peninjector. In addition, Novo Nordisk will generate an (b) (4).

Test Population

In the preceding usability test PDS290-UT54-2011, 5 distinct user groups were tested, namely health care professionals (HCPs), caregivers and three patient groups: children, adults and

elderly. The overall success rate for caregivers was similar to the adult patient population, whereas the HCP group success rate was higher. Consequently the proposed summative usability test for handling of the PDS290 pen-injector (UT86) includes 3 distinct user groups: Children with diabetes mellitus type 1 or type 2, 10-17 years of age, adults with diabetes mellitus type 1 or type 2, 18 to 64 years of age, and elderly with diabetes mellitus type 1 or type 2, _ 65 years of age.

Study Methodology
The supplemental summative usability test will include two parts.

- Part A will include up to 36 participants (18 children, 9 adults, and 9 elderly) who receive formal training on how to use the PDS290 pen-injector from a diabetes educator. As described in *Section 7: Participant Training*, [redacted] reviewing the IFU in detail. Part A participants will have the option to read the IFU and [redacted] before and while performing the hands-on tasks during the usability test session.
- Part B will include up to 18 untrained participants (9 adults and 9 elderly) who are required to read the IFU before starting the hands-on tasks (i.e., at the start of the test session). These participants will also be required (and reminded, as needed) to refer to the IFU before performing each hands-on task. [redacted], but the test administrator will not explicitly direct them to do so.

A delay between training and actual test will be built in the study. The test sessions will take place 2-32 hours after the end of the training session. Prior to administering the hands-on tasks, the test administrator will direct Part B (untrained) participants to review the IFU. The test administrator will provide Part A (trained) participants with the option to review the IFU. The hands-on portion of the test will require participants to perform four or five simulated injection tasks

After the participant completes (or attempts to complete) each task, [redacted] will ask him/ her to rate the ease of performing the task on a 1-7 scale (1 = poor, 7 = excellent). [redacted] will ask follow-up questions as needed to gain a full understanding of the root cause associated with any reported use errors, close calls, operational difficulties, and deviations. [redacted] will also seek to collect information regarding what the participant might have done differently (if anything) if performing the task at home.

The test administrator [redacted] Novo Nordisk will to perform a follow-up analysis of every use error, close call, and operational difficulty described in the usability test report. This analysis will determine if any of the interactive difficulties pose an unacceptable risk to device users. The analysis will also serve to determine whether any task failures occurred during testing.

Review Comments
The reviewer believes based on the significant proportion of the use errors and the nature of the use errors, and the additional analysis provided by Novo Nordisk, in particular those associated

with the dose counter mechanism, as well as other issues, the design of the device as well as training in addition to the proposed changes to IFU, should also be considered and should be further optimized. Novo Nordisk did not provide a rationale of why they believe the IFU changes and the proposed supplemental study will be adequate in addressing use-related issues identified in the prior study.

Furthermore, the reviewer notes that the methodology of proposed study does not represent realistic use i.e. participants will be forced read the IFU, and selected participants will receive training. Furthermore, the think aloud approach does not represent realistic way users would normally behave. This methodology was also employed in the prior study. The reviewer believes that these studies are more exploratory in nature where forced and unrealistic conditions are applied. In the Human Factors/usability validation study, the participants should use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, Novo Nordisk should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete. In addition the extent and level of training should be identical to the training that actual users will receive. Furthermore, the validation study requires that users across all users group be represented, and (b) (4) while performing simulated use.

Preliminary Response to Novo Nordisk's letter dated January 10, 2012, Proposed Questions to FDA (page 4 of 4)

Question 1: Does the Agency agree that the Usability Test Synopsis sufficiently addresses the FDA concerns and requests for validation of further optimization and would be adequate pending satisfactory outcome of the test to support approval of the PDS290 pen-injector?

Proposed Response: No, we do not agree. We believe that that the significant proportion of use errors, and the nature of the use errors, and the additional analysis that you provided, in particular those associated with the dose counter mechanism, as well as other issues, the design of the device as well as training in addition to the proposed changes to IFU, should also be considered and should be further optimized. You did not provide a rationale of why you believe the IFU changes and the proposed supplemental study will be adequate in addressing use-related issues identified in the prior study.

In addition, we have the following remaining concerns regarding your analysis of use errors, response to question # 6, FDA Information Request letter dated 23-DEC-2011.

- 11 participants did not set the dose correctly for their injection:

You reported that 9 participants experienced issues associated with device feedback with the dose counter. For example, the participant might have dialed the dose correctly i.e. 36 units but when attempting to inject the dose not realizing that there is a blocked needle, the dose counter did not show "0" but showed "28". You reported that with the blocked needle condition, the dose counter may decrease up to a maximum 7 units due to internal compression inherent with pen injectors and cartridges. However, the users were not aware of the block needle and how the dose counter functions. The Agency is concerned that the dose counter, which serves as a visual feedback to the users, can decrease up to a maximum

of 7 units when the needle is blocked. In this case, the users were not aware and therefore misinterpreted that some insulin has been delivered because the number on the dose counter is less than what they originally set. However, in fact, no insulin was delivered. As a result, when users then tried to deliver what they think was the remaining amount, 28 units, which in fact it should have been 36, this could result underdosing, which could be clinically significant. While the dose counter works properly, the Agency believes that these test findings demonstrated that the design of the dose counter as designed can be misleading and confusion.

Of these participants, 1 participant did not know how to change the dose from 41 to 27 units because they did not know that it was possible to reverse dose. This would have resulted in an overdosing. This test finding demonstrated that training and/or instructions for use did not provide adequate mitigations to prevent these types of use errors.

Of these participants, 1 participant was confused by the instructions and delivered 2 units more than prescribed. The participant indicted that they read the instructions for priming the device and interpreted to mean that they should inject 2 units. This testing finding demonstrated that the instructions for use might have been confusing for this particular user, which resulted in an overdosing.

Of these participants, 1 participant inserted the needle with out setting a dose. It was unclear if this user received training and/or did review the IFU before use.

Of these participants, 1 participant delivered 48 units less than prescribed because there was the current pen was nearly empty. They did not know how to resolve this type of situation i.e. use a new pen to deliver a full dose, or use both pens to deliver a full dose (2 units from one pen and 48 units from another pen). This issue is discussed further in the immediate section below.

Overall, these test findings demonstrate that the device design, instructions for use, and training have not been optimized for the use of the product. The Agency notes that you proposed to make revisions to IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

- 9 participants miscalculated the second dose when using two pens

Your reported that of these participants, 1 child user did not know how to carry out the split dose task between two pens. This participant was described to in-experienced and they were forced to perform a task which they had not performed before, where they would have received assistance. As a result the test administrator provided assistance, and a correct dose was delivered. You stated that the test set up reflect actual use where when assistance was provided to a child user, the child was able to perform self-injection. Please note that the Agency has a different perspective. First, the test conditions and set up did not reflect actual use i.e. pairing of a child user and a parent/caregiver. Second, if child users are not expected to self-inject, they should not be asked to self-inject. The test set-up let the child user to first self-inject, and then noted that they had issues, where moderator's assistance was then provided to correct the issues. If children are not expected to self-inject, they should not self-inject, and this information should be made clear in both the device labeling/instructions for use as well as in communications to prescribing physicians.

Of these participants, 9 participants did not calculate correctly the proper dose for each of the two pens resulting in mis-dosing. Of these 9 participants, the majority did not realize that they mis-calculated and delivered incorrect dose.

Overall, these test findings demonstrate that many users can not perform the split dose calculations between two pens. The Agency notes that you proposed to make revisions to IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

- 2 participants did not hold the dose button down until it scales back to the 0 position

You reported that there are existing mitigations such as visual (dose counter), audible (clicking sound), tactile (tapping sensation), and instructions for use, to minimize the occurrence of use errors. However, one participant misunderstood the dosing task three times, and did not hold the dose button down until the scale was back to "0". The Agency notes that you proposed to make revisions to IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

- 47 participants did not hold the needle in the skin for an appropriate amount of time (6 seconds)

In addition to waiting for the dose counter to scale back to "0", you recommended that the needle should be held in the skin for 6 seconds to ensure that a full dose has been delivered. You indicated that the 6 seconds hold time can be regarded as a safety precaution. In the same response, you also provided summarized data from dose accuracy testing, which did not clearly show the amount of insulin delivered between 0-1 seconds, 1-2 seconds, 2-3 seconds, 3-4 seconds, 5-6 seconds, and >6 seconds. Please decide whether the 6 second hold time is clinically relevant, and whether the high proportion of use errors reported should be of concerned. The Agency notes that you proposed to make revisions to IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

- 8 participants experienced needlestick injuries

You reported that in order to alert the user and make the user handle the pen-injector and needle in the most safe way possible to avoid needle sticks, statements and instructions are made in the IFU to mitigate this use error. However, participants continue to commit use errors that resulted in needlestick injuries. The Agency notes that you proposed to make revisions to IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

- 7 participants either did not remove the needle or reused the needle

You reported that to mitigate these use errors, the IFU states to always use a new needle, and to always remove the used needle. If the user omits to change the needle and omits performing the required priming step, the user may be alerted that the needle is blocked, when attempting to inject the insulin dose, as the dose counter will not return to "0". Consequently, a series of mitigation steps have to be disregarded in order to not detect a blocked needle. However, participants continue to commit use errors. The Agency notes that you proposed to make revisions to IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

- 3 participants did not detect a blocked needle

You reported that a blocked needle will be very unlikely to occur for a user, who uses a new needle for each injection and carefully attaches the needle as recommended in the training material. However, as previously discussed in relation to the dose setting task, the dose counter is not designed to account for the decrease up to a maximum of 7 units when the needle is blocked. The Agency notes that you proposed to make revisions to IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

CDRH Human Factors Review Recommendations

Please transmit the following comments to Novo Nordisk:

Question 1: Does the Agency agree that the Usability Test Synopsis sufficiently addresses the FDA concerns and requests for validation of further optimization and would be adequate pending satisfactory outcome of the test to support approval of the PDS290 pen-injector?

CDRH Human Factors Proposed Response: No, we do not agree based on our review of your response to our IR letter and the proposed test protocols for both NDAs, 203313 and 203314. The significant proportion of use errors, and the nature of the use errors that were previously identified, and the additional analysis that you provided, in particular those associated with the dose counter mechanism, as well as other reported issues, indicate that specific modifications are necessary that may not be limited to IFU. Furthermore, you did not provide a rationale or evidence that the IFU changes will adequately address the use-related issues in your prior study.

The proposed study is not acceptable as described since (b) (4) . This approach does not represent realistic use. (b) (4) These studies are more exploratory in nature (b) (4) . In the Human Factors/usability validation study, we expect that the participants to use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, you should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete. In addition the extent and level of training should be identical to the training that actual users will receive. Furthermore, the validation study requires that users across all users group be represented, (b) (4) while performing simulated use.

We continue to remain concerned based on your analysis of use errors specifically with the response that you provided to question # 6 to FDA Information Request letter dated 23-DEC-2011. Some of our concerns are highlighted below:

- 11 participants did not set the dose correctly for their injection:

You reported that 9 participants experienced issues associated with device feedback with the dose counter. For example, the participant might have dialed the dose correctly i.e. 36 units but when attempting to inject the dose not realizing that there is a blocked needle, the dose counter did not show "0" but showed "28". You reported that with the blocked needle condition, the dose counter may decrease up to a maximum 7 units due to internal

compression inherent with pen injectors and cartridges. However, the users were not aware of the block needle and how the dose counter functions. The Agency is concerned that the dose counter, which serves as a visual feedback to the users, can decrease up to a maximum of 7 units when the needle is blocked. In this case, the users were not aware and therefore misinterpreted that some insulin has been delivered because the number on the dose counter is less than what they originally set. However, in fact, no insulin was delivered. As a result, when users then tried to deliver what they think was the remaining amount, 28 units, which in fact it should have been 36, this could result underdosing, which could be clinically significant. The Agency believes that these test findings demonstrated that the design of the dose counter as designed can be misleading and confusion. In addition, patients would either over-compensate or under-compensate for the amount of insulin that they require for subsequent injections.

- 9 participants miscalculated the second dose when using two pens

Your reported that of these participants, 1 child user did not know how to carry out the split dose task between two pens. This participant was described to in-experienced and they were forced to perform a task which they had not performed before, where they would have received assistance. As a result the test administrator provided assistance, and a correct dose was delivered. You stated that the test set up reflect actual use where when assistance was provided to a child user, the child was able to perform self-injection. The test set-up let the child user to first self-inject, and then noted that they had issues, where moderator's assistance was then provided to correct the issues. If children are not expected to self-inject, they should not self-inject, and this information should be made clear in both the device labeling/instructions for use as well as in communications to prescribing physicians. In addition, of these participants, 9 participants did not calculate correctly the proper dose for each of the two pens resulting in mis-dosing. Of these 9 participants, the majority did not realize that they mis-calculated and delivered incorrect dose. Overall, these test findings demonstrate that many users can not perform the split dose calculations between two pens despite mitigations that are currently in placed.

- 47 participants did not hold the needle in the skin for an appropriate amount of time (6 seconds)

In addition to waiting for the dose counter to scale back to "0", you recommended that the needle should be held in the skin for 6 seconds to ensure that a full dose has been delivered. You indicated that the 6 seconds hold time can be regarded as a safety precaution. In the same response, you also provided summarized data from dose accuracy testing, which did not clearly show the amount of insulin delivered between 0-1 seconds, 1-2 seconds, 2-3 seconds, 3-4 seconds, 5-6 seconds, and >6 seconds. Please decide whether the 6 second hold time is clinically relevant, and a rationale for why the high proportion of use errors reported should be of concerned.

- 8 participants experienced needlestick injuries

You reported that in order to alert the user and make the user handle the pen-injector and needle in the most safe way possible to avoid needle sticks, statements and instructions are made in the IFU to mitigate this use error. However, participants continue to commit use errors that resulted in needlestick injuries indicating that current mitigations are not effective.

- 7 participants either did not remove the needle or reused the needle

You reported that to mitigate these use errors, the IFU states to always use a new needle, and to always remove the used needle. If the user omits to change the needle and omits performing the required priming step, the user may be alerted that the needle is blocked, when attempting to inject the insulin dose, as the dose counter will not return to "0". Consequently, a series of mitigation steps have to be disregarded in order to not detect a blocked needle. However, participants continue to commit use errors indicating that current mitigations are not effective.

- 3 participants did not detect a blocked needle

You reported that a blocked needle will be very unlikely to occur for a user, who uses a new needle for each injection and carefully attaches the needle as recommended in the training material. However, as previously discussed in relation to the dose setting task, the dose counter is not designed to account for the decrease up to a maximum of 7 units when the needle is blocked.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.

Appendix C: Review of Applicant's Evaluation of Prior Human Factors Report (Dated June 29, 2011)

Review Materials

Links to submissions:
\\CDSESUB5\EVSPROD\NDA203314\203314.enx
\\CDSESUB5\EVSPROD\NDA203313\203313.enx
Sequence 0000 (original submission, part 1, quality, 3.2.P drug product, 3.2.P.7. Container Closure System)

CDRH Human Factors Review

Device Description

Insulin degludec is an ultra-long-acting basal insulin. Insulin degludec is intended for treatment of diabetes mellitus. Insulin degludec is administered once-daily at any time of the day, independent of meals, and is injected subcutaneously (s.c.) in the thigh, the upper arm or the abdominal wall.

For patients with type 2 diabetes mellitus, the recommended daily starting dose of insulin degludec is 10 units, followed by individual dosage adjustments. For patients with type 1 diabetes mellitus, insulin degludec is to be used once-daily with meal-time insulin and requires subsequent individual dosage adjustments. Insulin degludec has been developed in two strengths as insulin degludec 100 U/ml and insulin degludec 200 U/ml.

- Insulin degludec 100 U/ml is intended to be marketed (b) (4) as a pre-filled disposable PDS290 pen-injector with a dose range of 1-80 U/injection, which can be dialled in 1 U increments.
- Insulin degludec 200 U/ml is intended for the market in a pre-filled disposable PDS290 pen-injector with a dose range of 2-160 U/injection, which can be dialled in 2 U increments.

Volume and Strength

Formulation	Total volume in cartridge	Strength	Total units available in presentation	Max dose per injection	Dose increment
Insulin Degludec U100	3 mL	100 U/mL	300 U	80 U	1 U
Insulin Degludec U200	3 mL	200 U/mL	600 U	160 U	2 U
Insulin Degludec/Insulin Aspart	3 mL	100 U/mL	300 U	80 U	1 U

Figure 1: Insulin Degludec (100 U/mL) pen-injector (left), Insulin Degludec(200 U/mL) peninjector (centre) and Insulin Degludec/Insulin Aspart (100 U/mL) pen-injector (right). Pens are shown without caps.

PDS290 is a pen-shaped, prefilled device containing (b) (4) insulin. Therefore the drug is not in contact with the device. The device is intended to function with a (b) (4) needle

(b) (4). The PDS290-pen injector is currently approved by FDA for use with growth hormone (Norditropin FlePro).

PDS290 physical characteristics:

(b) (4)

PDS290 was developed to fulfil the international standard for drug injectors, ISO 11608-1 (Peninjectors for medical use - Part1: Requirements and test methods).
The design of the pen-injector enables the users to always have a display of the chosen amount of insulin units selected for injection, independent of drug concentration.

The PDS290 is different than the FlexPen regarding the following features:

- (b) (4)
-

Compared to FlexPen®, some of the new features of the PDS290 pen-injector are:

- (b) (4)
-
-
-
-
-
-

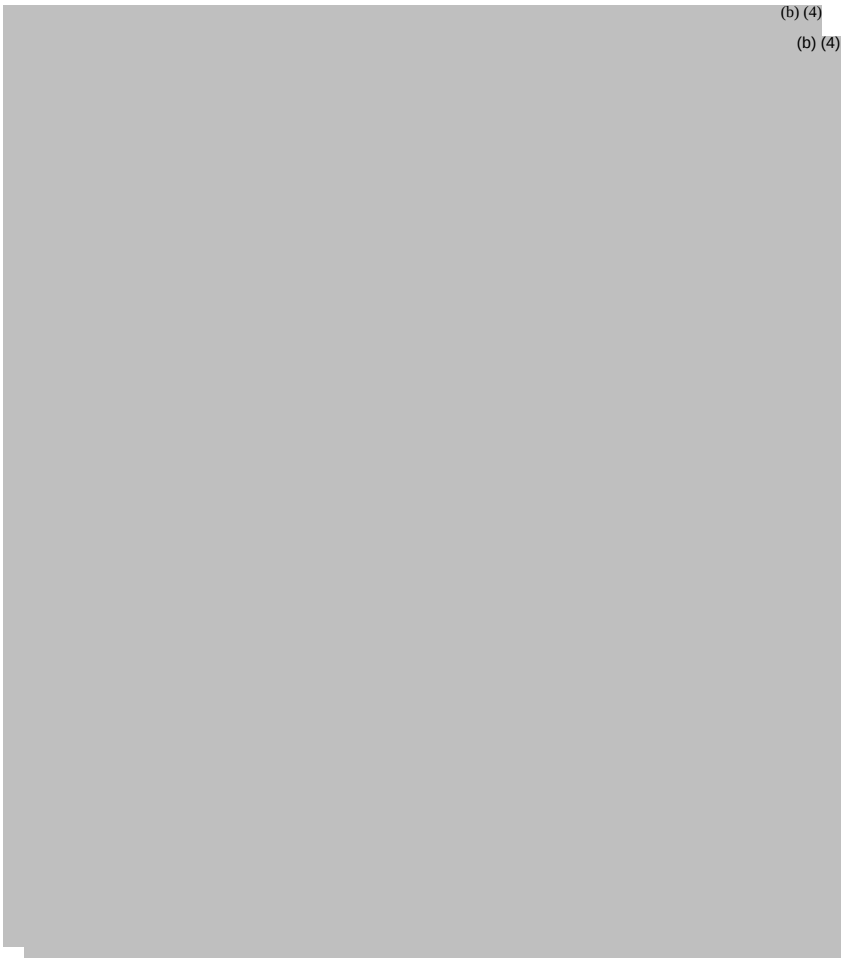


Figure 4: Exploded View of Internal Device Components

Summary of Human Factors Information

The sponsor submitted two main documents for Human Factors review:

- Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011)
- Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011)

The device will be used in the home environment and hospital setting. Training is required for use with the product including identifying insulin variant(s). Once prescribed, the users can inject themselves or are injected by a caregiver.

To prepare the pen-injector, a new needle is mounted by the user and the pen-injector is primed, thereafter the intended dose is set by rotating the dose selector clockwise (when looking directly at the PDS290 pen-injectors' dose button) until the required dose is visible in the display. The dose button does not protrude from the PDS290 pen-injector when dialling the dose selector. Dose delivery is accomplished by inserting the needle subcutaneously and pressing the dose button. During dose delivery, the PDS290 pen-injector (b) (4) . A distinct end-of-dose-click indicates when the display has returned to "0" (The clicks are only a supportive feedback). The full dose is delivered when the needle has been kept inserted into the skin at least 6 seconds after the display has returned to "0". The "6

second" duration is a conservative approach, and that exact duration is not safety critical, from a medical perspective provided that the timing is kept below 6 seconds, as the PDS290 pen-injector is within the dosage requirements, in accordance with ISO 11608-1 before the "6 second" duration.

When performing an injection with the PDS290 pen-injector, the following user steps/primary operation functions must be carried out.
Step 1: Pick the correct PDS290 carton/pen-injector with the intended insulin product
Step 2: Cap removal
Step 3: Verification via label and cartridge holder that it is the correct pen
Step 4: Check that the insulin in the pen-injector is clear and colourless
Step 5: Needle mounting
Step 6: Checking the insulin flow (priming)
Step 7: Setting intended dose (reversing the dose setting, if necessary)
Step 8: Understand the End-of-content indication (feature ensuring that no larger dose can be dialled than is left in the cartridge)
    o This step only applies if the user is going to inject a dose larger than the remaining left in cartridge
Step 9: Subcutaneous needle insert
Step 10: Injecting the dose, including checking that scale drum returns to "0", and 6 seconds waiting time with needle in the skin, that is, full dose has been delivered
Step 11: Needle removal and disposal of used needle
Step 12: Cap mounting

The intended users of the pen-injector include patients, caregivers and healthcare professionals. There are five distinct user groups:

- Children (age 10 to 17) who self inject without a parent's involvement. 15 participants were included in the study.
- Adults (age 18 to 64) who self-inject. 25 participants were included in the study.
- Elderly (age 65 and older) who self-inject. 21 participants were included in the study.
- Caregivers (age 18 to 64) who perform injections on others, such as young children, spouses and elderly. 22 participants were included in the study.
- Healthcare professionals who provide injection pen prescriptions and teach others how to perform injections. 22 participants were included in the study.

The sponsor noted the following potential User Impairment:

- The PDS290 pen-injector should not be used by people, who are blind or have severe visual problems, but should be assisted by a person who has functional eyesight and is trained to use the PDS290 pen-injector
- Dexterity and freedom to move arm/hand (left or right) to be capable of holding/dialling/dosing the PDS290 pen-injector is required

The testing included use scenarios which can result in potential hazards:
Scenario 1 – The user does not receive the correct insulin due to a mix-up

This scenario includes the hazards where the user does not receive or select his prescribed insulin due to a mix-up, which potentially can lead to medication errors. The hazard can take place when the product is dispensed e.g. at the pharmacy or at product selection in the home environment.
Scenario 2 – The user does not use the pen-injector as described in IFU
This scenario includes the hazards taking place in the normal use environment.

The following table/flowchart shows the methodology for training and testing different user groups.

DEGLUDEC overview of introduction/training and tests

	Children (age 10 to 17) who self inject without a parent's involvement. We are treating children as a distinct user population because their intellectual development and motor skills may be substantially different from adults in ways that could influence how they interact with a pen-injector.		**Adults (age 18 to 64)** who self inject. **Elderly (age 65 and older)** who self inject. Establishing this distinct user group recognises that there might be a substantial difference in the ability of elderly individuals, some of whom might have impairments, to interact effectively with a pen□injector as compared to people who are younger. **Caregivers (age 18 to 64)** who perform injections on others, such as young children, spouses and elderly.							**Healthcare professionals** who provide injection pen prescriptions and teach others how to perform injections. We have placed all of these individuals into a single group because they have clinical training (suggesting good aptitude when it comes to interacting with medication delivery pen injectors) and interact with pen injectors in a professional capacity.				
	Introduced/Trained		**Introduced/Trained**				**Untrained**			**Introduced/ Trained**		**Untrained**		
	Pen naive (non pen users)	**Current pen users**	**Pen naive (non pen users)**		**Current pen users**		**Pen naive (non pen users)**		**Current pen users**	**HCP except phamacists**		**HCP except phamacists**		**Pharmacists**
Differentiation														
Introduction to differentiation	X	X	X	X	X	X	No	No	No	No	No	No	No	No
Differentiation test, Pen-injector	X	X	X	X	X	X	No	No	No	No	No	No	X	No
Differentiation test, Carton	X	X	X	X	X	X	No	No	No	No	No	No	X	X
Handling														
Baseline, handling	No	X	No	No	X	X	No	X	X	X	X	X	X	No
Forced reading of IFU	No	No	No	X	No	X	X	No	X	No	X	X	No	No
Training, handling	X	X	X	X	X	X	No	No	No	X	X	No	No	No
Handling test	X	X	X	X	X	X	X	X	X	X	X	X	X	No

Review Comments
I have reviewed both documents and have several concerns.

Two separate studies were conducted: user differentiation and user handling. Each study consisted of the same group of 105 participants. Based on the above table, it is not clear why under the adults subgroup, the untrained participants did not undergo the differentiation evaluation. In addition, under the HCP subgroup, the trained HCP did not undergo the differentiation evaluation.

Also, the following items could not be located for review:

- A breakdown of the number of participants for the different user groups, trained and untrained. Include in this breakdown, the number of participants with visual, dexterity, and hearing impairment.
- A rationale for determining who should be receiving training, and who should not among the intended users
- A rationale for [redacted] (b) (4) is an approach that represents realistic use

The Agency understands that diabetic patients have medical symptoms such as retinopathy and neuropathy, and these symptoms are progressively worsening over time. Therefore, each medical symptom represents unique user profiles that can impact safe and effective use of the product. As a result, the study participants should consist of at least 15 diabetic patients with retinopathy and 15 diabetic patients with neuropathy.

In addition, in reviewing the UT54 final report, version 2, it appears that none of the devices used for the testing was the modified device [redacted] (b) (4) Flextouch). A discrepancy was also noted between the number of reported errors in the UT54 final report, and summary report (Validation of Device Use).

Regarding the study results for both studies, I have the following specific concerns:

User Differentiation Study:
The study reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions. Two participants had negative transfer from their use experience with other similar products, and one participant could not identify the green color carton.
The study also reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions, and this same participant committed three errors with the previous task of selecting the correct carton.

The Instructions for Use (IFU) does include a statement to have users check the [redacted] (b) (4) label. Based on the risk analysis if undetected when a patient injects a different type of insulin other than intended, the clinical outcome can be hypoglycemia or hyperglycemia. There are different use scenarios for which this hazard exists. Either the pharmacists/HCP chooses the wrong carton and dispenses to the patients, and the patient does not recognize the wrong insulin carton; or the patient has more than one type of insulin available, and the patient chooses the wrong carton. The results are not clear in terms of which user group (children/adult/cargiver/HCP) the three participants were part of.

It is concerning to the reviewer that not all users are able successfully complete these two tasks and that serious clinical impact can occur. The reviewer is concerned that participants were not able to identify the carton and pen-injector with the correct insulin despite the use of colors and instructions provided in the IFU, and therefore the risks associated with these aspects of use are not successfully mitigated. The reviewer believes that further design optimization can be done the pen label to clearly identify the insulin type, and the dose.

User Handling Study
A discrepancy was noted between the Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) report and test report PDS290-UT54-2011. The test report PDS290-UT54-2011 provided in several tables a listing of different types of injectors (FlexPen, KwikPen, SoloStar), and various baseline tasks. It was not clear if the product used for the final validation study represented the commercial product of the (b) (4) product.

The Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) reported 94 of 105 participants committed 226 errors across tasks associated with delivering an injection and some of the errors resulted in needle-prick injuries. The reviewer is most concerned with the following findings. Of the 105, participants,

- 11 participants did not set the dose correctly for their injection resulting in 12 use errors.
- 9 participants miscalculated second dose when using two pens resulting in 9 use errors.
- 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors
- 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors
- 7 participants either did not remove the needle or reuse the needle resulting in 10 use errors
- 8 participants experienced needle prick injuries resulting in 10 use errors
- 4 participants did not put the cab back on after use resulting in 4 use errors
- 3 participants did not detect blocked needle resulting in 3 use errors

Most of the use errors can result in underdosing, or when users not able to set the correct dose, can result in overdosing. Other use errors can result in needle-prick injuries, contamination, and infection. The sponsor provided some root cause analysis along with the position that the current mitigations are effective and that the residual risks are minimal. However, to fully assess the extent of the use errors, additional clarification is necessary for the following items:

- For the use errors associated with 11 participants did not set the dose correctly for their injection resulting in 12 use errors, the narrative provided in the root cause analysis section was not clear on how the use error occurred among the sequence of use interaction steps, and what "visual feedback" the users received or did not receive from the device. The report indicated that 7 of the use errors occurred after other use errors that previously occurred i.e. users neglected the priming step, or attempted to inject with a blocked needle. It was also not clear if any of the users recognize that a full dose has not been delivered, and what aspect of the device designed allowed them to do so. The sponsor should be asked to provide a side by side comparison of the correct injection sequence versus the sequence for which all of the use errors occurred, and to clearly describe how the user errors occurred along with screen shots of the device status at each of the steps, subjective feedback from users on the root cause of the use errors, and to indicate which of these participants ultimately delivered/did not deliver a correct dose. The sponsor will need to provide a clarification on the "visual feedback" and clarification on the clinical significance of the one participant who injected both a priming dose and a prescribed dose. It appeared that one participant committed the error twice but the report did not provide details on this participant. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence

demonstrating that the device can be used safely and effective. The sponsor should provide a table that clearly describe for each of the use errors, the sponsor should indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement the to device design will not fully mitigate those use related risks.

- For the use errors associated with 9 participants miscalculated second dose when using two pens resulting in 9 use errors, the report indicated that one use error was associated with one 10-year old participant found the instructions to be confusion, failed the split dose task and was assisted by the moderator. A discrepancy was noted in the sponsor's assessment of this use error. The sponsor stated in the report that in real-life situation, a 10 year-old child may perform the injection but never have the full responsibility for insulin administration. However, in the Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011), the sponsor stated that Children (age 10 to 17) are considered as part of the 5 distinct user groups, who self inject without a parent's involvement. Since the report showed that a representative test user in the children subgroup could not successfully perform an injection, and since they represent a group where special considerations should be incorporated in the design of the product, the reviewer recommends that this use-related risk be fully mitigated. In addition, the remaining 8 use errors did not the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. The report remained unclear in terms of which of these participants ultimately delivered/did not deliver a correct dose. The sponsor should be asked to provide information that address the above concerns.
- For the use errors associated with 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors, the reviewer notes that this is a critical task in ensuring that the patients receive a full dose of intended insulin. One participant repeatedly misunderstood the dosing task three times, and believed that by simply activating the dose button but did not hold the dose button down until the dose counter returned to 0. Another participant did not hold the dose button down. While there were only two participants who committed this use error, the clinical impact is significant in that the patients would not receive a full dose. It is also not clear if these two participants held the needle in the skin for the 6 seconds task. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.
- For the use errors associated with 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors, the sponsor indicated that dose accuracy testing showed that a full dose is delivered 1 second after the dose counter returns to "0" with the needle remains in the skin. However, 123 of the 171 use errors, the needle was removed 1 second or more, and 48 of the 171 use errors occurred when the needle was removed less than 1 second, which resulted in underdosing. It is unclear to reviewer why the sponsor specified that the needle should be held in the skin for 6 seconds, but stated that dose accuracy testing demonstrated that a full dose can be delivered 1 second after the dose counter returns to "0." The report did not include the necessary subjective data that are focused on identifying the root cause of the failures and

potential design improvements recommendations from the perspective of representative users. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

- For the use errors associated with 8 participants experienced needle prick injuries resulting in 10 use errors, the reviewer believes that needle prick injuries can result in patient harm during use with the product and requests that the sponsor optimize the IFU and training to minimize the rate of occurrence of needle prick injuries.
- For the use errors associated with 7 participants either did not remove the needle from the device or reuse the needle resulting in 10 use errors, the sponsor stated that these tasks are incorporated in the use of the product to prevent blocked needles, contamination, infection, and inaccurate dosing. Four participants committed 4 use errors in not removing the needle from the device, and 3 participants committed 3 use errors in reusing previously inserted needle. Again, please note that stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. Since these use errors can result in negative impact to the patients, the sponsor should provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.
- For the use errors associated with 4 participants did not put the cab back on after use resulting in 4 use errors, the sponsor stated these errors can result in underdosing. It is not clear how degradation caused by exposure to sunlight due to cap not mounted after use can result in underdosing. Furthermore, it is not clear what is the clinical impact of patients injecting insulin that has been degraded, and how would the patient detect that the insulin has been degraded. The reviewer believes the device user interface can be further optimized to improve use performance.
- For the use errors associated with 3 participants did not detect blocked needle resulting in 3 use errors , the sponsor stated that the resulting harm is that patient may miss a dose. It is not clear if the pen-injector provides any feedback to user in this situation, and whether or not the users recognize that they did not receive any insulin. The sponsor also clarified that the block needle task is an experimental artifact because in real life, the blocked needle only occurs if a patient reuses a needle or uses a defective needle. The testing showed that indeed 3 participants opt to reuse the needles, and therefore it is not an experimental artifact. The sponsor should indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement the to device design will not fully mitigate those use related risks.

The sponsor also reported deviations (page 95 of 102), and close calls (page 96 of 102). While these are “deviations” and “close-calls” that did no result in medical consequences, the sponsor did not discuss how users were able to recognize the potential failures and what steps they took correct themselves. The sponsor should include in their discussion how the design of the device and its labeling influenced the patient’s behavior for self-correction.

CDRH Human Factors Recommendations

Two separate studies were conducted: user differentiation and user handling. Each study consisted of the same group of 105 participants. Please address the following for both NDA submissions (NDA 203313 and 203314):

1. Based on the table provided on page 40 of the Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011), it is not clear to the Agency why under the adults subgroup, the untrained participants did not undergo the differentiation evaluation. In addition, under the HCP subgroup, the trained HCP did not undergo the differentiation evaluation.

2. Also, the following items could not be located for review, and should be submitted for review:
   - A breakdown of the number of participants for the different user groups, trained and untrained. Include in this breakdown, the number of participants with visual, dexterity, and hearing impairment.
   - A rationale for determining who should be receiving training, and who should not among the intended users
   - A rationale for (b) (4) is an approach that represents realistic use

3. The Agency understands that diabetic patients have medical symptoms such as retinopathy and neuropathy, and these symptoms are progressively worsening over time. Provide a justification for why test participants included in the study adequate representation of the intended user group.

Regarding the study results for both studies, please address the following specific concerns:

User Differentiation Study:

4. The study reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions. Two participants had negative transfer from their use experience with other similar products, and one participant could not identify the green color carton. The study also reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions, and this same participant committed three errors with the previous task of selecting the correct carton.

   The Instructions for Use (IFU) does include a statement to have users check (b) (4) label. Based on the risk analysis if undetected when a patient injects a different type of insulin other than intended, the clinical outcome can be hypoglycemia or hyperglycemia. There are different use scenarios for which this hazard exists. Either the pharmacists/HCP chooses the wrong carton and dispenses to the patients, and the patient

does not recognize the wrong insulin carton; or the patient has more than one type of insulin available, and the patient chooses the wrong carton. The results are not clear in terms of which user group (children/adult/cargiver/HCP) the three participants were part of.

It is concerning to the Agency that not all users are able successfully complete these two tasks and that serious clinical impact can occur. The Agency is concerned that participants were not able to identify the carton and pen-injector with the correct insulin despite the use of colors and instructions provided in the IFU, and therefore the risks associated with these aspects of use are not successfully mitigated. The Agency believes that further design optimization can be done the pen label to clearly identify the insulin type, and the dose.

User Handling Study

5. A discrepancy was noted between the Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) report and test report PDS290-UT54-2011. The test report PDS290-UT54-2011 provided in several tables a listing of different types of injectors (FlexPen, KwikPen, SoloStar), and various baseline tasks. It was not clear if the product used for the final validation study represented the commercial product of the (b) (4) product.

6. The Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) reported 94 of 105 participants committed 226 errors across tasks associated with delivering an injection and some of the errors resulted in needle-prick injuries. The Agency is most concerned with the following findings. Of the 105, participants,
   - 11 participants did not set the dose correctly for their injection resulting in 12 use errors.
   - 9 participants miscalculated second dose when using two pens resulting in 9 use errors.
   - 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors
   - 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors
   - 7 participants either did not remove the needle or reuse the needle resulting in 10 use errors
   - 8 participants experienced needle prick injuries resulting in 10 use errors
   - 4 participants did not put the cab back on after use resulting in 4 use errors
   - 3 participants did not detect blocked needle resulting in 3 use errors

   Most of the use errors can result in underdosing, or when users not able to set the correct dose, can result in overdosing. Other use errors can result in needle-prick injuries, contamination, and infection. You provided some root cause analysis along with the position that the current mitigations are effective and that the residual risks are minimal. However, to fully assess the extent of the use errors, additional clarification is necessary for the following items:
   a. For the use errors associated with 11 participants did not set the dose correctly for their injection resulting in 12 use errors, the narrative provided in the root cause

analysis section was not clear on how the use error occurred among the sequence of use interaction steps, and what "visual feedback" the users received or did not receive from the device. The report indicated that 7 of the use errors occurred after other use errors that previously occurred i.e. users neglected the priming step, or attempted to inject with a blocked needle. It was also not clear if any of the users recognize that a full dose has not been delivered, and what aspect of the device designed allowed them to do so. Please address the above concerns and provide a side by side comparison of the correct injection sequence versus the sequence for which all of the use errors occurred, and to clearly describe how the user errors occurred along with screen shots of the device status at each of the steps, subjective feedback from users on the root cause of the use errors, and to indicate which of these participants ultimately delivered/did not deliver a correct dose. Please also provide a clarification on the "visual feedback" and clarification on the clinical significance of the one participant who injected both a priming dose and a prescribed dose. It appeared that one participant committed the error twice but the report did not provide details on this participant. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective.

b. For the use errors associated with 9 participants miscalculated second dose when using two pens resulting in 9 use errors, the report indicated that one use error was associated with one 10-year old participant found the instructions to be confusion, failed the split dose task and was assisted by the moderator. A discrepancy was noted in your assessment of this use error. You stated in the report that in real-life situation, a 10 year-old child may perform the injection but never have the full responsibility for insulin administration. However, in the Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011), you stated that Children (age 10 to 17) are considered as part of the 5 distinct user groups, who self inject without a parent's involvement. Since the report showed that a representative test user in the children subgroup could not successfully perform an injection, and since they represent a group where special considerations should be incorporated in the design of the product, the reviewer recommends that this use-related risk be fully mitigated. In addition, the remaining 8 use errors did not the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. The report remained unclear in terms of which of these participants ultimately delivered/did not deliver a correct dose. Please provide additional information that addresses the above concerns.

c. For the use errors associated with 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors, the Agency notes that this is a critical task in ensuring that the patients receive a full dose of intended insulin. One participant repeatedly misunderstood the dosing task three times, and believed that by simply activating the dose button but did not hold the dose button down until the dose counter returned to 0. Another participant did not hold

the dose button down. While there were only two participants who committed this use error, the clinical impact is significant in that the patients would not receive a full dose. It is also not clear if these two participants held the needle in the skin for the 6 seconds task. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

d. For the use errors associated with 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors, you indicated that dose accuracy testing showed that a full dose is delivered 1 second after the dose counter returns to "0" with the needle remains in the skin. However, 123 of the 171 use errors, the needle was removed 1 second or more, and 48 of the 171 use errors occurred when the needle was removed less than 1 second, which resulted in underdosing. It is unclear to reviewer why the sponsor specified that the needle should be held in the skin for 6 seconds, but stated that dose accuracy testing demonstrated that a full dose can be delivered 1 second after the dose counter returns to "0." The report did not include the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.
e. For the use errors associated with 8 participants experienced needle prick injuries resulting in 10 use errors, the Agency is concerned with needle prick injuries associated with the use of this product and requests that you optimize the design and/or IFU and training to minimize the rate of occurrence of needle prick injuries.
f. For the use errors associated with 7 participants either did not remove the needle from the device or reuse the needle resulting in 10 use errors, you stated that these tasks are incorporated in the use of the product to prevent blocked needles, contamination, infection, and inaccurate dosing. Four participants committed 4 use errors in not removing the needle from the device, and 3 participants committed 3 use errors in reusing previously inserted needle. Again, please note that stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. Since these use errors can result in negative impact to the patients, please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

g. For the use errors associated with 4 participants did not put the cab back on after use resulting in 4 use errors, the sponsor stated these errors can result in underdosing. It is not clear how degradation caused by exposure to sunlight due to cap not mounted after use can result in underdosing. Furthermore, it is not clear what is the clinical impact of patients injecting insulin that has been degraded, and how would the patient detect that the insulin has been degraded. The Agency believes the device user interface can be further optimized to improve use performance.

h. For the use errors associated with 3 participants did not detect blocked needle resulting in 3 use errors , you stated that the resulting harm is that patient may miss a dose. It is not clear if the pen-injector provides any feedback to user in this situation, and whether or not the users recognize that they did not receive any insulin. You also provided a clarification that the block needle task is an experimental artifact because in real life, the blocked needle only occurs if a patient reuses a needle or uses a defective needle. The testing showed that indeed 3 participants opt to reuse the needles, and therefore it is not an experimental artifact. Please indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement the to device design will not fully mitigate those use related risks.

i. You also reported deviations (page 95 of 102), and close calls (page 96 of 102). While these are "deviations" and "close-calls" that did no result in medical consequences, you did not provide a discussion of how users were able to recognize the potential failures and what steps they took correct themselves. Please provide in your discussion how the design of the device and its labeling influenced the patient's behavior for self-correction.

7. Please note that the Agency expects to review a report of the human factors/usability evaluation and validation testing with any pattern of use errors, and a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions can be determined based on the test results. At this time, the Agency is concerned with that your testing did not provide the level of evidence to conclude that the device can be used safely and effectively. The Agency recommends that you take the results of these evaluations and use them to further optimize the training, IFU and/or device user interface so that use errors are effectively minimized. Please note that improvements should be demonstrated through focused HF/usability validation.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management,* available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460 htm. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748 htm.

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

/s/

RACHEL E HARTFORD

02/05/2013

on behalf of QuynhNhu Nguyen
Biomedical Engineer/Human Factors Reviewer
CDRH/ODE/DAGID

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 203313 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Ryzodeg Established/Proper Name: insulin degludec/insulin aspart [rDNA origin) Dosage Form: injection Strengths: 100 U/mL		
Applicant: Novo Nordisk Agent for Applicant (if applicable):		
Date of Application: 29Sep11 Date of Receipt: 29Sep11 Date clock started after UN:		
PDUFA Goal Date: 29July12 *Note: the PDUFA Goal Date was changed to 29Oct12 due to a major amendment.*	Action Goal Date (if different): 27July12 *Note: At the time of filing of the application, the action goal date was 27July 12. However, at the time of archival of this filing review, the action goal date is 08Feb13..*	
Filing Date: 28Nov11	Date of Filing Meeting: 18Nov11	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1, 4		
Proposed indication(s)/Proposed change(s): treatment of diabetes mellitus		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 073198 & IND 076496	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***		X		

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		Requested in 74day letter

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***		X		Requested in 74day letter
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***		X		Requested in 74day letter
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	X			
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			CDRH 10/20/11
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 02/24/09 ***If yes, distribute minutes before filing meeting***	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 06/17/11 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/18/11

BLA/NDA/Supp #: NDA 203313

PROPRIETARY NAME: Ryzodeg

ESTABLISHED/PROPER NAME: insulin degludec/ insulin aspart

DOSAGE FORM/STRENGTH: injection, 100 Units/mL

APPLICANT: Novo Nordisk

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of DM

REVIEW TEAM:
NDA 203313 Ryzodeg (insulin degludec/insulin aspart)
Clinical - Jean Marc Guettier
Pharm Tox - Miyun Tsai-Turton
RPM - Rachel Hartford
Clincal Pharmacology - Ritesh Jain
CMC - Muthukumar Ramaswamy
Stats - Dongmei Lui

NDA 203314 Tresiba (insulin degludec)
Clinical - Jean Marc Guettier
Pharm Tox - Miyun Tsai-Turton
RPM - Rachel Hartford
Clinical Pharmacology - Manoj Khurana
CMC - Joe Leginus
Stats - Cynthia Liu

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Rachel Hartford	Y
	CPMS/TL:	Enid Galliers	Y
Cross-Discipline Team Leader (CDTL)	Hylton Joffe		Y
Clinical	Reviewer:	Jean Marc Guettier	Y
	TL:	Hylton Joffe	Y

Clinical Pharmacology	Reviewer:	Ritesh Jain	Y
	TL:	Jaya Vsidyanathan	Y
Biostatistics	Reviewer:	Dongmei Lui	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Miyun Tsai-Turton	Y
	TL:	Karen Davis Bruno	Y
Product Quality (CMC)	Reviewer:	Muthukumar Ramaswamy	Y
	TL:	Su Tran	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Vinny Pawar	Y
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: ***the application did not raise significant safety or efficacy issues***
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Curtis Rosebraugh

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: **Filing/Planning Meeting Agenda**

1. Important dates

   Filing Review Templates in DARRTS: 21Nov11

   Filing Date: 28Nov11

   Day 74 Letter Date: 12Dec11

2. Discipline Overview of Application: **Team members come to the meeting prepared with completed filing review checklists (which have TL concurrence).** This preparation is critical to a focused discussion on filing, needed information requests, and review issues. **Communicate with other team members, including the project manager and team leader as soon as problems are identified.**

   Each reviewer makes a presentation on the high-level contents and fileability of their review section and presents findings thus far. During the meeting, each reviewer discusses the relevant content of the application covering the following:

   - A summary of the application
   - Any special issues
   - A description of any material needed for the review not included in the application
   - Any deficiencies that may warrant a refusal to file decision
   - Other substantive deficiencies that may have an impact on review completion or

application approval(to be transmitted in the Filing Communication)

- Issues that merit advisory committee input (goal: month 7-8)
- Need for any additional consult reviews or inspections

Enter discipline filing review templates into DARRTS by 21Nov11.

a. CMC
b. P/T
c. Clin Pharm
d. Clinical
e. Stats
f. OSI
g. Micro
h. CDRH (Device and Human Factors)
i. Labeling (DMEPA, DRISK, DDMAC)

3. Reach agreement on filing decision

4. Review Time Line

13Apr12 Consult Reviews (CDRH & DMEPA)

07May12 Substantially Complete PI to DRISK

01Jun12 Primary Reviews
01Jun12 Wrap up Meeting

08Jun12 Secondary Reviews
08Jun12 Send labeling/PMC/PMR/REMS (1week TAT for labeling)

15Jun12 CDTL Review
15Jun12 Begin labeling discussions with Novo Nordisk
15Jun12 Compile and circulate action letter and package

06Jul12 Division Director review

06Jul12 Action Letter and Package to Office Director

27Jul12 Office Director review and sign-off (Action Goal Date)

5. Meetings

20Jan12 Team Meeting

28Feb12 Mid-Cycle Review

24Apr12 Team Meeting

01Jun12 Wrap up Meeting

05Jun12 Labeling Meeting

28Jun12 Labeling Meeting

12Jul12 Labeling Meeting

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
	ACTIONS ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review:

	• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74 **Clinical** 1. You reference your December 21, 2010, background package and our March 21, 2011, advice letter but this approach does not adequately address in the NDA how you plan to fulfill the requirements of the Pediatric Research Equity Act (PREA). See "Required Pediatric Assessments" below. **Chemistry, Manufacturing, and Controls** 2. Clarify what the reference is for the units of the dosage strength (b) (4). In the proposed drug product specification, the content of insulin degludec in the formulation is measured as "nmol", and you state that 100 (b) (4) corresponds to 600 nmol/ml. Provide a reference for the units of the dosage strength (b) (4)", comparable to that submitted for your insulin detemir product (i.e., one unit (24 nmol) of insulin detemir corresponds to one IU of human insulin (6 nmol) based on clinical data). 3. Clarify how your proposed dosage strength of 100 (b) (4) for the combined content of insulin degludec and insulin aspart complies with 21 CFR 201.100, which requires the labeling to state "the quantity or proportion of each active ingredient in the drug product". **Office of Scientific Investigations (OSI)** 4. You notified us that the Osvaldo Brusco site was closed due to Good Clinical Practices (GCP) concerns (Studies N1250-3579, N1250-3580, N1250-3582). How have data from this site been handled in analyses and reported in Clinical Study Reports? 5. In the clinsite.xpt dataset virtually all investigators are reported as having financial disclosure amounts; however, only a small subset of these sites are reported to have disclosable information in the Tables of Financial Disclosure. Please clarify. **REQUIRED PEDIATRIC ASSESSMENTS** Under 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 note that you have not addressed how you plan to fulfill this requirement. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication proposed in this application. If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required.
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter

☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Rachel Hartford	01/31/2013
Regulatory Project Manager	Date
Julie Marchick	02/01/2013
Chief, Project Management Staff	Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

RACHEL E HARTFORD
02/03/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 203314 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Tresiba Established/Proper Name: insulin degludec [rDNA origin) Dosage Form: injection Strengths: 100 and 200 Units/mL		
Applicant: Novo Nordisk Agent for Applicant (if applicable):		
Date of Application: 29Sep11 Date of Receipt: 29Sep11 Date clock started after UN:		
PDUFA Goal Date: 29July12 *Note: the PDUFA Goal Date was changed to 29Oct12 due to a major amendment.*	Action Goal Date (if different): 27July12 *Note: At the time of filing of the application, the action goal date was 27July 12. However, at the time of archival of this filing review, the action goal date is 08Feb13.*	
Filing Date: 28Nov11	Date of Filing Meeting: 18Nov11	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): treatment of diabetes mellitus		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 073198 & IND 076496	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***		X		

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		Requested in 74day letter

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***		X		Requested in 74day letter
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***		X		Requested in 74day letter
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	X			
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			CDRH 10/20/11 OBP 11/22/11 BD7 11/22/11
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 02/24/09 ***If yes, distribute minutes before filing meeting***	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 06/17/11 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/18/11

BLA/NDA/Supp #: NDA 203314

PROPRIETARY NAME: Tresiba

ESTABLISHED/PROPER NAME: insulin degludec

DOSAGE FORM/STRENGTH: injection, 100 and 200 Units/mL

APPLICANT: Novo Nordisk

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of DM

REVIEW TEAM:
NDA 203313 Ryzodeg (insulin degludec/insulin aspart)
Clinical - Jean Marc Guettier
Pharm Tox - Miyun Tsai-Turton
RPM - Rachel Hartford
Clincal Pharmacology - Ritesh Jain
CMC - Muthukumar Ramaswamy
Stats - Dongmei Lui

NDA 203314 Tresiba (insulin degludec)
Clinical - Jean Marc Guettier
Pharm Tox - Miyun Tsai-Turton
RPM - Rachel Hartford
Clinical Pharmacology - Manoj Khurana
CMC - Joe Leginus
Stats - Cynthia Liu

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Rachel Hartford	Y
	CPMS/TL:	Enid Galliers	Y
Cross-Discipline Team Leader (CDTL)	Hylton Joffe		Y
Clinical	Reviewer:	Jean Marc Guettier	Y
	TL:	Hylton Joffe	Y

Clinical Pharmacology	Reviewer:	Manoj Khurana	Y
	TL:	Jaya Vsidyanathan	Y
Biostatistics	Reviewer:	Cynthia Lui	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Miyun Tsai-Turton	Y
	TL:	Karen Davis Bruno	Y
Product Quality (CMC)	Reviewer:	Joe Leginus	Y
	TL:	Su Tran	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Vinny Pawar	Y
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: ***the application did not raise significant safety or efficacy issues***
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Curtis Rosebraugh

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: **Filing/Planning Meeting Agenda**

1. Important dates

   Filing Review Templates in DARRTS: 21Nov11

   Filing Date: 28Nov11

   Day 74 Letter Date: 12Dec11

2. Discipline Overview of Application: **Team members come to the meeting prepared with completed filing review checklists (which have TL concurrence).** This preparation is critical to a focused discussion on filing, needed information requests, and review issues. **Communicate with other team members, including the project manager and team leader as soon as problems are identified.**

   Each reviewer makes a presentation on the high-level contents and fileability of their review section and presents findings thus far. During the meeting, each reviewer discusses the relevant content of the application covering the following:

   - A summary of the application
   - Any special issues
   - A description of any material needed for the review not included in the application
   - Any deficiencies that may warrant a refusal to file decision
   - Other substantive deficiencies that may have an impact on review completion or

application approval(to be transmitted in the Filing Communication)

- Issues that merit advisory committee input (goal: month 7-8)
- Need for any additional consult reviews or inspections

Enter discipline filing review templates into DARRTS by 21Nov11.

a. CMC
b. P/T
c. Clin Pharm
d. Clinical
e. Stats
f. OSI
g. Micro
h. CDRH (Device and Human Factors)
i. Labeling (DMEPA, DRISK, DDMAC)

3. Reach agreement on filing decision

4. Review Time Line

13Apr12 Consult Reviews (CDRH & DMEPA)

07May12 Substantially Complete PI to DRISK

01Jun12 Primary Reviews
01Jun12 Wrap up Meeting

08Jun12 Secondary Reviews
08Jun12 Send labeling/PMC/PMR/REMS (1week TAT for labeling)

15Jun12 CDTL Review
15Jun12 Begin labeling discussions with Novo Nordisk
15Jun12 Compile and circulate action letter and package

06Jul12 Division Director review

06Jul12 Action Letter and Package to Office Director

27Jul12 Office Director review and sign-off (Action Goal Date)

5. Meetings

20Jan12 Team Meeting

28Feb12 Mid-Cycle Review

24Apr12 Team Meeting

01Jun12 Wrap up Meeting

05Jun12 Labeling Meeting

28Jun12 Labeling Meeting

12Jul12 Labeling Meeting

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
	ACTIONS ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review:

	• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74 **Clinical** 1. Clarify why you are not proposing to label Study 1250-3586 entitled "*A 26-week randomised, confirmatory, controlled, open label, multicentre, multinational treat totarget trial comparing the efficacy and safety of NN1250 and insulin glargine, both injected once daily as add on to current OAD treatment in insulin naïve subjects with type 2 diabetes mellitus qualifying for more intensified treatment."* 2. You reference your December 21, 2010, background package and our March 21, 2011, advice letter but this approach does not adequately address in the NDA how you plan to fulfill the requirements of the Pediatric Research Equity Act (PREA). See "Required Pediatric Assessments" below. **Chemistry, Manufacturing, and Controls** 3. Clarify what the reference is for the units of the dosage strength (b) (4). In the proposed drug product specification, the content of insulin degludec in the formulation is measured as "nmol", and you state that 100 (b) (4) corresponds to 600 nmol/ml. Provide a reference for the units of the dosage strength (b) (4), comparable to that submitted for your insulin detemir product (i.e., one unit (24 nmol) of insulin detemir corresponds to one IU of human insulin (6 nmol) based on clinical data). **Office of Scientific Investigations (OSI)** 4. You notified us that the Osvaldo Brusco site was closed due to Good Clinical Practices (GCP) concerns (Studies N1250-3579, N1250-3580, N1250-3582). How have data from this site been handled in analyses and reported in Case Study Reports? 5. In the clinsite.xpt dataset virtually all investigators are reported as having financial disclosure amounts; however, only a small subset of these sites are reported to have disclosable information in Tables of Financial Disclosure. Please clarify. Clinical Pharmacology 6. Provide raw data (as SAS transport files) used for the population pharmacokinetic (PK) analysis conducted for Study NN1250-3586. A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. 7. Provide the NONMEM Model Codes for the population PK analysis conducted for Study NN1250-3586. In general, 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). **REQUIRED PEDIATRIC ASSESSMENTS** Under 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 note that you have not addressed how you plan to fulfill this requirement. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication proposed in this application. If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required.
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Rachel Hartford	01/31/2013
Regulatory Project Manager	Date
Julie Marchick	02/01/2013
Chief, Project Management Staff	Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

RACHEL E HARTFORD
02/03/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review
Office of Medication Error Prevention and Risk Management

Review of Usability Study, Labels, and Labeling

Date:	January 15, 2013
Reviewer:	Richard A Abate, RPh, MS, Safety Evaluator Division of Medication Error Prevention and Analysis
Deputy Director:	Kellie Taylor, PharmD, MPH, Deputy Director Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
Drug Name(s):	Ryzodeg (70% Insulin Degludec and 30% Insulin Aspart [rDNA origin]), 100 units/mL (U-100) FlexTouch Pen Tresiba (Insulin Degludec [rDNA origin]) Injection, 100 units/mL (U-100) and 200 units/mL (U-200) FlexTouch Pen
Application Type/Number:	NDA 203313 (Ryzodeg) NDA 203314 (Tresiba)
Applicant:	Novo Nordisk, Inc.
OSE RCM#:	2011-3894

CONTENTS

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA's) evaluation of the summative differentiation usability study, UT-59, submitted by Novo Nordisk in support of the colors chosen to differentiate the FlexTouch Pen Injector (PDS290) in their applications, NDA 203313 for Ryzodeg (70% Insulin Degludec and 30% Insulin Aspart [rDNA origin]) and NDA 203314 Tresiba (Insulin Degludec [rDNA origin]). In addition, DMEPA evaluated the proposed container labels and carton labeling for the FlexTouch presentations of these products in response to a request from the Division of Metabolism and Endocrinology Products. (b) (4)

1.1 REGULATORY HISTORY

The PDS290 pen injector device was discussed with the Applicant for use in several applications for different insulin products. The following timeline describes the requests, submissions, and reviews to date:

- August 2010: A Type C meeting with Novo Nordisk - DMEPA requested Novo Nordisk complete a differentiation study which demonstrates that users are able to select the appropriate insulin product in "real use" situations (INDs 076496 and 073198).
- January 2011: End of review meeting for Novolog (NDA 020986/S-061) and Levemir (NDA 021536/S-033), CDRH instructed Novo Nordisk that participants should only be trained on one type of insulin in the summative usability studies because they noted patients would only use one insulin pen injector at a time.
- April 2011: Novo Nordisk completed the user differentiation study (UT59) for the Flex Touch pen injectors (PDS290).
- June 2011: DMEPA notified Novo Nordisk that we found the proposed proprietary name, (b) (4), unacceptable for IND 073198 (Insulin Degludec and Insulin Aspart [rDNA origin]).
- August 2011: DMEPA notified Novo Nordisk that we found the proposed proprietary name, (b) (4) unacceptable for IND 076496 (Insulin Degludec [rDNA origin]).
- September 29, 2011: Novo Nordisk submitted the results of the user differentiation study (UT59) and user handling study (UT54).
- December 2011: DMEPA notified Novo Nordisk that we found the proposed proprietary name, Ryzodeg, conditionally acceptable for NDA 203313 (70% Insulin Degludec and 30% Insulin Aspart [rDNA origin]) and the proposed proprietary name, Tresiba, conditionally acceptable for NDA 203314 (Insulin Degludec [rDNA origin]).

- December 2011: The Center for Device and Radiologic Hazards (CDRH) human factors team provided comments regarding the deficiencies of the summative user handing study (UT54) which were communicated to Novo Nordisk.
- February 16, 2012: Novo Nordisk submitted a protocol for a summative usability study (UT86) which assesses the changes made to the proposed training and Instructions for Use for the FlexTouch Pen (PDS290) in these applications.
- March 30, 2012: DMEPA evaluated and provided comments on the proposed protocol for UT86 and the results to the user handling study UT54 in OSE review #2012-701.
- April 24, 2012: Novo Nordisk submitted the results of the summative usabilty study, UT86. This submission was 90 days prior to the original PDUFA goal dates for these applications.
- May 3, 2012: The Agency forwarded the comments CDRH and DMEPA provided on the protocol for UT86.
- May 18, 2012: Novo Nordisk responded to the Agency's comments.
- June 26, 2012: DMEPA provided review of the data reported in UT86, OSE review # 2012-1040.
- July 9, 2012: A Discipline Review Letter was forwarded to Novo Nordisk which communicated the comments on the results of UT86 from DMEPA and CDRH's human factors team.
- August 10, 2012: Novo Nordisk submitted a protocol for a supplemental usability UT103 and requested a Type A meeting to discuss the protocol with the Agency (DMEP, DMEPA, and CDRH).
- October 3, 2012: CDRH, DMEPA, DMEP and Novo Nordisk reached agreement on the protocol for UT103 during this Type A meeting.
- December 17, 2012: Novo Nordisk submitted the results of UT103 which will be reviewed separately, OSE review 2012-2962.

For clarification, Table 1 lists the NDAs for each product, the proprietary names of the products used in the differentiation study and the proposed proprietary names found conditionally acceptable by DMEPA.

Table 1. Names used in study and names approved.

NDA	Name used in UT59	Name DMEPA found conditionally acceptable
203313	(b) (4)	Ryzodeg
203314	(b) (4) U-100	Tresiba 100 units/mL
	U-200	Tresiba 200 units/mL

1.2 PRODUCT INFORMATION – TRESIBA (NDA 203314)

The following product information is provided in the draft insert labeling submitted September 29, 2011 as well as the October 5, 2011 proprietary name submission.

- Established name: Insulin Degludec [rDNA origin] Injection
- Indication of use: To improve glycemic control in adults with diabetes mellitus.
- Route of administration: Subcutaneously
- Strength: 100 units/mL (U-100) and 200 units/mL (U-200)
- Dosage form: Injection in a disposable prefilled pen injector (FlexTouch).
- Dose: The dose for insulin varies based on the patients needs but usual starting dose is 10 units for insulin naïve patients. The dose with the U-100 FlexTouch device ranges from 1 unit to 80 units in one unit increments. The dose of the U-200 FlexTouch device ranges from 2 units to 160 units in two unit increments. The dose is administered once daily, and the dose may be administered any time of the day. Conversion of patient currently on basal insulin may be converted unit to unit as a once daily dose.
- How supplied: 100 units/ml (U-100) in 3 mL FlexTouch disposable pen injector packaged five pens per carton. The 200 units/mL (U-200) in 3 mL FlexTouch disposable pen injector packaged three pens per carton. Professional samples of Tresiba FlexTouch pen injectors in each concentration will be packaged individually.
- Storage: The pens are stored between 2º and 8º C (36º and 46º F). Do not freeze. After initial use, the product in any configuration may be stored at room temperature, below 30º C (86º F) for up to (b) (4).
- Container and closure systems: The FlexTouch disposable pen-injector is the PDS290 device which a use validation study was included with the Application.

1.3 PRODUCT INFORMATION – RYZODEG (NDA 203313)

The following product characteristics were obtained from Request for Proprietary Name Review submitted October 5, 2011 and the draft insert labeling submitted September 29, 2011

- Established name: 70% insulin degludec and 30% insulin aspart [rDNA origin] injection
- Indication of use: To improve glycemic control in patients with diabetes mellitus.
- Route of administration: Subcutaneously
- Dosage form: injection in a prefilled disposable syringe (b) (4)
- Dose: The dose for insulin varies based on the patients needs but usual starting dose is 10 units for insulin naïve patients. The dose with the Flex Touch device ranges from 1 unit to 80 units. The dose is administered once daily before a meal or may be divided and administered twice daily (b) (4) a meal.

- How supplied: 100 units/ml (U-100) in 3 mL Flex Touch disposable pen injector. The pens are packaged five pens per carton for commercial sale and as individual pens for professional sample.
- Storage: The pens are stored between 2º and 8º C (36º and 46º F). Do not freeze. After initial use, the product may be stored at room temperature, below 30º C (86º F) for up to four weeks.
- Container and closure systems: The FlexTouch disposable pen-injector is the PDS290 device which a use validation study was included with the Application.

2 REVIEW METHODS AND MATERIALS

Using Failure Mode and Effects Analysis[1], the principles of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container labels submitted May 21, 2012 (Appendices E and G)
- Carton labeling submitted May 21, 2012 (Appendices F and H)
- Insert labeling - not pictured

Additionally, Novo Nordisk submitted a differentiation study (UT-59) to demonstrate that the patients and healthcare providers that use these pen injectors can select the appropriate pen. Novo Nordisk identified differentiation as the risk with the highest priority (See Appendix A). Thus, differentiation warranted a separate study. Novo Nordisk also submitted a user handling study (UT54) to demonstrate the safe and effective use of the PDS290. The evaluation of the Instructions for Use for the FlexTouch pen is deferred until the completion of this usability study and the data can be reviewed.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) using the strategy listed in Table 2 to identify medication errors involving Novo Nordisk FlexPens which present insulin products in a similar configuration and have a similar appearance. In addition, we conducted an updated query in FAERS using the same criteria on October 23, 2012.

Table 2: Database Search Strategy

	AERS	**FAERS**
Date	April 24, 2012 (no date limit)	from April 24, 2012 to present
Drug Names	(Verbatim terms) "FlexPen% " and "Flex_Pen%"	(Verbatim terms) "FlexPen% " and "Flex_Pen%"
MedDRA Search Strategy	Medication Errors (HLGT) Product Label Issues HLT Product Quality Issues (NEC) HLT	Medication Errors (HLGT) Product Label Issues HLT Product Quality Issues (NEC) HLT

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

The AERS database searches identified 197 reports. The FAERS gap analysis query identified no additional cases. Each AERS report was reviewed for relevancy and duplication. Duplicate reports were merged into a single case. After individual review, 105 cases were excluded for the following reasons:

- Report of a malfunction of the FlexPen device itself (e.g. the pen jammed).
- Report resulted from a laps in patient compliance with the use of the insulin product involved. (e.g. could not afford medication or did not use when prescribed)
- Report did not involve an insulin product in the FlexPen presentation (e.g. a vial).
- Report of an intentional overdose of insulin.
- Report of needle problem not related to the use of the pen injector.
- Report of the use of an expired product.
- Report of a product quality issue (e.g. new pen lacked medication, new product was inappropriately cloudy or contained floaters).
- Report involved the pharmacist knowingly made an inappropriate product substitution for the insulin (e.g. Novolog for Humalog).
- Report of an adverse event without an identifiable medication error.
- The insulin product was a concomitant medication not involved in the reported medication error.
- The reported medication error involved a product not marketed in the United States.

3 REVIEW RESULTS

DMEPA did not identify additional deficiencies following evaluation of the summative use handling study (UT-54) that were not included in the comments provided by CDRH (Appendix D) or included in our comments provided in OSE review #2012-701. Therefore, we have no other comments on this data at this time.

The following provides our evaluation of differentiation study (UT-59) and the container labels and carton labeling for the FlexTouch pen in these applications.

3.1 USABILITY STUDY (UT-59) OBJECTIVE

The objective for this study appears in Appendix B. DMEPA concludes the objective of the study was appropriate.

3.2 DESIGN OF THE STUDY (UT-59)

The study design for the user differentiation study is outlined in Appendix C.

Four or five products were provided during the caregivers and patients selection task. This design is not optimal because the participants are looking for one product from a group of cartons or pen injectors making these tasks more like a search exercise rather

than a selection task. A more realistic approach would require the patients to select from two or three pen injector products that may be used concomitantly in a real-world setting to treat Diabetes (e.g. each PDS290 with a Novolog pen injector).

Patients and caregiver participants were introduced to one product in the FlexTouch presentation ([(b) (4)] U-100, [(b) (4)] U-200, or [(b) (4)] U-100). This approach was recommended by CDRH in the January 2011 meeting for Levemir and Novolog supplements as they noted that patients are likely to be trained on and use only one insulin pen.

However, we note that the healthcare provider (HCP) participants in this study were not trained or introduced to any one specific product, but rather each HCP was requested to select the carton or the pen for each product in separate tasks. The selection of cartons tasks for healthcare providers included in this study was only capable of demonstrating that the participants can correctly select each product from amongst the Novo Nordisk product line of insulin in pen injectors included in each set. In addition, the design of the tasks involving the selection of [(b) (4)] (insulin degludec) product cartons and pens by healthcare providers lacked the ability to differentiate one strength of [(b) (4)] from the other (U-100 vs. U-200) or from Levemir, the currently marketed Novo Nordisk basal insulin. Not all of these products were included for the [(b) (4)] select tasks. Therefore, the design of the selection tasks only tested the Novo Nordisk product line and did not include tasks that differentiated long acting insulin products from one another.

3.3 RESULTS OF THE USABILITY STUDY (UT-59)

The results reported for the user differentiation study include the following:

Selection Errors

- User errors for cartons retrieval: When relying on the carton for selection, two out of 96 participants selected the wrong product from a refrigerator for a total four use errors (288 total selection tasks). Both participants were in the Adult user group. One participant selected the Novolog carton rather than the carton for [(b) (4)] U-200. The other participant committed the same use error by selecting [(b) (4)] U-200 rather than [(b) (4)] during all three retrieval tasks for the carton (Normal lighting, dim light and with vision impairment glasses).

  One participant in the Elderly group refused the task and did not select a product in dim lighting conditions.

- User errors for pen selection: When relying on the pen for selection, two out of the 90 participants selected the wrong pen from a cup on the counter for a total of four use errors (252 total selection tasks). One Child participant selected the Novolog Pen rather than the [(b) (4)] pen. One Adult participant selected [(b) (4)] U-200 rather than [(b) (4)] during all three selection tasks.

  One participant in the Elderly group did not select a product rather than the [(b) (4)] U-200 pen based on the pen in dim lighting conditions.

Reported Close Calls

- With the carton retrieval: Under dim lighting conditions, one Elderly participant out of 96 total participants selected the Novolog Mix 70/30 carton in instead of [(b) (4)] U-200 but noted the error and returning it and retrieved the correct carton.
- With the pen selection: Under dim lighting conditions, two of 90 participants encountered close calls during the pen selection tasks. One adult participant mistakenly selected the Novolog Mix 70/30 pen, noted the error and returned it to the bin then correctly selected [(b) (4)] U-200. A Child participant mistakenly selected the [(b) (4)] U-200 pen noted the error and returned it to the bin then correctly selected the [(b) (4)] U-100 pen.

Reported Root Causes of Selection Error:

The following root causes were reported by the patients when probed by the investigator:

- The adult participant who selected the Novolog rather that [(b) (4)] U-200 carton attributed the error to inattention.
- The elderly participant who selected no carton from a refrigerator could not identify the requested product in a dim lighting environment.
- The child participant selected the wrong pen because he thought "all the pens were blue."
- The Adult participant who selected [(b) (4)] U-200 instead of [(b) (4)] U-100 was attributed by investigators to task misinterpretation and possible memory limitation.

Human Factors Analysis of Close Calls

- All the close calls occurred under dim lighting conditions. This affected the participant's ability to see the colors clearly either in the refrigerator (cartons) or on the table (pens). Also, the report noted that the refrigerator used during the carton selection tasks had no inside light.

3.3.1 DMEPA Comments on Study Results

Overall, the selection errors that occurred were few. However, DMEPA disagrees with the root causes of these errors. One adult participant selected the insulin product he uses (Novolog) rather than the product he was introduced ([(b) (4)] U-200). The Applicant attributed this error to inattention. However, recall bias may have played a role in this section error.

The three carton selection errors committed by a single participant, A13, may not reflect actual confusion between the products but rather an issue with the participant. This participant selected [(b) (4)] U-200 rather than [(b) (4)]. However, the participant did not seem to recall the product he had been introduced during the training. Rather, he selected the first carton he saw in the refrigerator and continued to select that same product ([(b) (4)] U-200) for the other selection tasks (Carton and Pen). Furthermore, the

participant's selection of the same product suggests that he was able to identify the [redacted] U-200 product in each task.

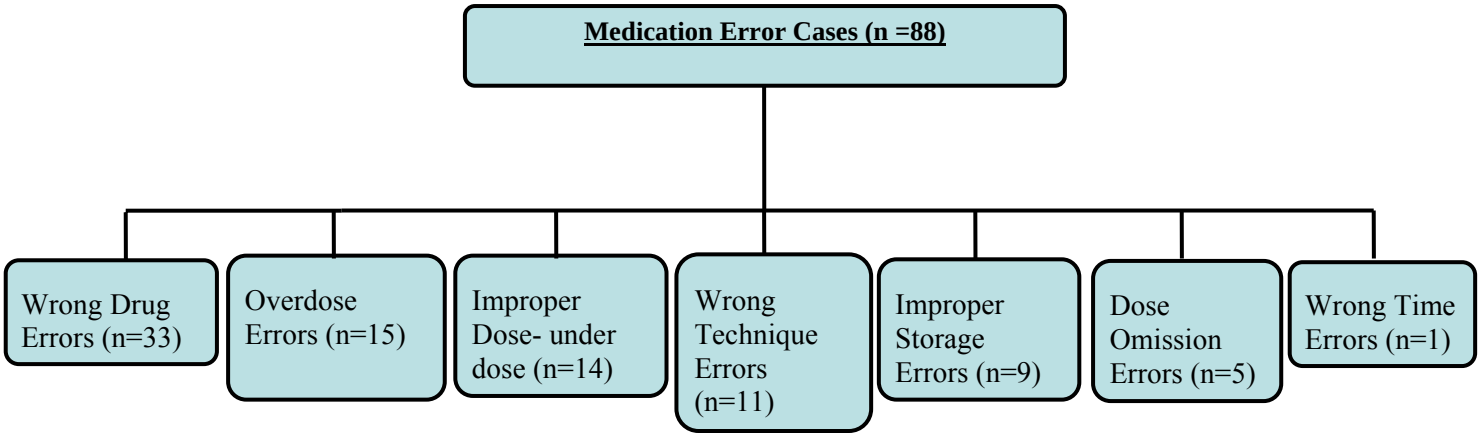
The pen selection errors and close calls appear to be due to the fact that all the pens used in this study are primarily the same color, blue. This confirmation bias was noted by the Child participant who committed a pen selection error. The effect of dim lighting or other visual impairment only enhances the similarity of the colors and makes the pens more difficult to differentiate. However, the use of predominant blue for the pen injector is no different than the Flex Pen injectors currently marketed. Furthermore, these products are not indicated for use in pediatric patients.

3.4 MEDICATION ERROR CASES

The following sections describe the results of our AERS search and the risk assessment of the FlexTouch product differentiation as well as the associated label and labeling.

Following exclusions as described in section 2.1, 88 FlexPen medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]. Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix J provides listings of all ISR numbers for the cases summarized in this review. Appendix K contains a more detailed listing of the cases including narrative summaries.

Figure 1: Insulin in the FlexPen presentation medication errors (n = 88) categorized by type of error



Wrong Drug errors were the most frequently reported type of error (n=33): These cases involve the patient receiving and/or administering the wrong insulin in the FlexPen presentation.

- Novolog for Novolog Mix 70/30

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

- Novolog for Levemir
- Novolog for Lantus
- Novolog Mix 70/30 for Novolog
- Levemir for Novolog
- Novolog Mix 70/30 for Novolin 70/30
- Novolog for Novolin N
- Humalog Kwikpen for Levemir FlexPen

The majority of wrong drug error cases involve the wrong insulin being dispensed by the pharmacy or the patient or caregiver selecting the wrong insulin prior to administration. However, it is unclear from the narratives of the cases involving dispensing the wrong insulin products if the pharmacy staff confused the product names or the product's carton labeling. Furthermore, all but one of the cases in which patients selected the wrong FlexPen presentation occurred prior to or soon after the approval of the use of differentiating color on the barrel of these pen injectors. The one more recent case (ISR 8024473-0, November 2011) noted the patient had "inadvertently grabbed" the wrong pen to deliver the remaining 19 units of his Levemir 50 unit dose, but lacked detail to identify a root cause. However, we noted that the dominant use of the color blue as the color on the Flex Pen devices was identified by reporters as a contributing factor in some of these errors. Finally, we note the confusion between short-acting insulin and long-acting or basal insulin is more likely to result in serious patient outcomes (e.g. hospitalizations).

Overdose cases (n=15) involve the patient receiving more insulin than intended. The contributing factors associated with these errors include the patient repeating a dose, the patient not understanding how to use the FlexPen, confusion of dose with that of another product when prescribed more than one insulin, and one case noted the numbers on the dial of the FlexPen were too small to read.

Improper dose resulting in an under dose cases (n=14) involve the patient receiving less insulin than prescribed. In the majority of these cases, the patient received a dose that was 10% of that prescribed as if they mistakenly forgot or missed the zero (2 units vs. 20 units) when dialing the dose. Two cases could be attributed to the fact the patients misunderstood how to use the device correctly.

Wrong technique cases (n=11) involve the patients not following the appropriate steps in using the pen injector. Of note, two cases involved the patients leaving needles on after use and re-using the needles for subsequent injections (ISR 5173910-8 and 6505355-X), and three cases of nurses using the same pen injector on multiple patients (ISR 6088172-7, 6071512-2 and 7768212-7).

Improper storage cases (n=9) involve the product not being store properly. Two cases resulted in the shipping/mailing of the product from the pharmacy to the patient and the product was replaced. The remaining cases resulted when the patients continued to store the product in the refrigerator after using it which resulted in no reported adverse events.

Dose omission cases (n=5) involve with the patient or caregiver believing the pen injector still contained insulin although the device was empty of medication.

Wrong time (n=1) case involves the patient incorrectly taking an insulin dose in the morning rather than in the evening as prescribed because he confused the dose times between two insulin products.

3.5 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Based on the results of the differentiation usability study and the postmarketing errors to date with Novo Nordisk insulin pens, we are mainly concerned with the patient or caregiver's ability to distinguish the 200 units/mL strength of Tresiba from the 100 units/mL strength. Additionally, the labels and labeling require revisions to highlight the fact that the pen should be used for a single patient.

3.5.1 Use of Colors for Differentiation

We note that Novo Nordisk proposes to use specific colors to help differentiate these products, Tresiba (green) and Ryzodeg (blue). These colors are used on the carton labeling, pen injector label, and barrel of the pen injector. The colors utilized by Novo Nordisk in these applications do not appear on the International Diabetes Federation's (IDF's) color code (Appendix L) for human insulin products.[2] However, Tresiba and Ryzodeg are novel insulin preparations and not included among the coded preparations (b) (4)

The differentiation study (UT59) compared the proposed products with the remaining Novo Nordisk insulin products available in the marketed FlexPen pen injector and in proposed FlexTouch pen injector presentations of marketed insulin. Although we noted that the two strengths of Tresiba were not tested together or with Levemir in the selection tasks, DMEPA believes that selection errors resulting from confusion between the strengths of Tresiba or between Tresiba and Levemir are not likely based on the differing shades of green used for each product. Furthermore, we believe patients are not likely to be using more than one basal insulin product or strength of Tresiba concurrently. The greatest risk to the patient with wrong drug medication errors involves confusion between a basal insulin product with a rapid acting insulin. This study demonstrated that the colors provide adequate differentiation to minimize confusion resulting in this type of medication error (basal insulin vs. rapid acting insulin).

3.5.2 Identified Label and Labeling Deficiencies

A review of the submitted labels and labeling identified the following deficiencies:

- The presentation of the proposed proprietary name, Ryzodeg, on the container label and carton labeling appears with the letter 'Z' as a graphic that provides for the base of the letter to appear beneath the adjacent letters 'Y' and 'O.' This

[2] Insulin Color Code of the International Diabetes Federation; http://www.idf.org/insulin-diabetes-supplies/colour-code, cited October 23, 2012.

presentation interferes with the contiguous flow between the proprietary name and the modifier (device name), 'FlexTouch."

- The established name lack prominence on the container label and carton labeling. (Note that with any revisions to their presentation, the proprietary name, established names and strengths should remain contiguous to provide readability prior to and following opening the carton at the perforation.)
- Use of an error prone abbreviation "U" for units throughout the container, carton and insert labeling.
- The statement "Single patient use only" lacks sufficient prominence on the container label and carton labeling (professional sample and trade).
- Product strength is presented in two lines above the proprietary name on the container labels (professional sample and trade) for 200 units/mL presentation and carton labeling for both strength presentations of Tresiba and the carton labeling for Ryzodeg.
- The NDC lacks prominence on the principal display panel. However, the NDC also appears contiguously with the barcode and thus the presentation of the NDC meets the requirements set forth in 21CFR 207.35.

4 CONCLUSIONS

The differentiation study adequately demonstrates that the proposed colors used for Ryzodeg FlexTouch (70% Insulin Degludec and 30% Insulin Aspart [rDNA origin]) Injection 100 units/mL (NDA 203313) and Tresiba FlexTouch (Insulin Degludec [rDNA origin]) Injection 100 units/mL and 200 units/mL (NDA 203314) pen injectors can be differentiated from the rapid acting insulin Novolog and Ryzodeg Flex Touch can be differentiated from the Tresiba Pen injectors. These colors should not contribute to selection errors between these basal (long acting insulin) with Novolog, the rapid acting insulin, included in Novo Nordisk products. Although the differentiation study lacked tasks that compared different shades of green of the two strengths presentations of Tresiba, DMEPA believes the proposed colors chosen should not contribute medication errors between the strengths of Tresiba and that no additional testing is necessary at this time.

Additionally, DMEPA concludes that the proposed container labels and carton labeling for these products can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

5 RECOMMENDATIONS

DMEPA provides the following recommendations regarding the proposed container and Carton labeling submitted in the corresponding applications which should be implemented prior to approval:

5.1 COMMENTS TO THE APPLICANT

5.1.1 Ryzodeg (NDA 203313)

A. Container Labels (FlexTouch Pen)

1. Revise the presentation of the proposed proprietary name so that all the letters including the 'Z' appear on the same line.
2. Revise the fonts of the proprietary and established names so that the established name is at least one half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
3. Revise the strength presentation adjacent to the proprietary name to read "100 units/mL" to remove the error prone abbreviation "U."
4. Revise the statement "For single patient use only" to the principal display panel of the product to a more prominent font and typeface to improve readability.

B. Carton Labeling (FlexTouch Pen)

1. See comments A1 through A4.
2. Ensure that the strength presentation appears on one line to improve readability.
3. Revise the location and increase the prominence of the NDC number so that it appears above the proprietary name to assist healthcare providers in identifying the product.

5.1.2 Tresiba (NDA 203314)

A. Container Labels (FlexTouch Pen)

1. Revise the fonts of the proprietary and established names so that the established name is at least one half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
2. Revise the strength presentations adjacent to the proprietary name to read "100 units/mL" or "200 units/mL" to remove the error prone abbreviation "U." In addition, ensure that the strength presentation appears on one line to improve readability.

3. Revise the statement “For single patient use only” to the principal display panel of the product to a more prominent font and typeface to improve readability.

B. Carton Labeling (FlexTouch Pen)

1. See Comments A1 through A3.
2. Revise the location and increase the prominence of the NDC number so that it appears above the proprietary name to assist healthcare providers in identifying the product.

6 REFERENCES

Databases

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonization. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Reviews

OSE review: 2011-3892 Label and Labeling for Ryzodeg (b) (4) and Tresiba (b) (4), July 12, 2011; Abate, R.

OSE Review 2012-1040 DMEPA Review of human Factors Study (UT-86), June 26, 2012, Abate, R.

Appendices

Appendix A: Risk priority based on the steps tested with the use of the PDS290 with these insulin products.

Table 7 List of steps to be included in the usability test and priority

Condition	Step to test	Final Priority
Scenario 1 – User does not receive the correct insulin due to mix-up		
Step are performed at dispensing eg. at the pharmacy and at home: Untidy or illogical storage system (only for pharmacies) Bad lighting Stressed or inattentive staff Colour blindness of user (staff for pharmacies)	**Step 1:** Pick the correct PDS290 carton/pen-injector with the intended insulin product. **Step 2:** Remove the PDS290 pen-injector cap (Not. pharmacist.) **Step 3:** Verify via label and cartridge holder it is the correct pen (Not pharmacist) For Step 1-3 the priority is based on the hazard with the highest severity and RPN (worst case),	1
Scenario 2 – The user does not use the pen-injector as described in IFU		
All steps performed at home: Wet hands when handling the pen-injector Bad lighting Stressed or inattentive user Dexterity and impairment	**Step 2:** Remove the PDS290 pen-injector cap	11
	Step 4: Check that the insulin in the pen-injector is clear and colourless	10
	Step 5: Needle mounting	9
	Step 6: Checking the insulin flow (priming)	5
	Step 7: Setting intended dose (reversing the dose setting, if necessary)	4
	Step 8: Understand the End-of-content indication (feature ensuring that no larger dose can be dialled than is left in the cartridge)	2
	Step 9: Subcutaneous needle insert	7
	Step 10: Injecting the dose, incl. checking that scale drum returns to "0", and 6 seconds waiting time with needle in the skin i.e., full dose has been delivered	3
	Step 11: Needle removal and disposal of used needle	6
	Step 12: Cap mounting	8

Appendix B: Objective for the User differentiation study (UT-59)

The summative usability test is to ensure that the PDS290 Pen Injector can be used safely and effectively, and is not vulnerable to dangerous use errors that could lead to patient injury or death, specifically with regard to carton and pen injector differentiation.

Appendix C: Study design for the user differentiation study (UT-59)

Participants:

The user groups included diabetic (Type I and Type II) patients broken up by age range. These patient groups were define as follows: Children (age 10 years to 17 years), Adults (age 18 years to 64 years), and Elderly (65 years and older). The patient groups included patients with and without prior insulin experience with pen, syringe and vials or pump. Each patient group included pen users and pen naïve patients. Patients without insulin experience would have a regimen including oral hypoglycemic medications. Also, two additional user groups were evaluated including Caregivers, who may administer insulin to a diabetic patient in the home, and Healthcare Professionals (HCP) made up of pharmacists, primary care physician office staff (PCP) including prescribers, and Certified and non-certified diabetic educators (CDE or DE) who will teach patients how to use the pen as well as pharmacists who fill prescriptions for these products. Each of the five user groups included 18 participants. HCP is one user group which consisted of four pharmacist, four PCP's and 10 CDE's or DE. Finally, the patients and caregiver participants had a range of education.

All patient and caregiver groups received an introduction to one specific injector pen ((b) (4) U-100, or (b) (4) U-200). HCP's received no introduction prior to

testing. For those participants receiving an introduction, a delay time following the introduction session of two hours to 24 hours prior to testing to simulate the fact that first independent injection within hours of training by healthcare providers.

Testing Environment:

The testing area was set up to simulate the respective environments of the participants (home setting, clinical setting, or pharmacy).

Selection Tasks:

Carton retrieval tasks: All participants would select pens based on the carton. The patient and caregiver groups were to select the product to which they had been introduced from a group of cartons in a refrigerator in the room. The sets of four or five products used the patient and caregiver groups for both the carton and pen selection tasks are in Figure 1. The checked products appeared along with the requested or introduced pen. The patient and caregiver groups were asked select the appropriate carton, remove one of the pens and remove the cap to verify the correct product was retrieved. In addition, the patient and caregiver groups were asked to repeat the task in normal and dim lighting. A subset of ten Adults and ten Elderly patient users performed the task a third time wearing color impairment glasses.

PDS290 Degludec Differentiationmatrix		Novo Nordisk PDS290 pen-injector/carton for Insulin degludec 100 U/ml	Novo Nordisk PDS290 pen-injector/carton for Insulin degludec 200 U/ml	Novo Nordisk PDS290 pen-injector/carton for insulin degludec/insulin aspart 100 U/ml
Product		(b) (4)		
Novo Nordisk PDS290 pen-injector/carton for Insulin degludec 100 U/ml	(b) (4)		–	✓
Novo Nordisk PDS290 pen-injector/carton for Insulin degludec 200 U/ml		–		✓
Novo Nordisk PDS290 pen-injector/carton for insulin degludec/insulin aspart 100 U/ml		✓	✓	
Novo Nordisk PDS290 pen-injector/carton for Levemir		–	–	✓
Novo Nordisk PDS290 pen-injector/carton for NovoLog		✓	✓	✓
Novo Nordisk PDS290 pen-injector/carton for NovoLog Mix 70/30		✓	✓	–

Figure 1: Pen injector and carton combinations to be tested by user and caregivers. Pen injector combinations to be tested by HCPs except pharmacist.

The HCPs group participants were asked to select the each product ((b) (4) U-100, and (b) (4) U-200), one at a time, based on the carton. The HCPs were asked to follow the same steps as the patient users and caregiver groups except he pharmacists were not asked to remove a pen to verify product selected. The order of product selection

was randomized in this user group. The carton was selected from a refrigerator mixed among a predetermined set of insulin products. The syringe sets for this user group included six or seven Novo Nordisk insulin products. See Figure 2. All HCP's performed all three selection tasks in both normal and dim lighting.

PDS290 Degludec Differentiationmatrix		Novo Nordisk PDS290 pen-injector/carton for Insulin degludec 100 U/ml	Novo Nordisk PDS290 pen-injector/carton for Insulin degludec 200 U/ml	Novo Nordisk PDS290 pen-injector/carton for insulin degludec/insulin aspart 100 U/ml
	(b) (4)			(b) (4)
Novo Nordisk PDS290 pen-injector/carton for Insulin degludec 100 U/ml	(b) (4)		–	✓
Novo Nordisk PDS290 pen-injector/carton for Insulin degludec 200 U/ml		–		✓
Novo Nordisk PDS290 pen-injector/carton for insulin degludec/insulin aspart 100 U/ml		✓	✓	
Novo Nordisk PDS290 pen-injector/carton for Levemir		–	–	✓
Novo Nordisk PDS290 pen-injector/carton for NovoLog		✓	✓	✓
Novo Nordisk PDS290 pen-injector/carton for NovoLog Mix 70/30		✓	✓	–
Novo Nordisk Levemir, FlexPen®		–	–	✓
Novo Nordisk NovoLog, FlexPen®		✓	✓	✓
Novo Nordisk NovoLog Mix 70/30, FlexPen®		✓	✓	–

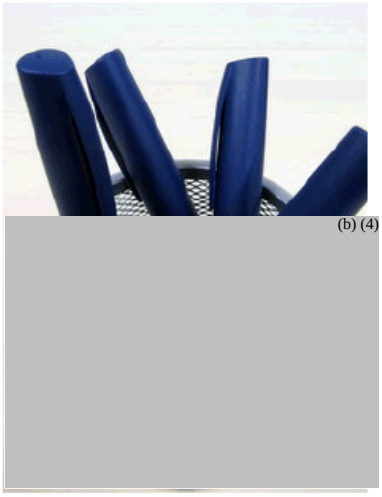
Figure 2: Carton combinations to be tested by HCPs

To assist with subjective data collection, the participants were observed and recorded on video during tasks. In addition, the participants were taught and encouraged to think out loud during the testing.

Pen selection tasks: The participants were instructed to select the introduced product from a group of pen injectors in a bin on the table top. The groupings were the same as the carton selection. (See the pen groupings and a picture of pen setup on the next page.) The participants, less the pharmacists from the HCPs group, completed the selection of the pens similar to the carton retrieval tasks including the randomized selection for HCPs, lighting variation (normal and dim), and the use of visual impairment glasses in the same subgroups of patients.

Requested pen injector	(b) (4) U100 or (b) (4) U200	(b) (4) U100
Other pen injectors	(b) (4) U100 NovoLog NovoLog Mix	(b) (4) U100 (b) (4) U200 Levemir NovoLog

Combinations of pen injectors in the bin for pen injector selection tasks performed by people with diabetes, caregivers, PCPs, CDEs and DEs.



Data Collection:

The study collected the following data:

- The use errors committed during the selection tasks. The use errors are defined as a case in which a user performs a task in an incorrect manner that will not lead to the intended outcome.
- Close calls which occur during the selection tasks. "Close calls" are defined as a case in which a user almost commits an error, but "catches" him or her in time to avoid making the error.
- Operational difficulties which occur during the selection tasks. "Operational difficulties are defined as a case in which a user appears to struggle to perform a task.
- Subjective data obtained to determine root causes of use errors were obtained from comments participants made during the selection tasks or use error debriefing questions.
- Ratings by test participants of the ease of using the packaging and pens to complete the task to fulfill IEC 62366's requirement to measure usability. (1= poor and 7 = excellent).

Appendix D: CDRH recommendations regarding the summative usabilty studies UT-54 (User handling) and UT-59 (User differentiation) provided by CDRH and forwarded to the Applicant December 23, 2011.

User Differentiation Study:

The study reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committing the same error on three occasions, and this same participant committed three errors with the previous task of selecting the correct carton. Two participants had negative transfer from their use experience with other similar products, and one participant could not identify the green color carton. The study also reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product.

The IFU includes a statement to have users check the name and color label. Based on the risk analysis, the clinical outcome can be hypoglycemia or hyperglycemia if a patient injects a different type of insulin other than intended and the error is undetected. There are different use scenarios for which this hazard exists – for example, either the pharmacist/HCP chooses the wrong carton and dispenses to the patient, and the patient does not recognize the wrong insulin carton; or the patient has more than one type of insulin available, and the patient chooses the wrong carton. The results are not clear in terms of which user group children/adult/ caregiver/HCP) the three participants were part of.

It is concerning that not all users were able to successfully complete these tasks and that serious clinical impact can occur. We are concerned that participants were not able to identify the carton and pen-injector with the correct insulin despite the use of colors and instructions provided in the IFU, and therefore the risks associated with these aspects of use are not successfully mitigated. Further design optimization can be done to the pen label to clearly identify the insulin type and the dose.

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

Appendix J: ISR numbers from AERS search

4176670	5094895	5451128	5981116	6292785	7058713	7913839
4243046	5119293	5465497	6020319	6332420	7115708	7917543
4243070	5173910	5465499	6071512	6359382	7170140	7945165
4243088	5206762	5465633	6079062	6379228	7198135	8005497
4243100	5206896	5465681	6082475	6403231	7217573	8005499
4421420	5206899	5466953	6082513	6410112	7272695	8022930
4446286	5233367	5504495	6082532	6456585	7272728	8022931
4470646	5233371	5504662	6082539	6456589	7272777	8022953
4492189	5241393	5504663	6082615	6456804	7272844	8023792
4504573	5268068	5504665	6082634	6480162	7273102	8024306
4516742	5273670	5505415	6082867	6498317	7273190	8024329
4634247	5279785	5505448	6083854	6498739	7273675	8024413
4662087	5289379	5507385	6083902	6503940	7275097	8024457
4725715	5317420	5507818	6084576	6505355	7277251	8024459
4731303	5318986	5508414	6088172	6505409	7277283	8024473
4808478	5319129	5513706	6120325	6516225	7277377	8024475
4808480	5319245	5525183	6173595	6537390	7277518	8024518
4826154	5345678	5551190	6184631	6544357	7292271	8024999
4833772	5345740	5596955	6196848	6550349	7299588	8036773
4852137	5345762	5596956	6212947	6609501	7299589	8107541
4887709	5345774	5599963	6238660	6672468	7348783	8240440
4896020	5345807	5717326	6239526	6676527	7416947	8287932
4953835	5345967	5774849	6240738	6687871	7417542	8304584
5011731	5385410	5798491	6241149	6763512	7551558	
5034771	5423362	5840003	6241274	6843671	7677008	
5051150	5423400	5866824	6241671	7010857	7712481	
5051154	5423506	5940516	6242990	7017913	7734077	
5051167	5423940	5963111	6263982	7020151	7768212	
5093847	5423979	5976630	6267122	7026610	7787131	

Appendix K Medication error cases with narrative summaries

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
6020319-0 23-Dec-08	Dose omission- Pen was empty	A 71 years old female stated her Levemir flexpen were empty. Her usual dose was 30 units every morning.
7299589-7 23-Dec-10	Dose omission- Operator error	This spontaneous case was initially reported by a pharmacy technician as "defective FlexPen and high blood sugars" and subsequently as "operator error nothing wrong with the FlexPen" and concerns a patient treated with Levemir Flex Pen. A pharmacy technician reported that a nurse tried to give 100 units of the product in question to a patient in the hospital however, by looking at the stopper in the Flex Pen, it appeared the product was not given and the patient's blood sugars went up to 400 mg/dl. She stated that she was pretty sure that patient did not receive insulin and the FlexPen was defective. Follow-up information was received in direct conversation with the pharmacy technician via phone who stated that they got the FlexPen to work, but rather that it was an operator error.
8005499-X 23-Nov-11	Dose omission-	A consumer reported nausea, omitted one dose of Novolog which resulted in high blood sugar". It concerned a patient treated with Novolog FlexPen and Victoza and Lantus insulin.
7273675-X 1-Dec-10	Dose omission- Pen was empty	A consumer's son used an empty pen and thought he was getting his insulin. A 74-year-old male patient treated with Novolog FlexPen (insulin aspart) for insulin-requiring type II diabetes mellitus. A man reported that his father had been administering his daily doses of insulin from Novolog Flex Pens which were apparently empty although the patient received them new approximately 2-3 weeks earlier. As a result of not receiving his insulin over the course of a few days, the patient's blood sugars increased and he was subsequently hospitalized for four days.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
6120325-1 12-Mar-09	Dose omission- Could not see the amount of insulin left in the pen injector due to the same orange color covering the insulin and on the plunger.	The patient brought his Novolog Insulin Flex pen to work, believing he had enough for the day. When he dialed up his lunch dose, he realized he only had 1 unit left in the pen, and required 6 units. The new pen design uses an orange coating around the insulin chamber. The orange plunger inside is very difficult to see inside.
	Total Dose Omission cases = 5	
5513706-8 13-Nov-07	Improper storage- Cold pack burst during shipping	A 74-year-old female patient treated with NovoLog Mix 70/30 FlexPen (dual-acting insulin aspart) reported that she received the product through a mail order pharmacy on 14-JUN-2007. She claimed that the freeze pack burst open and as a result, the product was given to her warm. She began to use the product while on vacation. The next morning, on (b) (6), she felt really nauseous and passed out. She was hospitalized. The woman was given another NovoLog Mix 70/30 FlexPen at the hospital and felt a lot better. She was discharged. She reported that she firmly believed that the cause of the event was from the "warm" NovoLog Mix 70/30 FlexPen insulin that she received through the mail order.
7299588-5 23-Dec-10	Improper storage Product shipped warm from mail order	A male patient treated with Levemir (insulin detemir) FlexPen was hospitalized with diabetic ketoacidosis on two separate occasions following use of Levemir FlexPens that arrived warm from a mail-order pharmacy. She stated that there were two such shipments. After the patient was administered insulin (type unspecified) from a local drugstore, he became stable. In a follow up letter, the patient's mother stated that there was not a problem with the product, but rather, a problem with shipping methods used by the pharmacy. The issue was resolved with the pharmacy.
6550349-1 25-Jan-10	Improper storage- Stored in refrigerator after use	A 77-year-old female patient being treated with NovoLog FlexPen (rapid acting insulin aspart) reported that she was hospitalized for congestive heart failure, an amputation, high blood pressure and high blood sugar. The patient also mentioned that she was storing her in-use FlexPen in the refrigerator after use. (The hospitalization cannot be definitively linked to improper storage.)

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
6456804-7 25-Nov-09	Improper storage- Stored in refrigerator after use	A 74-year-old male patient treated with Novolin N and NovoLog FlexPen (rapid-acting insulin aspart) experienced high blood sugars and bruising at the injection site. The patient's wife stated that she was storing the in-use FlexPens in the refrigerator. Of note, the patient continued to receive the products in question while the event was ongoing. (Adverse reaction cannot be definitively linked to improper storage.)
7417542-7 15-Apr-11	Improper storage- Stored in refrigerator after use	A 36-year-old female treated with NovoLog FlexPen (rapid acting insulin aspart) and Levemir FlexPen (insulin detemir) visited the emergency room (ER) with a complaint of nausea, vomiting and lower pelvic pain. In the ER her blood work and a urine analysis was done which showed no infection. The patient stated she was dehydrated and they treated her with intravenous (IV) fluids. She was released from the ER. In addition, the patient reported she was storing opened FlexPens in the refrigerator and was concerned that storing the pens incorrectly might have caused nausea and vomiting.
7170140-5 17-Dec-10	Improper storage- Stored in refrigerator after use	An 80-year-old female patient treated with NovoLog FlexPen (rapid-acting insulin aspart) and Lantus Solostar (insulin glargine) reported that she began feeling very weak and like she was falling asleep, dizzy and tired. While at an appointment with a diabetic educator, she was instructed to go to the emergency room because her "blood pressure was low." She reported that the only treatment she received was intravenous (IV) saline and an aspirin "in case it was a heart attack". She was released home that same day. The patient stated that the ER physicians did not mention any causal relationship between the events and the suspect products. The patient additionally reported that she had been storing the NovoLog FlexPen in the refrigerator, for the previous 2 weeks. When informed that such storage conditions were not recommended for NovoLog FlexPen, while in use, the patient questioned if the improper storage of her FlexPen may have contributed to the events.
6505409-8 18-Dec-09	Improper storage- Stored in refrigerator after use	A 73-year-old male patient treated with NovoLog FlexPen (rapid-acting insulin aspart) experienced falls on many occasions that resulted in approximately six hospitalizations A consumer reported that her husband felt weak, and fell, after he injured his toe As a result, the patient was admitted to the hospital. The patient was discharged from the hospital, but he was brought back "within hours" due to a high temperature. It was also reported that the patient used the NovoLog FlexPen, and the consumer always refrigerated the product after it was opened.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
7272844-2 1-Dec-10	Improper storage- Stored in refrigerator after use	The wife of a 46-year-old male patient treated with Novolog Mix 70/30 FlexPen (dual-acting insulin aspart) reported that her husband was slurring his speech, shaking and dazed while at work. The patient eventually passed out and the paramedics were immediately called. The paramedics arrived and found that the patient's blood sugar was between 30 and 35 mg/dl, and his jaw was locked. The paramedics administered intravenous glucose and the patient woke up. The patient felt better upon awakening, and did not wish to be taken to the hospital. The patient experienced shaking while at home. As a result, the woman checked her husband's blood sugar level and found it was 30 mg/dL. The consumer quickly gave her husband some candy and orange juice, and after some time, reported his blood sugar increased to 67 mg/dl. The consumer mentioned that her husband stored the in-use Novolog Mix 70/30 FlexPen in the refrigerator. The patient recovered and was fine at the time of the report.
7273190-3 1-Dec-10	Improper storage- Stored in refrigerator after use	A female patient treated with NovoLog FlexPen (rapid-acting insulin aspart) reported that she never used insulin before, and her diabetes mellitus was managed with Glucovance (glibenclamide; melformin hydrochloride). The patient's Glucovance therapy was temporarily stopped. As a result, the patient's physician gave her a sample of the NovoLog FlexPen to temporarily use. The patient took a dose of the product, and then stored the in-use NovoLog Flex Pen in the refrigerator. The patient experienced high blood sugars of 460 mg/dL later that same day. and went to the emergency room, and she was treated with intravenous insulin. The patient reported that her blood sugar went as high as 496 mg/dl in the emergency room. The suspect FlexPen was discarded and the patient was given a new NovoLog FlexPen. The patient was released with a blood sugar level of 192 mg/dl. She was not admitted into the hospital. The NovoLog Flex Pen was stopped and Glucovance was restarted. The patient then experienced high blood sugars of 267 mg/dl.
	Total Improper Storage cases = 9	

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5241393-5 20-Feb-07	Improper dose: Overdose	A 55-year-old female patient treated with NovoLog Mix 70/30 FlexPen reported that prior to her morning breakfast she accidentally administered 100 IU of NovoLog Mix 70/30 FlexPen instead of 25 IU. Her fasting blood glucose level that morning was 189 mg/dL. She went to bed to lie down, and woke up a few hours later and discovered the emergency paramedics personnel reviving her. Paramedics advised her that she experienced hypoglycemic unconsciousness and hypoglycemic seizure. She did not receive any medical treatment for the events. Her blood glucose level was 27 mg/dL. Paramedics had the woman drink a Coke and eat some peanut butter to resolve the low blood glucose level. She discovered that the FlexPen had 200 IU remaining, and she realized that she had accidentally administered 100 IU that morning.
6082475-8 26-Jan-09	Improper dose: Overdose- The patient could not see the dose dialed on the pen injector	A 64-year-old female patient treated with Levemir (long acting insulin detemir) FlexPen ate a normal breakfast and administered a dose of insulin around 9:15a.m. At 9:45a.m., the woman reported she was discovered unconscious by her caregiver. The caregiver measured her blood glucose level, which was 22 mg/dl and she placed a glucose tablet under the woman's tongue. The woman regained consciousness shortly afterward and she was administered two additional glucose tablets before the event fully resolved. The woman stated that she suspects that she administered more than her prescribed dose of insulin because she can not see the dose number that is dialed on the Flex Pen and was judging the amount of insulin administered by looking at the clear insulin reservoir on the FlexPen. The woman stated that she switched from utilizing Lantus (insulin glargine) 100 units at bedtime approximately one week prior to the event. She did not have any changes in diet, activity level or health status prior to or during the event.
7198135-6 27-Dec-10	Improper dose: Overdose- Extra dose administered because patient did not believe pen administered the dose initially,	The wife of an 80-year-old male patient treated with NovoLog FlexPen (rapid-acting insulin aspart) The patient's wife reported that her husband took his regular dose of NovoLog 3 units at night and felt the insulin did not get dispensed. Therefore, he gave himself another injection of 3 units of NovoLog and felt hypoglycemic and low heart beats. The patient went to the emergency room (ER) and was hospitalized. The patient was treated with intravenous glucose, IV fluids and close monitoring of his heart. He was in the hospital for 3 to 4 days and was released.
6241671-7 17-Jun-09	Improper dose: Overdose	A patient took 120 units instead of 60 units while using Levemir FlexPen.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
7277251-4 1-Dec-10	Improper dose: Overdose- Patient misunderstood how to use the pen injector.	A female patient treated with Novolog Mix 70/30 FlexPen (dual-acting insulin aspart) reported that she misunderstood the directions with her Novolog Mix 70/30 FlexPen and administered 100 units of insulin instead of her recommended amount of 52 units. As a result of the additional insulin, her blood glucose dropped in the range of 20's mg/dl (exact blood glucose results unknown). She ate food and took glucose tablets to increase her blood sugar, however that did not help. She was unsure if she passed out or was unconscious. Her significant other called the fire department and the emergency medical service (EMS). The EMS treated her with intravenous glucose and her blood sugar increased to 233 mg/dL. It was unknown if any treatment was provided for the high blood sugar. She stated that she was not taken to the hospital.
7917543-6 16-Nov-11	Improper dose: Overdose	A 59-year-old female patient treated with Levemir (insulin detemir) and NovoLog FlexPen (insulin aspart) reported that she experienced dizziness, seizure, and passed out. Per the physician, she was brought to the emergency room "apparently comatose in diabetic ketoacidosis". The patient reported to the physician that she was hospitalized for ten days and discharged (date unknown) upon recovering. Furthermore, the physician reported that on an unknown date the patient was taken to the emergency room once more due to overdosing with insulin which caused hypoglycemia. The patient reported to the physician that she was kept overnight in the emergency room until her blood sugars returned to normal and was instructed to take her Levemir (insulin detemir) twice a day and to avoid the NovoLog.
5206899-3 30-Oct-06	Improper dose: Overdose No details for overdose but concern noted for similarity of the pens making easy to confuse.	A female patient treated with Levemir FlexPen (Insulin Detemir) from and Novolog FlexPen (Insulin Aspart) reported that because the Novolog and Levemir FlexPens look so similar she is always afraid that she'll confuse them. She is supposed to take 20 units of Levemir in the a.m. and 10 units at night. For her nighttime dose on 13-JUL-2006, she mistakenly took 20 units of Levemir and did not take any Novolog. She ate something and recovered from the event on 13-JUL-2006. She also reported that she had a low blood sugar of 78 mg/dl in the nighttime on 12-JUL-2006. She ate something and two hours later it was 58 mg/dl so she ate some more. She was fine in the a.m..

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
7026610-3 4-Oct-10	Improper dose: Overdose- The patient did not understand his disease completely and did not understand how to dose the Novolog. These suggest a lack of training from the Healthcare provider.	An 85-year-old male patient treated with Levemir FlexPen (insulin detemir) and NovoLog FlexPen (rapid-acting insulin aspart) single dose felt acutely ill, was confused, hypoglycemic, EMT 911 was called and after treatment the patient woke up immediately. The patient reported he had a blood sugar reading of 146 mg/dL at 7:30am and then took Levemir FlexPen 20 units. He reported that at 1:20pm his blood sugar reading was 161 mg/dL and he decided to administer 20 units of NovoLog which he had never used previously. He reported that within two hours he became delirious and unconscious, which he described as insulin shock. His wife summoned emergency medical technicians (EMT) who, upon their arrival, could not get a blood sugar reading because it was too low. HIs physician reported there were no recent changes in diet or physical activity and a causal relationship was reported as a probable accidental overdose on Novolog. The patient's wife thinks the patient may have taken too much Novolog, by accident. The patient stated that he did not know his normal blood sugar range, he was not sure of how many units of insulin he generally required and stated that he would "wing it" (referring to the dose of Novolog). The outcome of insulin shock and loss of consciousness was reported as recovered.
8107541-4 23-Dec-11	Improper dose: Overdose Administered extra injection.	A 50-year-old female patient treated with Levemir FlexPen (insulin detemir) reported that she accidentally administered an extra injection of 34 units of Levemir on an unknown date. She went to the hospital, where she was admitted overnight. She reported that her blood glucose levels were monitored every hour, however, laboratory testing results and treatment details were not provided. The patient reported injection site pain due to the difficulty with the push button on the FlexPen. The outcome of "took an extra dose of Levemir" was recovered.
7272728-X 1-Dec-10	Improper dose: Overdose- The patient could not see the numbers on the dial because they were too small.	An 87-year-old female patient treated with FlexPen reported that her friend was previously using Novolin 70/30 Innolet (insulin human) and was switched to a "FiexPen". The reporter stated that because the numbers were so small on the Flex Pen dial and the patient was blind, the patient gave herself too much insulin and went into diabetic shock. The patient was brought to the hospital for the diabetic shock.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5345740-5 30-Apr-07	Improper dose: Overdose The patient repeated morning dose.	A 78 year-old male patient treated with Levemlr FlexPen (Insulin Detemir) reported that after consuming breakfast, he accidentally administered a duplicate dose of the product in question. His blood glucose level, prior to the administration of the product in question, was 47 mg/dl. His blood glucose level after the administration of the product in question was not measured. He did not treat the low blood glucose level, except that he consumed breakfast during his normal routine.
8036773-9 11-Jan-12	Improper dose: Overdose The patient thought he was supposed to hear a click for each unit administered and repeated the 5 units dose	A 78-year-old male patient treated with NovoLog FlexPen (rapid acting insulin aspart) concomitantly administers glipizide, Norvasc (amlodipine), carvedilol, Plavix (clopidogrel), Requip (ropinirole), finasteride, ursodiol and gabapentin. The patient, who administers NovoLog FlexPen on a sliding scale of 2-3 units for a blood sugar greater than or equal to 160 mg/dl, reported that his blood sugar level was 185 mg/dl. The patient exercised and ate his breakfast of oatmeal and his blood sugar level was 215 mg/dl. The patient administered a 5 unit dose of NovoLog FlexPen and fell asleep. Per the physician, the patient thought he should hear a "click" with each unit of insulin delivered. Since he didn't hear a "click", he re-administered his dose. When the patient's wife could not wake him up several hours later she called the Emergency Medical Technicians (EMT). The EMT noted the patient's blood sugar was 20 mg/dl and gave the patient "sugar injections" but that didn't arouse him so they slapped him to wake him up. The patient's blood sugar level had risen to 61-71 mg/dl and he was transported to the hospital. The patient was admitted to the hospital and he heard someone say that he had overdosed himself. All of the patient's symptoms resolved by the time he was discharged the next day.
7058713-1 22-Oct-10	Improper dose: Overdose – The patient confused evening dose of study drug with lunch time dose of Novolog	A 57-year-old female patient had started on trial drug and she experienced wrong drug administered. The patient was visiting family out of state and reported she was distracted when preparing to take insulin. The patient felt she took 61 IU of aspart instead of 10 IU as prescribed, however she was not sure. The patient was supposed to take SIBA/comparator 61 IU with dinner. The patient presented herself to the emergency room as she felt flushed after ingestion of extra insulin. The patient was awake, alert, oriented in time, place and person. The patient ate a meal. The blood glucose was 90 mg/dL. The patient had some bruising into the skin from the insulin spot.. The patient was observed over night and was monitored to make sure she was not hypoglycaemic. The patient had recovered from the event and was discharged from the hospital.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5318986-X 2-Feb-07	Improper dose: Overdose Patient used Novolog pen rather than Lantus Opticlik.	The woman stated that she had been using the NovoLog FlexPen for one week. The woman's blood sugar was 425 mg/dL. She confused her Lantus dose with her NovoLog dose and injected 60 units. The woman stopped at 60 units because the NovoLog FlexPen only dials to 60 units. Within 20 minutes her blood sugars dropped and she experienced dizziness, nausea, but did not pass out according to the physician. The patient stated that she was unconscious for a few minutes and then came to on her own without treatment. The patient had not eaten anything that day and her blood sugar level had only dropped to 375 mg/dL, so she administered another 40 units of the NovoLog FlexPen instead of the Lantus, and she became dizzy and nauseous again (blood sugar level unknown). The woman reported that during the second episode she did not lose consciousness at any time during the event. She ate a bowl of ice cream and her blood sugars levels normalized the same day. The woman reported that she was seen by her physician and switched her insulin regimen from the NovoLog FlexPen to NovoLog Mix 70/30 (dual-acting insulin aspart). At the time of the initial report the event had not recurred since she switched to NovoLog Mix 70/30.
6403231-4 16-Oct-09	Improper Dose: Overdose	The wife of a patient reported that after her husband was started on a sample of NovoLog FlexPen that he was hospitalized. She reported that he was admitted to the intensive care unit for a staph infection, which she described as "deadly infection". The infection was not related to his diabetes. While in the hospital, he was overdosed by being given too much insulin (type and dose unknown). At the time of the overdose, he was being administered insulin before and after each meal. She stated that for breakfast all he ate was a piece of toast. Three hours after insulin injections at the clinic, he would experience sweats, feel sick, and his sugars would drop about 40 to 50 mg/dL. She reported that she treated him with orange juice and food for his low blood sugar. She said that her husband was at home at the time of her report and was doing very well. She stated that she needed to use the FlexPen only once per week. During her report, she learned that the NovoLog FlexPen is not recommended to be utilized after 28 days in-use time. She reported that her physician and pharmacist did not know how long the product was good for. She reported that she was afraid to use the FlexPen in question, as it was over a month old, The patient, being on dialysis and the fact that the NovoLog FlexPen was reportedly used longer than what is recommended may have been the possible sources of the staph infection.
	Total Improper Dose Overdose cases = 15	

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5206896-8 30-Oct-06	Improper dose: Under dose Patient misunderstood how to set dose. (10% of prescribed dose)	A male 61 year old patient treated with Levemir FlexPen (Insulin Detemir) mistakenly only administered 4 units instead of the prescribed dose of 40 units at therapy initiation and each subsequent day afterwards. He reported that he did not realize that he had to turn the FlexPen dial to 40 units, resulting in high blood sugars. The patient was instructed on FlexPen usage and dial-up technique and was able to correctly use the dial-up technique. He stated that he will administer the correct dosage tonight. The high blood sugars were treated with additional units of insulin, but still persisted.
6242990-0 17-Jun-09	Improper dose: Under dose (10% of prescribed dose)	A patient (gender: Male, age: 66 Years) treated with Levemir FlexPen (Insulin Detemir) reported that he was incorrectly taking 1.5 international units of Levemir instead of the prescribed 15 International units.
6241274-4 17-Jun-09	Improper dose: Under dose Patient believes he received incorrect directions from pharmacist. (10% of prescribed dose)	A patient (gender: Male, age: 32 Years) treated with Levemir FlexPen (Insulin Detemir) reported that he experienced the event when utilizing the product in question. The man stated that the events were due to improper instructions by his pharmacist. He said that the pharmacist advised him to dial the pen to 6 units instead of 60 units. The patient stated that he was now dialing the pen correctly to sixty units and was continuing the product. The patient also added that he had been storing the pen in the refrigerator after use.
5507818-2 30-Oct-07	Improper dose: Under dose (10% of prescribed dose)	A 73-year-old female patient treated with Levemlr FlexPen (long acting insulin detemir) accidentally administered the incorrect dosage. She administered 2 units twice a day instead of 20 units twice a day and subsequently experienced high blood sugar levels. Her high blood glucose levels ranged from 300-500 mg/dl. She was seen at the emergency room for high blood sugar. Her blood glucose level at that time was 526 mg/dl. She was treated with two bags of sodium chloride intravenously and received 10 unit of insulin (name unknown) intravenously via an insulin drip. Her blood glucose level decreased to 408 mg/dL and she was discharged from the hospital the same day in stable condition. Furthermore, while in the hospital she realized that she was administering the wrong dose of the product and considered the medication error to be resolved. She stated that she would be following-up with her primary care physician. The following day, she administered the correct am dose of 20 units and experienced low blood sugar with symptoms of sweating, nausea, diarrhea, and weakness. She reported that her blood glucose level was 47 mg/dl. She ate a plum and drank soda to treat the event and her blood glucose level increased to 428 mg/dl. No medical treatment was received.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5094895-9 28-Jul-06	Improper dose: Under dose Patient misunderstood how to use the device.	A patient (gender: Female, age: 57 Years) treated with Levemir FlexPen (Insulin Detemir) reported experiencing high blood sugar readings after she injected one unit instead of her prescribed dose of fifty units when she utilized the product for the first time. She stated didn't realize she had to turn the FlexPen dial to the number 50 to deliver fifty units of insulin. The woman reported that she did not receive any treatment for the event.
5504663-9 30-Oct-07	Improper dose: Under dose- The patient and caregiver were new to the FlexPen. (10% of prescribed dose)	A patient (gender: Male, age: 80 Years) was treated with Levemir FlexPen (Insulin Detemir) for Insulin-requiring type II diabetes mellitus. A woman reported that her husband experienced high blood sugar readings while using the product in question. Since he just started using the product today, I went through the directions for using the device and discovered that she only gave her husband two units instead of 20 units as prescribed.
6238660-5 17-Jun-09	Improper dose: Under dose (10% of prescribed dose)	A patient (gender: Female, age: unknown) treated with Levemir FlexPen (Insulin Detemir) for "Diabetes mellitus" reported that she experienced dehydration, very sick, high blood sugars and taking 2 units instead of 20 while utilizing the product in question.
5345774-0 30-Apr-07	Improper dose: Under dose The pen dials to 60 units.	A patient (gender. Male, age: 48 Years) treated with Levemir FlexPen (Insulin Detemir) reported that his physician prescribed one injection of 100 units daily of Levemir FlexPen; however, the man only administered 60 units dally instead because the FlexPen dialed only to 60 units, and he did not want to perform two injections.
5504495-1 30-Oct-07	Improper dose: Under dose	A patient (gender. Female, age: 52 Years) treated with Levemir FlexPen (Insulin Detemir) reported that she experienced high blood sugars because she administered the wrong dose of insulin. The woman stated that she started the product about a week ago August 21, 2007 and administered 6 units instead of 60 units. She stated that she had a very light dinner the night before she woke up with high blood sugars of 234 mg/dl. No treatment was received for the event reported.
6083854-5 4-Feb-09	Improper dose: Under dose	A woman treated with NovoLog FlexPen (Insulin Aspart) reported that she took 3 units of the Novolog instead of 5 units. It concerns a 26 year old female. Her blood glucose level in the morning was 207 mg/dL.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5345678-3 30-Apr-07	Improper dose: Under dose	A patient (gender: Female, age: 37 Years) treated with Levemir FlexPen (Insulin Detemir) reported that she accidentally administered two units of the product in question instead of ten units.
5423979-8 27-Jul-07	Improper dose: Under dose	The woman reported that her 55 year old husband accidentally administered 7 units instead of 15 units of the product in question and then experienced buzzed feelings.
5423362-5 27-Jul-07	Improper dose: Under dose	A male patient." treated with Levemir FlexPen (Insulin Detemir) was only dialing the pen to 3 when he really needed to be dialing to 30 for 30 units
5505415-6 30-Oct-07	Improper dose: Under dose Patient misunderstood how to use the device. (10% of prescribed dose)	A 54 year-old woman reported that experienced high blood sugars on September 20, 2007 because she dialed her FlexPen to 6 units instead of 60 units. She did not realize that she had to dial up to the number 60 to get 60 units.
	Total Improper Dose: Under dose cases =14	
4852137-0 12-Dec-05	Wrong drug The pens are difficult to differentiate, only the orange button.	Novolog Flex Pen was dispensed by a pharmacy instead of Novolog Mix 70/30 Flex Pen. The patient was independent with administration of his insulin; he was taught ahead of time using a practice pen. Therefore a home visit was not made initially. The patient reported by telephone that his blood glucose was 498. A diabetic nurse specialist therefore made a home visit to assess the situation and discovered the dispensing error. Without the packaging for identification, the pen apparently has a small orange mark on top for identification. This was not readily observable until a close look was done. The situation was immediately corrected by the diabetic nurse specialist.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5963111-5 24-Nov-08	Wrong drug	A 71 year old male patient treated with NovoLog FlexPen (rapid-acting insulin aspart) and Lantus (insulin glargine) mixed up his medicines and injected the wrong insulin. He was supposed to administer his normal daily dose of 18 units of Lantus; however, he confused the pens and mistakenly administered 18 units of the NovoLog instead. He developed spinning sensation and lost consciousness, fell and cut his head. His wife called the emergency medical services (EMS) and they arrived to the house. The paramedics tested his blood glucose which was 23 mg/dl and he was given intravenous glucose (type unknown) he was taken to the emergency room and was given some food. He received a couple of stitches for the cut on his head, and then sent home. The patient's wife now double checks before her husband administers insulin.
6082539-9 2-Feb-09	wrong drug confused Novolog pen for Lantus Opticlik	A wife reported that her husband mixed up his medicines and took the wrong insulin. He was supposed to administer his normal daily dose of Lantus; however he confused the pens and mistakenly administered 21 units of the Novolog instead. His normal daily dose of Novolog was 5-9 units (sliding scale) TID. As a result, his blood glucose decreased and he became incoherent. His wife was present at that time and she immediately gave him something to eat. He still was incoherent and subsequently she administered an injection of Glucagon, using a Glucagen Hypokit. His blood glucose level normalized (level unknown) and no other treatment was received.
7277283-6 1-Dec-10	Wrong drug The patient was distracted .	A 69-year-old female patient treated with Novolog FlexPen (rapid-acting insulin aspart) and Levemir FlexPen (long-acting insulin detemir) reported that one evening in (b) (6) she got distracted and injected 20 units of Novolog when she was only supposed to administer 60 units of Levemir at that time. She then administered 60 units of Levemir to correct her mistake. Once she realized that what she had done was incorrect, she went directly to the hospital. She was given a full meal to eat to treat the event and remained in the emergency room for 4 hours and was then sent home.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
8024473-0 30-Nov-11	Wrong drug The patient confused insulin in the same FlexPen presentation when administering a partial dose remainder.	A 71-year-old male patient treated with Levemir FlexPen (insulin detemir) and NovoLog FlexPen (rapid-acting insulin aspart) administered 31 units of insulin from one of his Levemir FlexPens. As that pen was then empty, he reached for another FlexPen to administer the remaining 19 units of his Levemir dose. He inadvertently grabbed a Novolog FlexPen and administered 19 units of Novolog insulin. The patient was concerned that his blood glucose would drop severely, so he called his physician, who advised him to drink orange juice. The patient called the poison control center as well and again was advised to drink orange juice. the poison control center summoned emergency medical services to the patient's home. The patient was taken by ambulance to a hospital. He was administered intravenous saline solution and monitored. He was released approximately three hours after his arrival.
5034771-0 2-May-06	Wrong drug The similarity of the pens. The patient covered the label with her hand when injecting the insulin.	A 75-year-old woman, treated with Novolog FlexPen (insulin aspart) prefilled disposable pens and Levemir FlexPen (insulin detemir) mistakenly administered Novolog FlexPen instead of Levemir FlexPen The woman called the paramedics to her home after she realized she had mistakenly given herself 75 units of Novolog at bedtime instead of 75 units of Levemir. She reported that the paramedics started intravenous fluids and then transported her to the emergency room. Her blood glucose level in the ER was 59 mg/dl. Intravenous treatment was changed to a dextrose solution. She was given something to eat, She was discharged the next day. The woman reported that the label with the product name was covered by her hand when she administered the erroneous Novolog injection.
5423506-5 27-Jul-07	Wrong drug FlexPen and Kwikpen are both blue.	A 57 year old woman reported that she accidentally administered the wrong product. She was supposed to take 14 units of Levemir (Insulin Detemir) using a FlexPen, however; she confused the two pens because they are the same color blue and administered 14 units of Humalog Pen (Insulin) instead. She immediately noticed the mistake and drank two glasses of orange juice. She drove herself to the emergency room and at the hospital her blood glucose level was 179mg/dl. She was treated intravenously with a glucose drip (dose unknown) and drank an additional glass of orange juice. Her blood glucose increased to 200-300mg/dL and was discharged that same day in stable condition.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5345762-4 30-Apr-07	Wrong drug The patient gave herself the morning Novolog dose with Levemir FlexPen.	A woman reported that she administered 46 units of the Levemir FlexPen (insulin detemir) instead of the NovoLog (rapid-acting insulin aspart) FlexPen by accident. The woman reported that she usually administers 116 units per day at night of Levemir and 45 units per day of the Novolog FlexPen. The woman did not experience any adverse event after she administered the wrong insulin. No treatment was received and her physician told her to check her blood sugar level throughout the day and decrease her Levemir dosage that evening.
4808480-4 21-Oct-05	Wrong drug The reporter noted inadequate differentiation noted. Dispensing error by pharmacy.	Physician prescribed Novolog Flexpen and the patient received Novolog 70/30 from the pharmacy. Error was caught when patient brought the device in to his physician's office for teaching. Second time this happened within a 1 month time period. Labeling is not adequate to prevent dispensing errors.
6083902-2 4-Feb-09	Wrong drug	The wife of a 66 year-old male patient treated with Novolog FlexPen (rapid-acting insulin aspart) and Levemir FlexPen (insulin detemir) reported that her husband mistakenly had injected 60 units Novolog FlexPen instead of his prescribed 60 units of Levemir FlexPen at bedtime. As a result, the patient subsequently experienced a blood glucose level of 30 mg/dl. The patient went to the emergency Room where he received intravenous glucose (amount unknown) and the event resolved that same day. The reporter is also a medical doctor
6196848-6 20-May-09	Wrong drug	A 67-year-old female patient treated with NovoLog FlexPen (Aspart, rapid acting insulin) and NovoLog Mix 70/30 FlexPen (dual-acting insulin aspart) reported that the FlexPen was not working properly. She stated she does not perform air shots prior to injecting. The patient additionally reported that the pharmacist dispensed wrong insulin Novolog FlexPen instead of correct insulin NovoLog Mix 70/30 FlexPen The patient did not take the wrong dispensed insulin (NovoLog FlexPen).

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
4634247-6 13-Apr-05	Wrong drug Physician office dispensed Novolog for Novolog Mix 70/30. The patient noted the cap was orange and the insulin was clear but administered the incorrect product.	An 82-year-old woman who was mistakenly introduced to NovoLog FlexPen (insulin aspart) instead of her prescribed NovoLog Mix 70/30 FlexPen (dual acting insulin aspart). The woman received two boxes of NovoLog FlexPen (insulin aspart) from her physician's office. While preparing her injection with the first NovoLog FlexPen (insulin aspart) prefilled disposable pen, she noticed that the cap was orange and the insulin was clear, unlike her normally prescribed NovoLog Mix 70/30 FlexPen (dual-acting insulin aspart) prefilled disposable pens. She reported that even though she noticed a visible difference, she administered an injection, and her blood glucose levels became elevated. Over the next 2 weeks, she continued using the insulin in question from the first and second suspect boxes of insulin. During that 2 week time period, her blood glucose levels remained intermittently elevated. She was able to temporarily decrease her blood glucose levels by taking additional sliding scale doses of the insulin in question. She reported that she eventually went to see her physician because her blood glucose levels were "higher than ever and she just wasn't feeling well". She stated that she did not bring the insulin in question with her so her physician was under the assumption that she was using her prescribed insulin. The physician tested her blood glucose level in the office and it was 400 mg/dL. She reported that he told her to go home and watch her glucose levels over the next few days, and if they continued to be elevated she was to call him back and he would admit her to the hospital. She called the following day to report her blood glucose levels were in the 400-500 mg/dL range and she still did not feel well. Her physician admitted her through the emergency room. After her husband brought the insulin in question into the hospital and showed it to the doctors, they were able to determine that her high blood glucose levels were caused by her using NovoLog FlexPen (insulin aspart) instead of her prescribed NovoLog Mix 70/30 FlexPen (dual-acting insulin aspart). She was discharged to home once her blood sugars normalized.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5319129-9 2-Feb-07	Wrong drug The patient receiving two insulin and confused the doses of the two products.	A 76-year-old man, treated with Novolog FlexPen (rapid-acting insulin aspart) since 2004 and other suspected drug, Lantus (insulin glargine) 3 ml cartridge system since 2004 for type 2 diabetes mellitus. Medical history includes decreased vision. On 03-JUN-2006, the man's blood sugar was 121 mg/dl prior to administering his insulin that morning before breakfast. The man stated that he mistakenly dialed up 11 units on his Novolog FlexPen, and four units on his OptiCiik pen which he uses to deliver his Lantus insulin, instead of his prescribed dose of four units of NovoLog and 11 units of Lantus. He reported that he was at a service station a short while afterward and felt his blood sugar becoming low (level unknown). He sat down in his truck and subsequently passed out until someone knocked on the truck window two hours later. The man was given approximately four ounces of grape juice and the paramedics were called. The man reported his blood sugar was 99 mg/dL upon the arrival of the ambulance. He received treatment with unspecified intravenous fluids in the ambulance and he was admitted to the hospital that day. The man continued to receive treatment with intravenous fluids in the hospital and he underwent unspecified diagnostic testing, which he reported showed venous stasis. During the hospitalization, the man was evaluated by an endocrinologist, who increased his dose of Lantus insulin to 12 units at night and decreased his NovoLog insulin dose by 1 unit prior to breakfast, lunch, and dinner. The man reported that the endocrinologist prescribed his Lantus dose to be administered at night to decrease the chances of confusing the insulin and doses again.
4421420-5 6-Jul-04	Wrong drug The pharmacy dispensed Novolog FlexPen rather than Novolog Mix 70/30.	A 41-year-old man, who was mistakenly introduced to Novolog FlexPen (insulin aspart) prefilled insulin syringes on (b) (6) when his pharmacy dispensed this product instead of his prescribed Novolog Mix 70/30 FlexPen (dual-acting human insulin) prefilled insulin syringes and experienced intermittently decreased blood glucose levels and one episode with a loss of consciousness for which he received medical treatment. The man reported that while in his physician's office, he lost consciousness for a duration of one hour and was transported to the emergency room with a blood glucose level of 22 mg/dL. In the emergency room, he received treatment with intravenous glucose, intravenous fluids and was also given soda and a meal. He was in the emergency room for three to four hours and was discharged.
6082513-2 4-Feb-09	Wrong drug The patient confused the pens.	The physician reported that the patient had confused their Levemir and Novolog FlexPens and had switched doses of the product. The patient was hospitalized

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5551190-9 12-Dec-07	Wrong drug The reporter stated the pen colors are too similar.	A male patient, who is also the reporting physician, who mistakenly administered NovoLog FlexPen (rapid-acting insulin aspart) instead of Levemir FlexPen (long acting insulin detemir) accidentally administered the wrong insulin which resulted in a syncopal episode and he was hospitalized. It was reported that the patient should have used Levemir FlexPen and instead administered NovoLog FlexPen. It was reported that the patient stated that the pen colors are too similar. The overall outcome is reported as "recovered".
5319245-1 2-Feb-07	Wrong drug The reporter noted that the pens look too similar.	The wife of a 47-year-old man treated with Novolog FlexPen (rapid-acting insulin aspart) and Levemir FlexPen (insulin detemir) reported that her husband confused his Novolog and Levemir FlexPens. He administered a bedtime dose of 5-7 units of Novolog instead of Levemir and went to bed. At 2:45a.m., she awoke and her husband was unresponsive with a blood sugar level of 7 mg/dl. She called 911 and administered one tube of oral glucose gel into his mouth. The paramedics arrived and administered intravenous glucose and he recovered from the event. She stated that her husband continued to use the same two Flex Pens after the event occurred and did not have any additional problems. The woman reported that the mix up of the two insulin caused the event because the Novolog and Levemir FlexPens are identical in all aspects except for the orange and green push buttons. She suggested that a change in colour of the complete pen housing would help other people avoid making similar errors.
4516742-3 5-Oct-04	Wrong drug	A physician reported that a male patient received NovoLog FlexPen prefilled insulin aspart in error instead of his prescribed NovoLog Mix 70/30 FlexPen prefilled insulin aspart and experienced a low blood glucose level which was treated with an injection of intravenous dextrose. The physician reported that after the medication error was discovered the patient was placed on another type of insulin (unspecified) and he has not had any further problems.
5596956-4 20-Dec-07	Wrong drug The pharmacy dispensed the wrong pen injector Novolog Mix 70/30 rather than Novolog.	A 50-year-old female patient treated reported that her pharmacy mistakenly dispensed Novolog Mix 70/30 FlexPen instead of her prescribed NovoLog FlexPen (rapid-acting insulin aspart) which she used from JUL-2005 to OCT-2005 . In AUG-2005, the patient experienced low blood glucose levels and was found unconscious. Her blood glucose readings ranged between 30 mg/dL to 50 mg/dl. She was treated in an ambulance by paramedics She was not taken to an emergency room and was not admitted to a hospital.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5051154-8 14-Jul-06	Wrong drug The patient stated that only the button on the pen differs.	A 50-year old woman was mistakenly treated with NovoLog (rapid-acting insulin aspart) FlexPens rather than her prescribed NovoLog Mix 70/30 (dual-acting insulin aspart) FlexPens. The woman experienced a low blood sugar level after her insulin injection and passed out. The woman reported that she did not know how long she passed out for, but when she awoke, she went to the emergency room. The woman reported that she received treatment with unspecified intravenous fluids and was discharged later that same day. The woman stated that she noticed the push button on her FlexPen was orange, instead of black like it usually is and discovered that she had been utilizing the incorrect insulin.
7734077-2 7-Sep-11	Wrong drug The pharmacy dispensed Novolog rather than Novolog Mix 70/30 in error.	A 59-year-old female patient treated with NovoLog Mix 70/30 FlexPen (insulin aspart) and NovoLog FlexPen (insulin aspart) reported she experienced high blood sugar with the use of the NovoLog. The patient received the NovoLog in error from the company from which she receives her insulin. The patient took NovoLog for approximately 3 weeks in error. The patient normally takes NovoLog Mix 70/30, but had not received it for approximately 3 weeks due to the wrong drug being dispensed. The patient felt that the change in insulin resulted in the high blood sugar.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
4176670-2 21-Aug-03	Wrong drug The pharmacy dispensed Novolog FlexPen rather than Novolog Mix 70/30 PenFill in error.	A nurse reported that a 24-year-old man, who was mistakenly introduced to NovoLog FlexPen prefilled insulin syringes (insulin aspart) when his pharmacy had dispensed the product instead of his prescribed Novolin 70/30 PenFill insulin (dual-acting human insulin). The patient's mother originally received an unknown type of insulin at the pharmacy but she returned it as the insulin did not fit in her son's NovoPen 3. The pharmacist then gave her a Novolin 70/30 vial until he could get her a box of the Novolin 70/30 PenFill insulin. The pharmacist mistakenly gave her a box of NovoLog FlexPen prefilled insulin syringes. When she questioned the pharmacist why the insulin product did not look the same as the insulin she normally administers to her son, the pharmacist had told the mother that the product was the correct one and thus she went home with NovoLog FlexPen prefilled insulin syringes instead of his prescribed Novolin 70/30 PenFill insulin. Even though she noticed that the insulin product looked different than usual, she continued to use the NovoLog FlexPen prefilled insulin for the next 3-4 weeks. Her son became lethargic, complained of headaches and was "out of it" during that time. She noticed that his glucose levels always became high around 3:00 p m. However, she thought the blood glucose levels may be elevated because his right thumb had become infected. The mother took her son to the emergency room for his continued high blood glucose levels and for his complaint of stomach pain. The nurse reported that after he received insulin therapy his blood glucose levels normalized and he was discharged. The mother restarted using the insulin in question (NovoLog FlexPen insulin) still not realizing that it was not his prescribed insulin and within 2 - 3 days, his blood glucose level became elevated again. She called her son's physician to inform him that his blood glucose levels had become elevated again, and he prescribed a new dose of the Novolin 70/30, not realizing the mother was using NovoLog FlexPen. Her son's blood glucose levels remains elevated. The son then had bleeding from his mouth so his mother took him to the emergency room. He was admitted with increased blood glucose levels. The patient has recovered from the event.
4896020-3 30-Jan-06	Wrong drug The pharmacy dispensed Novolog rather than Novolog Mix 70/30 in error.	A 52-year-old male mistakenly treated with NovoLog FlexPen (insulin aspart) instead of NovoLog Mix 70/30 FlexPen (dual-acting insulin aspart) when he was dispensed the wrong insulin (NovoLog FlexPen) by the pharmacist and experienced right upper quadrant abdominal pain and high blood sugars. The man reported he went to the emergency room that same day. He reported that he received no intravenous fluids and that he was discharged that evening The patient reported that he saw his physician the following day and it was at that time that the patient realized that he had been dispensed the wrong insulin by the pharmacist. He discontinued the suspected insulin and switched back to the correct insulin (NovoLog Mix 70/30 FlexPen).

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5525183-1 26-Nov-07	Wrong drug The reporter noted confusingly similar packaging between the products.	A male patient was mistakenly treated with NovoLog FlexPen (rapid acting insulin aspart) instead of his prescribed NovoLog Mix 70/30 FlexPen (dual acting insulin aspart) The pharmacy mistakenly dispensed NovoLog FlexPen instead of his usual NovoLog Mix 70/30 FlexPen. The consumer was transported by ambulance, and admitted to the hospital. The consumer was given intravenous intervention. It was reported that the events were the result of confusingly similar packaging between the products. The packaging was reported as being virtually identical, such as to cause confusion and likelihood of error upon dispensing.
4887709-0 19-Jan-06	Wrong drug	Pt received Novolog Flexpen U-100 instead of Novolog Mix 70/30 Flexpen. She gets both products at the same time and the pharmacist labeled the 70/30 Flexpen on a Novolog flexpen box.
5599963-0 23-Jan-08	Wrong drug The patient was prescribed Novolog Mix 70/30 rather than Novolog.	A 52-year-old male patient treated with NovoLog Mix 70/30 FlexPen (Insulin Aspart) reported that he had passed out while he was sleeping. His wife was present at that time and was unable to wake him up. She immediately called emergency medical services The patient was given fluids and he regained consciousness. His blood glucose was reported as 30-40 mg/dL. On another night, the patient passed out a second time while he was sleeping. His wife was again present was unable to wake him up. She immediately called EMS. The patient was taken to the emergency room for further evaluation. He was discharged from the hospital that same day in stable condition. The patient realized that he had been using the wrong product for several weeks. He should have been taking NovoLog (insulin aspart), however he was prescribed the wrong insulin, NovoLog Mix 70/30, by his primary care physician. He discontinued the NovoLog Mix 70/30 and switched back to NovoLog.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
4504573-X 18-Nov-04	Wrong drug Reporter noted the pharmacy place the prescription label (for the correct product) on the wrong box of insulin.	February 24, 2004 A physician telephoned a prescription for his patient into the pharmacy. The prescription was for NovoLog Mix 70/30 FlexPen (dual-acting insulin aspart). Sometime after the prescription was called in, the patient picked up the prescription. However, the medication that was given to the patient was for NovoLog (insulin aspart), not the 70/30 mix that was prescribed. The pharmacist placed the correct prescription label on the wrong box of insulin. On the morning of (b) (6) the 82-year-old female patient took the insulin supplied by the pharmacy and had a ham sandwich for breakfast. The insulin was administered from a pre-filled syringe, and the correct amount prescribed was injected. About 9:45 a.m. that morning, she began to feel ill. Her vision became blurred and she became totally unresponsive. When the ambulance arrived, the attendant found the patient unresponsive, and a test of her blood sugar level revealed that it had plunged to 25. The attendant administered 1 amp of Dextrose 50 i.v. with subsequent blood glucose of 252. The patient was then taken to the Emergency department. She was given some food, but her blood sugar level remained low at 55, and she continued to feel disoriented at 11:30 a.m. She remained in the hospital overnight until her blood sugar level was stabilized and was discharged. The patient's physician diagnosed the patient's condition as hypoglycemia caused by taking the wrong insulin.
4446286-9 7-Sep-04	Wrong drug	A nurse practitioner reported that an 84-year-old man, who was given NovoLog FlexPen prefilled insulin syringes instead of NovoLog Mix 70/30 FlexPen prefilled insulin syringes by a pharmacist, experienced hypoglycaemic coma which required hospitalization The reporter stated that the patient was prescribed NovoLog Mix 70/30 FlexPen prefilled insulin syringes. He went to the pharmacy to fill his prescription for NovoLog Mix 70/30 FlexPen prefilled insulin syringes and was mistakenly given NovoLog FlexPen prefilled insulin syringes. The man followed the prescribed regimen for the NovoLog Mix 70/30 insulin, which was 30 units twice a day. Several days after using the NovoLog FlexPen prefilled insulin syringes, he experienced his first hypoglycemic event and he became confused but did not lose consciousness. His blood glucose level was 40 mg/dL. His daughter treated the event with orange juice and he recovered. Two days later, the patient lost consciousness while driving and was involved in a minor motor vehicle accident. He was taken to the hospital where his blood glucose level was 45 mg/dL. He spent four days in the hospital and upon discharge, he was seen in his physician's office where it was discovered he had been using a NovoLog FlexPen prefilled insulin syringe instead of a NovoLog Mix 70/30 FlexPen prefilled insulin syringe. The patient recovered from the event

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5451128-9 13-Sep-07	wrong drug Patient unclear if prescribing or dispensing error. Patient received Novolog Flex Pen rather than Novolog Mix FlexPen	A 51-year-old female treated with NovoLog (rapid-acting insulin aspart) FlexPens f and NovoLog Mix 70/30 (dual-acting insulin aspart) FlexPens reported that her physician possibly prescribed the wrong insulin and called into the pharmacy NovoLog FlexPens instead of her normally prescribed NovoLog Mix 70/30 FlexPens. The patient was not sure if this was what actually happened. She reported that in addition, the pharmacist dispensed NovoLog FlexPens instead of her usual NovoLog Mix 70/30 FlexPens. She reported that she started taking the incorrect insulin, NovoLog FlexPens and she did not question either the pharmacy or physician or think that anything was unusual that she received different colour FlexPens than she normally uses (orange colour instead of blue). The patient experienced three episodes of very low blood sugars while taking the incorrect insulin, NovoLog. At the time of each episode, she reported symptoms of profuse sweating, nausea, and confusion. The patient stated that she eventually passed-out each time, and her husband called 911 and administered liquid glucose. For all three episodes, the paramedics arrived and administered intravenous dextrose and transported her to the emergency room. She reported that during each emergency room visit, she was treated with intravenous fluids (unspecified) and food, and her blood sugars normalized. The event resolved that same day for each episode and the patient was discharged from the emergency room on the current dose of NovoLog insulin. The patient went to her endocrinologist office for a medical clearance for elective surgery on her drooping eyelids. At that time, she noticed NovoLog and NovoLog Mix 70/30 FlexPen brochures at the receptionist desk and realized that there was a difference in colour between the NovoLog FlexPens (orange) and NovoLog Mix 70/30 FlexPens (blue). After her visit, she immediately stopped taking the NovoLog Flex Pens and notified her primary physician's office of the insulin mix-up. The nurse instructed her to stop the NovoLog insulin and take the NovoLog Mix 70/30 insulin, as she normally did. Her blood sugars have been fine since she stopped taking the incorrect insulin, NovoLog, and restarted her NovoLog Mix 70/30 FlexPens.
4243088-3 24-Nov-03	Wrong drug Confused Novolog for Novolin.	A 73-year-old woman, who was introduced to NovoLog Mix 70/30 FlexPen prefilled insulin syringes has experienced elevated blood glucose levels since she began using the product. The event began after the woman was mistakenly dispensed the insulin in question instead of Novolin 70/30 Prefilled insulin syringes. The woman has poor eyesight and did not realize she was using the wrong insulin so she used the insulin daily. Her blood glucose levels elevated (142 mg/dL- 182 mg/dL) they remain elevated as of the report date.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5051150-0 14-Jul-06	Wrong drug	A 50-year-old woman treated with NovoLog FlexPens (fast-acting insulin aspart) since JUN-2006, rather than her prescribed NovoLog Mix 70/30 FlexPens (dual-acting insulin aspart) for type 2 diabetes mellitus. In (b) (6) on an unspecified date, the woman experienced a low blood sugar level (value unknown) after her insulin injection and she passed out. The woman reported that she did not know how long she passed out for, but when she awoke, she went to the emergency room. The woman reported that she received treatment with unspecified intravenous fluids and was discharged later that same day. On 02-JUL-2006, the woman stated that she noticed the push button on her FlexPen was orange instead of black like it usually is and that was when she discovered that she had been utilizing the incorrect insulin. She stated that she did not know if her pharmacy had dispensed the NovoLog FlexPens to her by mistake. The woman reported that she did not have any changes in her diet, activity level, insulin administration schedule, or health status prior to or during the event. The woman reported that she passed out from low blood sugar on two other occasions in JUN-2006 which have been reported in case numbers 254640 and 254641.
5774849-7 17-Jun-08	wrong drug	A78-year old female patient mistakenly treated with NovoLog FlexPen (rapid-acting insulin aspart) for diabetes mellitus. The pharmacist reported that the patient during hospitalization used NovoLog FlexPen instead of Novolin N (insulin human). Subsequently, the patient experienced atrial fibrillation, low blood pressure, and low blood sugar. Hospital staff cannot confirm whether the error prolonged the patient's hospitalization. Medical intervention was limited to increased monitoring and administration of dextrose. The overall outcome was reported as "unknown". Reporter's causality: unknown Novo Nordisk's causality: reportable Comment: company comment Only limited information was provided in this case. Relevant medical history, concomitant disease /medication, patient's condition at the time of the event and indication for hospitalization are missing. As it is not clear if patient has any concomitant cardiovascular diseases, the event "atrial fibrillation" and "low blood pressure" might be secondary due to the hypoglycemia, which is caused by "medication error". Age is another confounding factor as the patient is 78 years old.
5940516-X 3-Nov-08	wrong drug	Novolog Flexpen was dispensed in place of Novolog 70/30 Flexpen. The label was the correct product, the error was made in technician medication choice and not caught in pharmacist review of the dispensing. This error was reported by patient's caregiver/daughter after noticing a difference in appearance of the product. Patient did use for 1-2 doses with no adverse effects on blood sugar.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
	Total wrong drug cases = 33	
8024459-6 30-Nov-11	wrong technique incorrect teaching by healthcare provider.	A 62-year-old female patient treated with Levemir FlexPen (insulin detemir) and NovoLog (insulin aspart) reported that she was incorrectly instructed by her physician's office, in the use of FlexPens. She stated that she was told that she could "twist the plunger down instead of pushing the plunger" and that as a result, she "did not receive any insulin for a month." She reported that her blood sugar reading was over 1000 and that she experienced blurry vision and muscle cramps in her feet and hands. She was hospitalized and treated with intravenous insulin. Her symptoms resolved except for the blurry vision. At the time of the report, the patient was receiving treatment with both Levemir and Novolog FlexPens twice a day on a sliding scale.
6505355-X 18-Dec-09	wrong technique	An 83-year-old female patient treated with Levemir FlexPen (insulin detemir) reported that she was also leaving the needle attached to Levemir FlexPen between use, was reusing needles, and was not performing a two unit air shot before every injection.
6410112-9 22-Oct-09	wrong technique not completing the air shots and not holding the needle under the skin	A 60-year-old male patient treated with Levemir (insulin Detemir) and ongoing and Actrapid (human insulin) after using Levemir FlexPen for about 6 weeks, noticed that after a few uses of the FlexPen there were air bubbles in the device. The patient reported that he uses a new needle with each injection however he does not perform an air shot before each injection. The patient also advised that he has noticed that after he does his injection that there is some insulin leaking out via the needle tip after he withdraws the needle from under his skin.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
7272777-1 1-Dec-10 8022930-4 30-Nov-11 (Duplicate)	wrong technique pulling the needle out before the injecting the insulin	A pharmacist and a physician reported that the patient would pull the needle out of his skin before the insulin was injected and concerns an 18-year-old male patient treated with NovoLog Mix 70/30 FlexPen. The patient went to the emergency room "recently" due to high blood sugars while on therapy with NovoLog Mix 70/30 FlexPen. The pharmacist subsequently indicated that he consulted the patient's physician about the event and was told that the patient had a high blood sugar of 683 mg/dL and therefore took 30 units of the NovoLog Mix 70/30, and then he took 40 units and another 30 units after that with no response. The patient subsequently went to the emergency room where he was administered 5 units of insulin (type unknown) intravenously, which brought his blood sugars under control. The patient was reported to be fully recovered from the event. The pharmacist stated that the physician believed that the events were due to patient's poor injection technique since the patient would pull the needle out of his skin before the insulin was injected. The patient was retrained by his physician on the proper technique for injecting insulin.
6240738-7 17-Jun-09	wrong technique The patient was not pressing the button to administer the dose of insulin.	An 85 year old male patient A daughter reported that her father experienced the event while utilizing the product in question. His blood glucose was 170 mg/dl. He was dialing the FlexPen to 15 units and removing it with the 15 units still inside. He was not pushing the pushbutton of the Flex Pen to go back down to 0 units.
7768212-7 22-Sep-11	wrong technique reuse of same pen on more than one patient	Emergency Room nurse got two orders for two patients to get Novolog insulin -we only stock this in Insulin pens-, which we do not keep in Emergency Dept. Nurse went to patient care unit and retrieved one Novolog Flexpen, and came back to the emergency dept and gave dose of insulin using pen to the first patient. She then changed out the needle, but used the same flexpen on the second patient. Pharmacy discovered this error the next day during chart review and reported it to the Emergency Room Manager, who then involved infection control, and risk management. The second patient was contacted and came back for Hepatitis testing. The first patient also came back to be tested. All tests were negative.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
5173910-8 14-Dec-06	wrong technique reuse of the needle	A 49-year-old female patient treated with Levemir insulin detemir cleans the injection site with alcohol prior to injection but reuses the needle. The patient developed cellulitis on the panicula, which then went to both thighs. She was given Omnicef 300 mg twice daily. The wound was cultured that same day and revealed Staphylococcus aureus. Her medication was changed to Levaquin 750 mg PO daily. The infection sites appeared to have worsened, and the patient was admitted to a hospital for treatment with Zyvox (linezolid) 600 mg IV every 12 hours for 2 days. She had complained of pain and some redness at the injection sites of the abdomen, and later thighs. The patient was discharged. also indicated he suspects the event of cellulitis is most likely secondary to the patient's injection technique. In addition, the patient reuses the needle for injection which increases the risk for infection.
7292271-1 23-Dec-10	wrong technique The instructions for use missing information to attach needle to pen injector.	A male patient treated with Levemir FlexPen (long-acting insulin detemir) and NovoFine needle (exact gauge unknown) reported that when he first started using the Levemir FlexPen, he had low blood sugars so he fell and broke his finger. The patient used the Levemir FlexPen with Novo Fine 6 millimeter needles, The patient reported that this all happened because there were no instructions on how to properly attach and use the needle to the Levemir FlexPen. No further information was provided.
6088172-7 19-Feb-09	wrong technique	Pre-filled insulin pen devices from different manufacturers (Novolog Flexpen, Novo-Nordisk; Humulin-R Innolet pen, Novo-Nordisk; Humalog Pen, Lilly, Lantus Solostar pen, Sanofi-Aventis) potentially used as multiple-patient injections on as many as 15 hospitalized patients. Nursing staff were trained to use these insulin pen devices as single-patient use and were trained to attach a new sterile pen needle prior to each use, but the manufacturer of these devices need to do more to call attention to the fact that these devices are for single-patient use only. Precautionary/warning labeling to that effect should be prominent on each pen (not just the cardboard package that holds the pens) stating that the pen is for single-patient use only. Additionally, some sort of break-away / tear-away, tamper-evident or opening-evident seal should attach each pen cover to the body of each pen so that when the pen cover is removed, the tamper/open-evident seal is conspicuously torn or opened. The manufacturer of these devices has not done enough to help ensure that safe and appropriate use of these products from the standpoint of in-hospital care.

ISR number & Date received by FDA	Type of medication error (NCCMERP) – Causes or contributing factors	Narrative Summary
6071512-2 6-Feb-09	wrong technique	This facility began using a multi-dose insulin injection pen system. This pen is designed for repeated use on a single patient with a new disposable sterile needle being attached for each injection. Although new sterile needles were used on all patients with every injection, the pen portion of the system may have been used on more than one patient. The facility has taken extra measures to ensure this practice ceases. The facility is working to contact the 2114 patients administered insulin with an insulin pen during this time period and will provide appropriate testing. These pens do not have manufacturing labeling stating that they are for single patient use.
6359382-6 17-Sep-09	wrong technique Incorrect teaching provided by healthcare provider on how to administer the medication.	A 61-year-old female patient treated with Levemir FlexPen (insulin detemir) and NovoLog FlexPen (rapid-acting insulin aspart) reported that her doctor's nurse instructed her to "dial down the dose" instead of depressing the push button to administer the FlexPen insulin. She used the Levemir and NovoLog FlexPens in this manner for approximately four months. She experienced frequent urination and loss of vision. She was taken to the hospital where her blood glucose level registered near 1000 mg/dL. She was treated with intravenous insulin and remained in the hospital for nine days.
	Total Wrong technique cases = 11	
5423940-3 27-Jul-07	Wrong Time The patient misunderstood the directions given by his physician.	A man reported he experienced the events while utilizing the products in question. He misunderstood his physician's directions and administered both insulin at the same time, instead of administering the insulin at separate time intervals. His blood glucose level was 239 mg/dl. He discontinued the Levemir FlexPen and continued to use the Novolog Mix 70/30 FlexPen.
	Total Wrong Time Cases = 1	

Appendix L: International Diabetes Federation Color Code for human insulin

International colour code for human insulin preparations

Product Group	Product	Colour Name	Pantone Colour No.	Colour
Fast acting insulin	Regular	Yellow	123C	
	Regular Buffered	Red	185C	
	Hoechst Pump Insulin	Blue	072C	
Insulin Mixtures (Regular/NPH)	50/50	Grey	445C	
	40/60	Violet	253C	
	30/70	Brown	471C	
	25/75	Turquoise	313C	
	20/80	Magenta	Magenta C	
	15/85	Olive	104C	
	10/90	Blue-Green	328C	
Long acting insulin	NPH	Light Green	375C	
	Lente	Turquoise	312C	
	Ultralente	Dark Green	363C	
	Similente	Light Blue	545C	

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/s/

RICHARD A ABATE
01/15/2013

KELLIE A TAYLOR
01/15/2013

CAROL A HOLQUIST
01/15/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	November 27, 2012
Reviewer(s):	Richard Abate, RPh, MS, Safety Evaluator Division of Medication Error Prevention and Analysis
Deputy Director:	Kellie Taylor, PharmD, MPH Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name(s)/Strength(s):	Tresiba (b) (4) (Insulin Degludec [rDNA origin]) Injection), 300 units/3 mL (100 units/mL) (b) (4) Ryzodeg (70% Insulin Degludec and 30% Insulin Aspart [rDNA origin] Injection) 300 units/3 mL (100 units/mL) (b) (4)
Application Type/Number:	NDA 203314 (Tresiba) NDA 303313 (Ryzodeg)
Applicant:	Novo Nordisk, Inc.
OSE RCM #:	2011-3982-1

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RICHARD A ABATE
11/27/2012

KELLIE A TAYLOR
11/27/2012

CAROL A HOLQUIST
11/27/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	July 12, 2012
Reviewer(s):	Richard A. Abate, RPh, MS, Safety Evaluator Division of Medication Error Prevention and Analysis
Deputy Director	Kellie Taylor, PharmD, MPH Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength(s):	Tresiba (b) (4) (Insulin Degludec [rDNA origin]) Injection, 300 units/3 mL (100 units/mL) (U-100) (b) (4) Ryzodeg (70% Insulin Degludec and 30% Insulin Aspart [rDNA origin]) Injection 300 units/3 mL (100 units/mL) (U-100) (b) (4)
Application Type/Number:	NDA 203314 (Tresiba) NDA 303313 (Ryzodeg)
Applicant/sponsor:	Novo Nordisk, Inc
OSE RCM #:	2011-3892

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/s/

RICHARD A ABATE
07/12/2012

KELLIE A TAYLOR
07/12/2012

CAROL A HOLQUIST
07/13/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: July 26, 2012

TO: Rachel E. Hartford, Regulatory Project Manager
Jean-Marc Guettier, M.D., Medical Officer
Hylton Joffe, M.D., Clinical Team Leader
Division of Metabolism and Endocrinology Products

FROM: Jean Mulinde, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 203314

APPLICANT: Novo Nordisk, Inc.

DRUG: Tresiba™ (insulin degludec [rDNA origin] injection) solution for subcutaneous injection

NME: Yes

REVIEW PRIORITY: Standard Review

INDICATION: To improve glycemic control in adults with Type 1 and Type 2 diabetes mellitus.

CONSULTATION REQUEST DATE: December 6, 2011
CLINICAL INSPECTION SUMMARY DATE: June 30, 2012
DIVISION ACTION GOAL DATE: July 29, 2012
PDUFA DATE: July 29, 2012

I. BACKGROUND:

Tresiba™ (insulin degludec [rDNA origin] injection, IDeg) solution for subcutaneous injection is a soluble insulin analogue product for the treatment of patients with diabetes mellitus (Type 1 and Type 2) (b) (4). IDeg is a new molecular entity, insulin degludec, an ultra-long-acting human insulin analog. The product is intended for once-daily dosing that can be used alone or in combination with rapid-acting or short-acting insulin and/or oral antidiabetic agents (OADs). IDeg is a basal insulin analogue that has been modified such that soluble and stable multi-hexamers are formed upon injection, resulting in a depot in the subcutaneous tissue. The gradual separation of IDeg monomers from the multi-hexamers results in a slow and continuous delivery of IDeg from the subcutaneous injection site into the circulation, leading to ultra-long pharmacokinetic and pharmacodynamic profiles. Binding of the fatty acid moiety of IDeg to albumin contributes to some extent to the protraction mechanism. Once injected into the subcutaneous tissue, the IDeg di-hexamers form soluble multi-hexamers, which in themselves are of a molecular size too large to be absorbed, leading to a depot from which IDeg monomers are slowly and continuously absorbed into the circulation. At the target tissues, IDeg monomers bind to and activate insulin receptors, triggering the same cellular effects as human insulin such as promoting glucose uptake.

In support of the efficacy and safety of Tresiba™ (IDeg) for the treatment of adults with diabetes mellitus (b) (4), the Applicant has submitted data from nine pivotal Phase 3 studies (NN1250-3579, NN1250-3580, NN1250-3582, NN1250-3583, NN1250-3585, NN1250-3586, NN1250-3668, NN1250-3672, and NN1250-3770). Brief descriptions of these studies follow.

1. **Protocol NN1250-3579, entitled "A 52-Week Randomised, Controlled, Open Label, Multicentre, Multinational Treat-To-Target Trial Comparing the Efficacy and Safety of SIBA and Insulin Glargine, Both Injected Once Daily in Combination with Oral Anti-Diabetic Drugs (OAD), in Subjects with Type 2 Diabetes Mellitus Currently Treated with OAD(s) and Qualifying for More Intensified Treatment"**

   Study NN1250-3579 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target two-arm parallel group study that evaluated the safety and efficacy of IDeg (SIBA) and insulin glargine (IGlar), both injected once daily (OD) in combination with OADs in subjects with type 2 diabetes mellitus currently treated with OAD(s) and who qualified for more intensified treatment. The total duration of the study was approximately 55 weeks, including three treatment periods (1 week screening period, 52 week treatment period, and a 1 week follow-up period). Once determined to be eligible,

subjects were randomized (Visit 2) in a 3:1 ratio: IDeg or IGlar in combination with OAD(s) (metformin ± DPP-4 inhibitor). The study was conducted (subjects randomized) at 166 clinical investigator sites in 12 countries: Austria (6 sites), Belgium (5 sites), Canada (17 sites), Czech Republic (5 sites), Denmark (6 sites), Finland (6 sites), France (7 sites), Germany (16 sites), Norway (8 sites), Serbia (5 sites), Spain (9 sites) and United States (U.S.) (76 sites). A total of 1597 subjects were screened and 1030 subjects were randomized into the trial. Subjects were enrolled in the study from September 1, 2009 through December 13, 2010 (Date of final study report: May 31, 2011).

Novo Nordisk A/S, Denmark was responsible for the preparation of the protocol, electronic case report forms (eCRFs), supply of trial products and stated equipment, monitoring (frequency determined by outcome of remote monitoring of eCRFs, but interval between visits not to exceed 6-8 weeks), safety monitoring, data management, and statistics. Novo Nordisk Inc., USA was responsible for the preparation of the clinical trial report (CTR). The titration of insulin doses was monitored by (b) (4) and reviewed by an internal titration committee composed of members from Novo Nordisk, and any significant changes from the titration algorithm were addressed. (b) (4) was responsible for overall data management activities (after trial lock, source data shipped to Novo Nordisk). With the exception of insulin antibody analyses, all other laboratory analyses were provided by (b) (4) (multiple regional locations used). Insulin antibody analyses were provided by (b) (4). Electronic case report forms (eCRF) services were provided by (b) (4). Site specific eCRF data (in an electronic readable format) was to be provided to the Investigator site and this data was to be retained by the site. [Of note, the following paper CRF forms were also used by sites: Safety Information Forms, Pregnancy Forms, hypoglycemic event questionnaires and the PRO questionnaires.] An interactive voice/web response system (IV/WRS), provided by (b) (4), was used to perform enrollment, randomization, discontinuation of screening failures, withdrawals, allocation of trial product, drug accountability and document subject completion of the trial. An independent external Event Adjudication Committee (EAC) was constituted for the trial to perform ongoing adjudication, standardization and assessment of cardiovascular events in accordance with pre-defined classifications. The following events were to be evaluated and adjudicated by the EAC in an independent and blinded manner: acute coronary syndrome (including myocardial infarction), stroke, and cardiovascular death. Management of cardiovascular event adjudication was contracted by the sponsor to (b) (4)

The primary efficacy endpoint was defined as change from baseline in HbA1c (%) after 52 weeks of treatment (analyzed by central laboratory). Safety measurements included assessment of adverse events, number of hypoglycemic episodes (ADA definitions and minor episodes, clinical laboratory measurements (chemistry, hematology, lipids, cardiovascular risk markers, antibodies, and urinary albumin-to-creatinine ratio), 12-lead electrocardiograms (ECGs), vital signs, funduscopy/fundo photography, and physical examinations. The following were designated as medical events of special interest: injection site reactions, severe hypoglycemia (by ADA definition), cardiovascular events

(acute coronary syndrome, stroke, death), neoplasms, and immunogenicity reactions (events related to immune mechanisms to trial product).

2. **Protocol NN1250-3580, entitled "A Trial Comparing Efficacy and Safety of NN1250a with Sitagliptin in Insulin-Naïve Subjects with Type 2 Diabetes"**

Study NN1250-3580 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target two-arm parallel group study that evaluated the safety and efficacy of IDeg and sitagliptin each dosed once daily in a population of insulin-naïve subjects with type 2 diabetes mellitus qualifying for intensified treatment and currently treated with 1-2 OADs (metformin, sulphonylurea [SU], glinides, or pioglitazone) in any combination at an unchanged dosing for at least 3 months prior to screening. The total duration of the study was up to 29 weeks, including three treatment periods (1 week screening period, 26 week treatment period, and a 1 week follow-up period). Once determined to be eligible, subjects were randomized (Visit 2) in a 1:1 ratio to IDeg or sitagliptin, both in combination with their current OAD regimen. The study was conducted (subjects randomized) at 78 clinical investigator sites in seven countries: Argentina (2 sites), Canada (11 sites), India (8 sites), Mexico (2 sites), South Africa (3 sites), Turkey (5 sites), and the U.S. (47 sites). A total of 724 subjects were screened, and 458 subjects were randomized into the trial. Subjects were enrolled in the study from January 8, 2010 through November 4, 2010 (Date of final study report: May 31, 2011).

The study was conducted by Novo Nordisk A/S, Denmark utilizing essentially the same study conduct model and 3rd party vendors as were described for Study NN1250-3579, above.

The primary efficacy endpoint was change from baseline in HbA1c (%) after 26 weeks of treatment (analyzed by central laboratory). Safety measurements were identical to those described for Study NN1250-3579, above.

3. **Protocol NN1250-3582, entitled "A 52-Week Randomised, Controlled, Open Label, Multicentre, Multinational Treat-To-Target Trial Comparing Efficacy and Safety of SIBA and Insulin Glargine Both Administered Once Daily in a Basal-Bolus Regimen with Insulin Aspart As Mealtime Insulin ± Treatment with Metformin, ± Pioglitazone in Subjects with Type 2 Diabetes Currently Treated with Insulin Qualifying for Intensified Treatment"**

Study NN1250-3582 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target three-arm parallel group study that evaluated the safety and efficacy of IDeg and IGlar in a basal-bolus regimen in subjects with type 2 diabetes mellitus. The total duration of the study was approximately 55 weeks, including three treatment periods (1 week screening period, 52 week treatment period, and a 1 week follow-up period). Once determined to be eligible, subjects were randomized (Visit 2) in 3:1 ratio to IDeg or IGlar in a basal-bolus regimen both in combination with IAsp as mealtime insulin ± metformin ± pioglitazone. The study was conducted (subjects randomized) at 123 clinical investigator sites in 12 countries: Bulgaria (8 sites), Germany (8 sites), Hong

Kong (1 site), Ireland (4 sites), Italy (11 sites), Romania (5 sites), Russia (6 sites), Slovakia (4 sites), South Africa (5 sites), Spain (9 sites), Turkey (3 sites), and the U.S. (59 sites). A total of 1440 subjects were screened and 1006 subjects were randomized into the trial. Subjects were enrolled in the study from September 1, 2009 through October 28, 2010 (Date of final study report: May 31, 2011).

The study was conducted by Novo Nordisk A/S, Denmark utilizing essentially the same study conduct model and 3rd party vendors as were described for Study NN1250-3579, above.

The primary efficacy endpoint was change from baseline in HbA1c (%) after 52 weeks of treatment (analyzed by central laboratory). Safety measurements were identical to those described for Study NN1250-3579, above.

4. Protocol NN1250-3583, entitled "A 52 Week Randomised, Controlled, Open Label, Multicentre, Multinational, Parallel, Treat-To-Target Trial Comparing Efficacy and Safety of SIBA and Insulin Glargine Both Administered Once Daily in a Basal-Bolus Regimen with Insulin Aspart As Mealtime Insulin in Subjects with Type 1 Diabetes"

Study NN1250-3583 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target three-arm parallel group study that evaluated the safety and efficacy of IDeg with IGlar, both administered subcutaneously OD in a basal-bolus regimen with IAsp as mealtime insulin, in subjects with type 1 diabetes mellitus. The total duration of the study was approximately 55 weeks, including three treatment periods (1 week screening period, 52 week treatment period, and a 1 week follow-up period). Once determined to be eligible, subjects were randomized (Visit 2) in a 3:1 ratio to IDeg or IGlar both in combination with IAsp at mealtimes. The study was conducted (subjects randomized) at 79 clinical investigator sites in six countries: France (6), Germany (5), Russia (7), South Africa (3), United Kingdom (U.K.) (6), and U.S. (52). A total of 722 subjects were screened and 629 subjects were randomized into the trial. Subjects were enrolled in the study from September 1, 2009 through November 8, 2010 (Date of final study report: July 18, 2011).

The study was conducted by Novo Nordisk A/S, Denmark utilizing essentially the same study conduct model and 3rd party vendors as were described for Study NN1250-3579, above.

The primary efficacy endpoint was change from baseline in HbA1c (%) after 52 weeks of treatment (analyzed by central laboratory). Safety measurements were identical to those described for Study NN1250-3579, above.

5. Protocol NN1250-3585, entitled "BEGIN™: BB T1 A Trial Investigating the Efficacy and Safety of NN1250 Compared to Insulin Detemir in Subjects with Type 1 Diabetes Mellitus in a Basal/Bolus Treatment Regimen"

Study NN1250-3585 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target two-arm parallel group study that evaluated the safety and efficacy of IDeg

OD + mealtime IAsp with that of IDet (Insulin Detemir) OD + mealtime IAsp in subjects diagnosed with type 1 diabetes. The total duration of the study was 28 weeks, including three treatment periods (1 week screening period, 26 week treatment period, and a 1 week follow-up period). Once determined to be eligible, subjects were randomized (Visit 2) 2:1 ratio: IDeg OD + mealtime IAsp or IDet OD + mealtime IAsp. The study was conducted (subjects randomized) at 55 clinical investigator sites in seven countries: Brazil (2), Finland (8), India (10), Italy (6), Japan (15), Macedonia (1), and the U.K. (13). A total of 512 subjects were screened and 456 subjects were randomized into the trial. Subjects were enrolled in the study from February 22, 2010 through December 8, 2010 (Date of final study report: May 31, 2011).

The study was conducted by Novo Nordisk A/S, Denmark utilizing essentially the same study conduct model and 3rd party vendors as were described for Study NN1250-3579, above.

The primary efficacy endpoint was change from baseline in HbA1c (%) after 26 weeks of treatment (analyzed by central laboratory). Safety measurements were identical to those described for Study NN1250-3579, above.

6. Protocol NN1250-3586, entitled "BEGIN™: ONCE ASIA A Pan Asian Trial Comparing Efficacy and Safety of Insulin NN1250 and Insulin Glargine As Add On to OAD(s) in Subjects with Type 2 Diabetes"

Study NN1250-3586 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target two-arm parallel group study that evaluated the safety and efficacy of IDeg OD with that of IGlar (Insulin Glargine), both in combination with OADS in subjects diagnosed with type 2 diabetes, not optimally controlled with OADs alone that qualified for intensified treatment. The total duration of the study was 28 weeks, including three treatment periods (1 week screening period, 26 week treatment period, and a 1 week follow-up period). Once determined to be eligible, subjects were randomized (Visit 2) in a 2:1 ratio to IDeg OD or IGlar OD both in combination with OADs. The study was conducted (subjects randomized) at 52 clinical investigator sites in six countries: Hong Kong (1 site), Japan (12 sites), Malaysia (8 sites), South Korea (19 sites), Thailand (6 sites), and Taiwan (6 sites). A total of 579 subjects were screened and 435 subjects were randomized into the trial. Subjects were enrolled in the study from February 1, 2010 through December 16, 2010 (Date of final study report: May 13, 2011).

The study was conducted by Novo Nordisk A/S, Denmark utilizing essentially the same study conduct model and 3rd party vendors as were described for Study NN1250-3579, above.

The primary efficacy endpoint was change from baseline in HbA1c (%) after 26 weeks of treatment (analyzed by central laboratory). Safety measurements were identical to those described for Study NN1250-3579, above.

7. Protocol NN1250-3668, entitled "A 26 Week Randomised, Controlled, Open Label, Multicentre, Multinational, Three-Arm, Treat To Target Trial Comparing Efficacy

and Safety of Three Different Dosing Regimens of Either Soluble Insulin Basal Analogue (SIBA) or Insulin Glargine with or without Combination with OAD Treatment, in Subjects with Type 2 Diabetes Mellitus"

Study NN1250-3668 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target three-arm parallel group study that evaluated the safety and efficacy of IDeg OD at defined intervals of approximately 8 to 40 hours between doses (IDeg Flex) or IDeg OD at evening meal with IGlar OD in subjects with type 2 diabetes who were inadequately treated with OADs alone, basal insulin alone, or OADs in combination with basal insulin. The total duration of the study was 28 weeks, including three treatment periods (1 week screening period, 26 week treatment period, and a 1 week follow-up period). Once determined to be eligible, subjects were randomized (Visit 2) in 1:1:1 ratio to IDeg OD, IDeg Flex, or IGlar OD in combination with OADs (subjects previously receiving OADs were to continue on same dose). The study was conducted (subjects randomized) at 69 clinical investigator sites in 14 countries: Hungary (3 sites), Macedonia (1 site), Serbia (3 sites), Finland (7 sites), Norway (6 sites), United Kingdom (6 sites), Argentina (4 sites), Mexico (2 sites), South Africa (3 sites), India (10 sites), Malaysia (5 sites), Taiwan (3 sites), Russian Federation (8 sites), and Israel (8 sites). A total of 946 subjects were screened and 687 subjects were randomized into the trial. Subjects were enrolled in the study from November 30, 2009 through September 6, 2010 (Date of final study report: June 16, 2011).

The study was conducted by Novo Nordisk A/S, Denmark utilizing essentially the same study conduct model and 3rd party vendors as were described for Study NN1250-3579, above.

The primary efficacy endpoint was change from baseline in HbA1c (%) after 26 weeks of treatment (analyzed by central laboratory). Safety measurements were identical to those described for Study NN1250-3579, above.

8. Protocol NN1250-3672, entitled "Comparison of NN12501 with Insulin Glargine in Subjects with Type 2 Diabetes (BEGIN™)"

Study NN1250-3672 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target three-arm parallel group study that evaluated the safety and efficacy of IDeg 200 U/mL and IGlar both administered OD in combination with metformin ± DPP-4 inhibitor in insulin-naïve subjects diagnosed with type 2 diabetes mellitus currently treated with oral antidiabetic drugs (OADs) qualifying for intensified treatment. The total duration of the study was 28 weeks, including three treatment periods (1 week screening period, 26 week treatment period, and a 1 week follow-up period). Once determined to be eligible, subjects were randomized (Visit 2) in a 1:1 ratio to IDeg or IGlar, both in combination with OAD treatment. The study was conducted (subjects randomized) at 106 clinical investigator sites in eight countries: Canada (11 sites), France (6 sites), Ireland (3 sites), Russian Federation (7 sites), South Africa (4 sites), Ukraine (2 sites), United Kingdom (18 sites) and United States (U.S.) (55 sites). A total of 697 subjects were screened and 460 subjects were randomized into the trial. Subjects were enrolled in the study from March 1, 2010 through November 26, 2010 (Date of final

study report: May 31, 2011).

The study was conducted by Novo Nordisk A/S, Denmark utilizing essentially the same study conduct model and 3rd party vendors as were described for Study NN1250-3579, above.

The primary efficacy endpoint was change from baseline in HbA1c (%) after 26 weeks of treatment (analyzed by central laboratory). Safety measurements were identical to those described for Study NN1250-3579, above.

9. Protocol NN1250-3770, entitled "Begin™: Flex T1 A 26-Week Trial Investigating the Dosing Flexibility, Efficacy and Safety of NN1250 in Subjects with Type 1 Diabetes"

Study NN1250-3770 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target three-arm parallel group study that evaluated the safety and efficacy of IDeg OD at defined intervals of approximately 8 to 40 hours between doses (IDeg Flex) or IDeg OD with evening meal with IGlar OD in subjects with type 1 diabetes mellitus. The total duration of the original study was 28 weeks, including three treatment periods in the main treatment period (1 week screening period, 26 week treatment period, and a 1 week follow-up period). Protocol Amendment 1 added a 6 month safety extension period to the study, which subjects could optionally participate in. Once determined to be eligible, subjects were randomized (Visit 2) in a 1:1:1 ratio to IDeg OD, IDeg Flex, or IGlar OD. Subjects that were in the IDeg OD arm switched to the IDeg Flex arm during the extension period of the study if they elected to participate. The study was conducted (subjects randomized) at 71 clinical investigator sites in six countries: Belgium (5 sites), Germany (7 sites), Norway (5 sites), Poland (5 sites), U.K. (12 sites) and U.S. (37 sites). A total of 549 subjects were screened and 493 subjects were randomized into the trial. Subjects were enrolled in the study from March 03, 2010 through November 12, 2010 (Date of final study report: May 27, 2011).

The study was conducted by Novo Nordisk A/S, Denmark utilizing essentially the same study conduct model and 3rd party vendors as were described for Study NN1250-3579, above.

The primary efficacy endpoint was change from baseline in HbA1c (%) after 26 weeks of treatment (analyzed by central laboratory). Safety measurements were identical to those described for Study NN1250-3579, above.

The clinical investigator sites were selected for inspection based on enrollment characteristics, impact of site data on efficacy outcomes, prior inspection history, adverse event reporting profiles, and feasibility to review data for more than one study during an inspection at the site.

II. RESULTS (By Site)

Name of CI	Protocol # Site# Subject#	Inspection Dates	Final Classification
Jain, Rajeev K 3003 West Good Hope Rd Milwaukee, Wisconsin 53209	Protocol: 3579 Site: #2050/906 Enrolled: 8 Protocol: 3583 Site: #2050/607 Enrolled: 4 Protocol: 3672 Site: #2050/517 Enrolled: 5	January 25- February 13, 2012	NAI
Norwood, Paul 550 East Herndon Avenue, Suite 101 Fresno, CA 93720	Protocol: 3580 Site: #2332/725 Enrolled: 3 Protocol: 3583 Site: #2332/644 Enrolled: 13 Protocol: 3770 Site: #2332/730 Enrolled: 6	February 1-27, 2012	VAI
Hollander, Priscilla 3600 Gaston Ave. Wadley Tower, Suite 656 Dallas, TX 75246	Protocol: 3582 Site: #2116/127 Enrolled: 25 Protocol: 3583 Site: #2116/632 Enrolled: 16 Protocol: 3770 Site: #2116/711 Enrolled: 6	January 23 – February 6, 2012	VAI
Wise, Jonathan K 3901 Houma Blvd, Suite 103 Metairie, Louisiana 70006-2930	Protocol: 3582 Site: #15195/164 Enrolled: 16	March 5-14, 2012	VAI
Kumar Sethi, Bipin 6-3-248/1/1A, Benjara Hills Hyderabad, 600034 India	Protocol: 3668 Site: #3077/806 Enrolled: 14 Protocol: 3585 Site: #3077/203 Enrolled: 11	March 26-30, 2012	NAI

Name of CI	Protocol # Site# Subject#	Inspection Dates	Final Classification
Franek, Edward CSKMSWiA, Centrum Diabetologiczne Budynek "S", pokój 210, ul. Woloska 137 Warszawa, 02-507 Poland	Protocol: 3770 Site: #918/400 Enrolled: 15	April 16-19, 2012	NAI
Wan Bebakar, Wan M School of Medical Sciences Hospital Universiti Sains Malaysia Kubang Kerian Kota Bharu, Kelantan 16150 Malaysia	Protocol: 3586 Site: #3022/301 Enrolled: 15 Protocol: 3668 Site: #3022/851 Enrolled: 21	April 1-5, 2012	VAI (Issuance of Final Correspondence to Clinical Investigator Pending)
Deerochanawong, Chaicharn Diabetes and Endocrinology Unit Department of Medicine Rajavithi Hospital Bangkok, 10400 Thailand	Protocol: 3586 Site: #377/501 Enrolled: 23	March 26-30, 2012	NAI (Issuance of Final Correspondence to Clinical Investigator Pending)
Novo Nordisk A/S Vandtaarnsevej 114 DK 2860 Soeborg Denmark	Protocols NN1250- 3579 3580 3582 3583 3585 3586 3668 3672 3770	April 16-30, 2012	Pending (Preliminary classification VAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
Pending = Preliminary classification based on information in 483 and preliminary communication with the field; the EIR has not been received from the field and complete review of EIR is pending.

1. **Rajeev K. Jain, M.D.**
   3003 West Good Hope Rd
   Milwaukee, Wisconsin 53209
   Site #2050

   a) **What was inspected:**
   For Study NN1250-3579, at this site, 10 subjects were screened, 8 subjects were enrolled, and 2 subjects completed the study. All 10 subjects' records were reviewed during the inspection. For Study NN1250-3583, at this site, 4 subjects

were screened, 4 subjects were enrolled, and 4 subjects completed the study. All 4 enrolled subjects' records were reviewed during the inspection. For Study NN1250-3672, at this site, 9 subjects were screened, 5 subjects were enrolled, and 5 subjects completed the study. All 5 enrolled subjects' records were reviewed during the inspection. For each study, the record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, compliance with drug titration guidelines, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated the site's use of the Clinphone system (used for subject enrollment, randomization, etc.) and data entry on electronic case report forms, clinical laboratory report documentation, protocol deviation reports, concomitant medication usage, monitoring and sponsor correspondence with the site, and IRB approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203314 were compared. Generally, the investigator's execution of the protocols was found to be adequate and a Form FDA 483 was not issued.

The ORA field investigator noted in the EIR that the CI did not always follow the study drug titration guidelines provided in the protocols. When the CI deviated from titration guidelines, however, this was documented in source records and a comment was included as to the reason the CI deviated from the guidelines as was required by the Titration Guidelines that were present in the protocols.

c) Assessment of data integrity:
The data provided by Dr. Jain's site for Studies NN1250-3579, NN1250-3583, and NN1250-3672 that were submitted to the Agency in support of NDA 203314 appear to be reliable and acceptable for use in support of the pending application.

2. Paul Norwood, M.D.
550 East Herndon Avenue, Suite 101
Fresno, CA 93720
Site #2332

a) What was inspected:
For Study NN1250-3580, at this site, 6 subjects were screened, 3 subjects were enrolled, and 2 subjects completed the study. All 3 enrolled subjects' records were reviewed during the inspection. For Study NN1250-3583, at this site, 13 subjects were screened, 13 subjects were enrolled, and 13 subjects completed the study. All 13 enrolled subjects' records were reviewed during the inspection. For Study

NN1250-3770, at this site, 6 subjects were screened, 6 subjects were enrolled, 5 subjects completed the study through the Week 26 visit, and 2 of the originally enrolled subjects participated in the 26 week extension phase of the study. All 6 enrolled subjects' records were reviewed during the inspection. For each study, the record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, compliance with drug titration guidelines, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated GCP and study specific training of site staff, the site's use of the IV/WRS system (used for subject enrollment, randomization, etc.) and data entry on electronic case report forms, clinical laboratory report documentation, ECG documentation, protocol deviation reports, concomitant medication usage, monitoring and sponsor correspondence with the site, and IRB approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203314 were compared. A Form FDA 483, Inspectional Observations, was issued to the CI for:

i. Failure to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60]. In Study NN1250-3583, specifically for:

   a. Not ensuring all study subjects signed revised informed consent documents, when required, at their next scheduled visit.
   b. Using expired tubes in special chemistry laboratory kits for collection of Week 41 fasting glucose and hemoglobin A1c assessments for four subjects (Subjects #644001, #644002, #644003, and #644004). The use of expired kits resulted in inability of the central laboratory to confirm whether test results for these subjects at their Week 41 Visits were correct; rather test results for these subjects were listed as canceled on final laboratory reports.

<u>OSI Reviewer Comment:</u> According to Dr. Norwood's response letter, dated March 14, 2012, to the Form FDA 483 observations, site staff had recognized that the laboratory tubes in question were expired and they replaced them with tubes within expiry from their bulk supplies for the subject specimens noted above. He states they then noted this substitution on the laboratory requisition forms that were sent with the tubes to the central laboratory. While it is likely that specimen results were valid, had the site discarded the entire kit containing expired tubes and used a kit with all components within expiry date this issue could have been avoided and these data points would have been retained in the

study database. In any case, the loss of these data points appears to be an isolated issue that will not impact primary efficacy analyses.

ii. Failure to report promptly to the sponsor and/or IRB all unanticipated problems involving risk to human subjects or others [21 CFR 312.66]. Specifically for:
   a. Delayed reporting of one episode of hypoglycemia (one subject in Study NN1250-3770) to the sponsor. According to guidelines in the protocols, these episodes were to be reported within 24 hours to the Sponsor as Medical Events of Special Interest, but in this case reporting was delayed beyond the required timeframe.
   b. Delayed reporting to the IRB of a SAE of squamous cell carcinoma, which occurred in one subject.

iii. Failure to ensure that investigational drug disposition records were adequate with respect to dates, quantity, and use by subjects [21 CFR 312.62(a)]. Specifically, in each study, drug accountability records at the site could not be fully reconciled because available records for drug units that were returned for destruction from the site were inaccurate.

OSI Reviewer Comment: In his March 14, 2012 response to Form FDA 483 observations, Dr. Norwood provided additional explanation as to how unused study drug was returned for destruction; in each case, he states that issues with documentation are related to failures of documentation by NovoNordisk monitors and/or clerical errors. While ultimately Dr. Norwood is responsible for ensuring the adequacy of documentation maintained at his site related to drug accountability, based on information retrieved from alternate sources (additional records retrieved from drug return and destruction vendors) it appears likely that the vast majority of unused study drug in question can be accounted for. This observation, while valid, does not impact study analyses or subject welfare.

c) Assessment of data integrity:
Not withstanding the observations noted above, the data provided by Dr. Norwood's site for Studies NN1250-3580, NN1250-3583, and NN1250-3770 that were submitted to the Agency in support of NDA 203314 appear to be adequately reliable and acceptable for use in support of the pending application.

3. Priscilla Hollander, M.D.
3600 Gaston Ave.
Wadley Tower, Suite 656
Dallas, TX 75246
Site #2116

a) What was inspected:

For Study NN1250-3582, at this site, 44 subjects were screened, 25 subjects were enrolled, and 23 subjects completed the study. Twelve enrolled subjects' records were reviewed during the inspection. For Study NN1250-3583, at this site, 21 subjects were screened, 16 subjects were enrolled, and 14 subjects completed the study. Eight enrolled subjects' records were reviewed during the inspection. For Study NN1250-3770, at this site, 7 subjects were screened, 6 subjects were enrolled, and 5 subjects completed the study through the Week 26 visit. Three enrolled subjects' records were reviewed during the inspection. For each study, the record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, compliance with drug titration guidelines, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated protocol deviation reports, concomitant medication usage, monitoring and sponsor correspondence with the site, and IRB approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203314 were compared. A Form FDA 483, Inspectional Observations, was issued to the CI for:

i. Failure to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically for:
   a. Failing to use the most current version of IRB approved Informed Consent document to consent six subjects in Study NN1250-3582 and one subject in Study NN1250-3583.
   b. In Study NN1250-3583, for failing to correctly calculate study drug dosage based on directions contained on Version 2 of the Insulin Titration Worksheet provided to the site by the Sponsor.

<u>OSI Reviewer Comment:</u> This observation will not be considered a regulatory violation. The Insulin Titration Worksheets that were provided to the sites permitted transcription of data from subjects' dairies (self measured plasma glucose and doses of insulin used) for 3 days prior to a visit. The use was optional based on documentation obtained during inspection of the Sponsor, NovoNordisk. This information was used to calculate revised doses to be taken until the next visit according to the Dosing Titration Guidelines provided in the protocol. At issue with this study is that a second version of the worksheet was created and distributed by the Sponsor during the study, which did not contain the fifth instruction bullet for dose calculation ("If one or more value(s) are below ≤3.9 mmol/L (≤70 mg/dL), then the lowest value is used"). This was an inadvertent omission on the part of the Sponsor as evidenced by the fact that

neither the protocol nor the eCRF were amended to make this change. The site continued to follow the instructions on the earlier version of the worksheet, which is fortunate since if Version 2 directions had been followed, it would likely have resulted in calculation of excessively high dosages that would have placed subjects at increased risk of hypoglycemic events. Of note, the recommended dosage adjustments were correctly automatically calculated on the eCRF, according to the Dosage Titration Guidelines in the protocol, when the site entered the subject diary information into the eCRF.

ii. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent [21 CFR 312.62(b)]. Specifically:
   a. In Studies NN1250-3582, NN1250-3583, and NN1250-3770, there were documentation errors in completion of source document worksheets that were used by the site to collect visit related information for subjects.

   OSI Reviewer Comment: While documentation errors on worksheets did appear to occur sporadically in each study, these errors infrequently actually resulted in incorrect information being collected on subjects' eCRFs. This Form FDA 483 observation is unlikely to impact efficacy or safety analyses, nor were subjects placed at undue risk.

   b. In Studies NN1250-3582 and NN1250-3583, documentation errors in transcription of bolus or basal insulin recorded by subjects in subjects' diaries to the subjects' eCRFs. In Study NN1250-3582 documentation errors of this nature were identified to have occurred in 7 of 25 subjects' diaries reviewed during the inspection. In Study NN1250-3583 documentation errors of this nature were identified to have occurred in 4 of 16 subjects' diaries reviewed during the inspection.

   OSI Reviewer Comment: Given the duration of these studies, the number of data points of this nature collected for each subject during each study, and the fact that the described documentation errors were generally sporadic in nature for most of the subjects described, it is unlikely that the reported data transcription errors would significantly impact efficacy or safety analyses for these studies.

Dr. Hollander responded to Form FDA 483 observations in a letter dated February 6, 2012. In her response she stated that she has implemented new procedures and staff training to prevent the occurrence of the types of errors listed on the Form FDA 483 in future studies.

c) Assessment of data integrity:

Not withstanding the observations noted above, the data provided by Dr. Hollander's site for Studies NN1250-3582, NN1250-3583, and NN1250-3770 that

were submitted to the Agency in support of NDA 203314 appear to be adequately reliable and acceptable for use in support of the pending application.

4. **Jonathan K. Wise, M.D.**
3901 Houma Blvd, Suite 103
Metairie, Louisiana 70006-2930
Site #15195

a) What was inspected:

For Study NN1250-3582, at this site, 18 subjects were screened, 16 subjects were enrolled, and 16 subjects completed the study. All 18 screened subjects' records were reviewed during the inspection. For this study, the record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, subject randomization procedures, inclusion/exclusion criteria compliance, compliance with drug titration guidelines, primary efficacy endpoint data, documentation and reporting of hypoglycemic events, subjects' diary entries, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated the study related training received by site personnel from the sponsor/monitor, the site's use of the electronic case report form system, clinical laboratory report documentation, protocol deviation reports, concomitant medication usage, monitoring and sponsor correspondence with the site, IRB approvals and correspondence, and completion of financial disclosures by Dr. Wise and his staff. There were no limitations to the inspection.

b) General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203314 were compared. A Form FDA 483, Inspectional Observations, was issued to the CI for:

> Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent [21 CFR 312.62(b)].
>
> Dr. Wise did not ensure that all AEs and/or concomitant medications identified in source records at the site were reported on eCRFs. This inspectional observation was present for 5 of 16 enrolled subjects' records that were reviewed during the inspection. Specifically, for:
>
> a. Subject #164001 received ciprofloxacin, tigecycline, and a tetanus vaccine for a leg injury occurring in May 2010, but these medications were not reported in the subject's eCRF.
> b. Subject #164008 took Tylenol for a stomach virus in January 2010, but the AE and medication usage were not reported in the subject's eCRF.

c. Subject #164011 took Tylenol for headaches in August 2009 and October 2009, Carafate for heartburn in August 2009, and Mucinex for sinus congestion in October 2009, but none of these AEs or medication usages were reported in the subject's eCRF.
d. Subject #164013 took aspirin for temperature and feeling sluggish in August 2009, but these AEs and the medication usage were not reported in the subject's eCRF.
e. Subject #164015 had a SAE of sixth nerve palsy requiring hospitalization in (b) (6), which was reported in the subject's eCRF; however, medications (aspirin, Flonase, and Travatan) given during this hospitalization were not reported on the subject's eCRF.

OSI Reviewer Comment: While the site failed to report these AEs and concomitant medications, based on the nature of the AEs and the types of medications, it appears unlikely that inclusion of these reports in NDA analyses will significantly impact overall efficacy or safety conclusions made by the review division for this product. In addition, reporting deficiencies by the site do not appear to have impacted subject welfare.

Although not included as an observation on the Form FDA 483 issued to Dr. Wise, the EIR received for this inspection also noted sporadic cases of transcription errors related to the site's reporting of hypoglycemic events recorded in subjects' diaries. These errors included occasional discrepancies in time recorded for event or last meal, whether event was symptomatic or asymptomatic, recent exercise, and/or general documentation of event.

c) Assessment of data integrity:
Not withstanding the observations noted above (incomplete AE and concomitant medication usage reporting for 5 of 16 enrolled subjects, and sporadic eCRF transcription errors related to subject reported hypoglycemic events), the data provided by Dr. Wise's site for Study NN1250-3582 that were submitted to the Agency in support of NDA 203314 appear to be adequately reliable and acceptable for use in support of the pending application.

5. Bipin Kumar Sethi, M.D.
6-3-248/1/1A, Benjara Hills
Hyderabad, 600034
India
Site #3077

a) What was inspected:
For Study NN1250-3585, at this site, 15 subjects were screened, 11 subjects were enrolled, and 10 subjects completed the study. Six enrolled subjects' records were reviewed during the inspection. For Study NN1250-3668, at this site, 15 subjects were screened, 14 subjects were enrolled, and 12 subjects completed the study.

Eight enrolled subjects' records were reviewed during the inspection. For each study, the record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, randomization procedures, drug accountability, inclusion/exclusion criteria compliance, compliance with drug titration guidelines, primary efficacy endpoint data, concomitant medication usage, protocol deviations, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated the site's use of electronic case report forms, financial disclosure reporting, monitoring logs, monitoring and sponsor correspondence with the site, and Ethics Committee approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203314 were compared and verified. Studies NN1250-3585 and NN1250-3668 were not conducted under IND at this site; therefore, Dr. Sethi did not sign a Form FDA 1572. The investigator's execution of the protocols, however, was found to be adequate and a Form FDA 483 was not issued to the CI.

c) Assessment of data integrity:
The data provided by Sethi's site for Study NN1250-3585 and Study NN1250-3668 that were submitted to the Agency in support of NDA 203314 appear to be reliable and acceptable for use in support of the pending application.

6. **Edward Franek, M.D.**
CSKMSWiA, Centrum Diabetologiczne
Budynek "S", pokój 210, ul. Woloska 137
Warszawa, 02-507
Poland
Site #918

a) What was inspected:
For Study NN1250-3770, at this site, 15 subjects were screened, 15 subjects were enrolled, and 15 subjects completed the study. Nine enrolled subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, randomization procedures, drug accountability, inclusion/exclusion criteria compliance, compliance with drug titration guidelines, primary efficacy endpoint data, concomitant medication usage, protocol deviations, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated the site's use of electronic case report forms, financial disclosure reporting, monitoring logs, monitoring and

sponsor correspondence with the site, and Ethics Committee approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203314 were compared and verified. Study NN1250-3770 was not conducted under IND at this site; therefore, Dr. Franek did not sign a Form FDA 1572. The investigator's execution of the protocols, however, was found to be adequate and a Form FDA 483 was not issued to the CI.

c) Assessment of data integrity:
The data provided by Franek's site for Study NN1250-3770 that were submitted to the Agency in support of NDA 203314 appear to be reliable and acceptable for use in support of the pending application.

7. Wan M. Wan Bebakar, M.D.
School of Medical Sciences
Hospital Universiti Sains Malaysia
Kubang Kerian
Kota Bharu, Kelantan 16150
Malaysia
Site #3022

a) What was inspected:
For Study NN1250-3586, at this site, 19 subjects were screened, 15 subjects were enrolled, and 13 subjects completed the study. All screened subjects' records were reviewed during the inspection. For Study NN1250-3668, at this site, 30 subjects were screened, 21 subjects were enrolled, and 21 subjects completed the study. Nineteen screened subjects' records were reviewed during the inspection. For each study, the record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, compliance with drug titration guidelines, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated drug accountability, GCP and study specific training of site staff, the site's use of the IV/WRS system (used for subject enrollment, randomization, etc.) and data entry on electronic case report forms, clinical laboratory report documentation, monitoring and sponsor correspondence with the site, Ethics Committee approvals and correspondence, and staff completion of financial disclosure forms. There were no limitations to the inspection.

b) General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203314 were compared and verified. Study NN1250-3586 and Study NN1250-3668 were not conducted under IND at this site; therefore, Dr. Wan Bebakar did not sign Form FDA 1572s for these studies. A Form FDA 483, Inspectional Observations, was issued to the CI for:

> Failure to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically for permitting Study Coordinators to titrate insulin doses for three subjects when this responsibility was not designated to them in the Study NN1250-3668 Log of Staff and Delegation of Task at the Trial Site record. During the inspection, Dr. Wan Bebakar acknowledged that he had reviewed and discussed titrations for these subjects with the Study Coordinators, but that he had not countersigned their notes.

Dr. Wan Bebakar responded to the Form FDA 483 observation in a letter dated April 11, 2012. Dr. Wan Bebakar acknowledged the error in study conduct as listed on the Form FDA 483 and promised corrective actions to prevent the occurrence of similar deficiencies in future studies.

c) Assessment of data integrity:

Not withstanding the minor observation noted above, the data provided by Wan Bebakar's site for Study NN1250-3586 and Study NN1250-3668 that were submitted to the Agency in support of NDA 203314 appear to be reliable and acceptable for use in support of the pending application.

Note: The final correspondence for this inspection has not yet issued to the inspected entity; however, the final classification for the inspection is not anticipated to change as the general observations described above are based on review of the EIR and associated exhibits for this inspection as provided by the ORA investigator and the Clinical Investigator's response to Form FDA 483 Inspectional Observations.

8. Chaicharn Deerochanawong, M.D.

Diabetes and Endocrinology Unit
Department of Medicine
Rajavithi Hospital
Bangkok, 10400
Thailand
Site #377

a) What was inspected:
For Study NN1250-3586, at this site, 33 subjects were screened, 23 subjects were enrolled, and 21 subjects completed the study. All screened subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, compliance with drug titration guidelines, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated drug accountability, GCP and study specific training of site staff, the site's use of the IV/WRS system (used for subject enrollment, randomization, etc.) and data entry on electronic case report forms, clinical laboratory report documentation, monitoring and sponsor correspondence with the site, Ethics Committee approvals and correspondence, and staff completion of financial disclosure forms. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203314 were compared and verified. Study NN1250-3586 was not conducted under IND at this site; therefore, Dr. Deerochanawong did not sign a Form FDA 1572. The investigator's execution of the protocols, however, was found to be generally adequate and a Form FDA 483 was not issued to the CI.

c) Assessment of data integrity:
The data provided by Deerochanawong's site for Study NN1250-3586 that were submitted to the Agency in support of NDA 203314 appear to be reliable and acceptable for use in support of the pending application.

Note: The final correspondence for this inspection has not yet issued to the inspected entity; however, the final classification for the inspection is not anticipated to change as the general observations described above are based on review of the EIR and associated exhibits for this inspection as provided by the ORA investigator.

9. Novo Nordisk A/S
Vandtaarnsevej 114
DK 2860 Soeborg
Denmark
Sponsor Inspection

a) What was inspected:
The sponsor, Novo Nordisk A/S, was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. Studies

NN1250-3579, NN1250-3580, NN1250-3582, NN1250-3583, NN1250-3585, NN1250-3586, NN1250-3668, NN1250-3672, and NN1250-3770 were conducted globally, and during this sponsor/monitor inspection clinical site records for the CI sites listed in the table above were focused on. In addition, the Investigator Trial File (ITF) for Site #111 (Richard Cherlin) was reviewed during the inspection to follow-up on a statement in the NN1250-3582 Clinical Study Report regarding this site having undergone a "For Cause" audit by the sponsor of the study. The record review included review of documents associated with the IRB approvals, site and investigator qualifications, monitoring activities, drug accountability records, serious adverse events, and the Sponsor's handling of protocol deviations and violations.

b) General observations/commentary:

Studies NN1250-3579, NN1250-3580, NN1250-3582, NN1250-3583, NN1250-3585, NN1250-3586, NN1250-3668, NN1250-3672, and NN1250-3770 were found to be generally well executed by the Sponsor, Novo Nordisk; however, a one item Form FDA 483 was issued at the inspection closeout with the following observation:

> Failure to ensure proper monitoring of a study and ensure that the study was conducted in accordance with the investigational plan [21 CFR 312.50]. Specifically, for having not ensured that monitoring reports were completed according to the investigational plans for Studies NN1250-3579, NN1250-3580, NN1250-3582, NN1250-3583, NN1250-3586, NN1250-3668, and NN1250-3672. For each of these studies it was observed that monitoring reports were missing and/or unsigned and/or completed outside of required time frames.

<u>OSI Reviewer Comment:</u> *Deficiencies related to completion of monitoring reports may have resulted in less than optimal investigator oversight and may have contributed to observations made during CI inspections conducted for these studies; however, based on the nature of the regulatory violations identified during the CI inspections it does not appear that the Sponsor's failure to ensure proper monitoring of the studies resulted in harm to subjects or significant problems with data reliability in support of primary efficacy or safety analyses.*

The Applicant, Novo Nordisk, responded to the Form FDA 483 observation in a letter dated May 14, 2012. In their response they stated that corrective actions, including implementation of systematic tracking of review and approval of monitoring reports, is being implemented to prevent recurrence of this type of issue in future studies.

c) Assessment of data integrity:

The data generated, as it pertains to Studies NN1250-3579, NN1250-3580, NN1250-3582, NN1250-3583, NN1250-3585, NN1250-3586, NN1250-3668, NN1250-3672, and NN1250-3770 were inspected in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. Not withstanding the

Form FDA 483 observation noted above, Studies NN1250-3579, NN1250-3580, NN1250-3582, NN1250-3583, NN1250-3585, NN1250-3586, NN1250-3668, NN1250-3672, and NN1250-3770 appear to have been conducted adequately by Novo Nordisk and the data submitted by the Applicant for these studies may be used in support of the pending Application.

Note: The EIR and associated exhibits for this inspection were not available at the time this CIS was written. The general observations described above are based on review of preliminary summary information provided by the ORA investigator. An inspection summary addendum will be generated if conclusions change upon review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for the inspection of Novo Nordisk, as well as final review of inspectional findings for clinical investigators Dr. Jain, Dr. Norwood, Dr. Wise, Dr. Hollander, Dr. Sethi, Dr. Deerochanawong, Dr. Wan Bebakar, and Dr. Franek the data submitted by the Applicant for Studies NN1250-3579, NN1250-3580, NN1250-3582, NN1250-3583, NN1250-3585, NN1250-3586, NN1250-3668, NN1250-3672, and NN1250-3770 appear reliable in support of NDA 203314.

The preliminary classification for the inspection of Novo Nordisk is Voluntary Action Indicated (VAI) based on identification of errors in monitoring report documentation.

The final classifications for the inspections of Dr. Norwood (Site #2332, Studies NN1250-3580, NN1250-3583, and NN1250-3770), Dr. Hollander (Site #2116, Studies NN1250-3582, NN1250-3583, and NN1250-3770), Dr. Wise (Site #15195, Study NN1250-3582), and Dr. Wan Bebakar (Site #3022, Studies NN1250-3586 and NN1250-3668) are Voluntary Action Indicated (VAI). While regulatory violations occurred at these sites, as discussed above, they are considered minor in nature and unlikely to significantly impact primary safety or efficacy analyses, nor were they likely to have jeopardized subject safety.

The final classifications for the inspections of Dr. Franek (Site #918, Study NN1250-3770), Dr. Sethi (Site #3077, Studies NN1250-3668 and NN1250-3585), Dr. Jain (Site #2050, Studies NN1250-3579, NN1250-3583, and NN1250-3672), and Dr. Deerochanawong (Site #377, Study NN1250-3586) are No Action Indicated (NAI).

Note: All observations noted above related to the inspection of Novo Nordisk are based on the Form FDA 483, and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR for this inspection.

{See appended electronic signature page}

Jean Mulinde, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

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Department of Health and Human Services
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DMEPA Review of Human Factors Study Report

Date:	June 26, 2012
Reviewer(s):	Richard Abate, RPh, MS, Safety Evaluator Division of Medication Error Prevention and Analysis
Deputy Director	Kellie Taylor, PharmD., MPH Division of Medication Error Prevention and Analysis
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Drug Name(s):	Tresiba (Insulin Degludec [rDNA origin]) Injection FlexTouch 100 units/mL and 200 units/mL pen injectors Ryzodeg (70% Insulin Degludec and 30% Insulin Aspart [rDNA origin]) Injection FlexTouch 100 units/mL pen injector
Application Type/Number:	NDA 203313 (Ryzodeg) NDA 203314 (Tresiba)
Applicant:	Novo Nordisk, Inc
OSE RCM #:	2012-1040

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review summarizes the Division of Medication Error Prevention and Analysis' evaluation of the supplemental summative usability test report (UT86) submitted by Novo Nordisk to support the approval of NDAs 203313, Ryzodeg FlexTouch (70% insulin degludec and 30% insulin aspart) pen injector and 203314, Tresiba FlexTouch (insulin degludec) pen injectors. From a medication error perspective, this study, UT86, provides adequate support to demonstrate that Ryzodeg FlexTouch 100 units/mL and Tresiba FlexTouch 100 units/mL pen injectors may be used safely and effectively by patients, and the device for these product strengths is suitable for approval. The overall number of use errors in UT86 was low, and the majority of errors observed with this pen injector are also seen in the use of marketed pen injectors (lack of priming, not holding the needle under the skin for sufficient time, and needle sticks). However, the study does not adequately demonstrate the safety for the Tresiba FlexTouch 200 units/mL pen injector due to the fact that a new use error was identified in UT86 with this presentation, yet Novo Nordisk failed to provide identify an appropriate measure to mitigate and demonstrate such measure would mitigate the risk of dosing errors.

The introduction a higher concentration (200 units/mL) insulin in a pen injector device is novel and thus introduces the opportunity for dosing errors. The supplemental study suggests additional risks with the 200 units/mL concentration of Tresiba FlexTouch as demonstrated by a participant dividing the numeric dose when setting the dose on the pen injector. In addition, this study lacked a sufficient number of participants from the intended users with the Tresiba FlexTouch to demonstrate safety and efficacy of the 200 units/mL concentration. Human Factors studies are not meant to characterize the extent of the problem we would expect to see with a product, but rather, the purpose of these studies is meant to identify problems along with the appropriate corrective actions to reduce the risk. Therefore, DMEPA provides recommendations in Section 6.1 for an additional usability study focusing on the use of Tresiba FlexTouch 200 unit/mL pen injector to demonstrate safe and effective use prior to the approval of this strength presentation.

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA's) evaluation of the supplemental summative usability test report (UT86) submitted by Novo Nordisk to support the approval of NDAs 203313, Ryzodeg (70% insulin degludec and 30% insulin aspart) and 203314, Tresiba (insulin degludec) which include a presentation of these insulins in the PDS290 pen injector device. The Division of Metabolism and Endocrinology Products requested DMEPA review the report of this use validation study to evaluate if the revised patient instructions for use were adequate to minimize the risks associated with the use of the PDS290 with these insulin products (referred to as the FlexTouch Pen in the applications) as identified in the original summative use validation test, UT54, which was included in the original application submissions.

1.1 BACKGROUND

Many marketed insulin products are configured with pen injector devices. The use of these pens has inherent risks which were noted by Novo Nordisk in the validation of use final report submitted September 29, 2011. Novo Nordisk stated that the development of the PDS290 evolved from the identified risks from the marketed FlexPen products.

However, if approved the Tresiba would (1) be the first concentrated (200 units/mL) insulin prefilled pen device to be marketed (2) be the first prefilled pen available in two concentrations (100 units/mL and 200 units/mL) necessitating the need for healthcare providers to distinguish between the two Tresiba products in prescribing, teaching, dispensing, and administering the insulin and (3) be the first insulin pen device that dials in increments of 2 units; currently marketed pen devices dial doses in 1 unit increments with the exception of Luxura HD which is designed to deliver doses in one-half unit increments. During the IND, the some of these differences were identified as an expected source of error and human factors testing was to be conducted to evaluate the risks and implement appropriate actions to improve the safe and effective use of this pen device.

1.2 REGULATORY HISTORY

DMEPA and the Center for Devices and Radiological Health's (CDRH's) human factors team provided comments for the initial usability study protocols for the PDS290 with these insulin products in a letter August 19, 2010. The comments noted that the study was primarily to demonstrate "ease of handling" and inadequately addressed all the risks associated with the use of the PDS290 to demonstrate the pen is safe and effective. In addition, the differentiation study focused the user on the colors of the product which is not the only means to differentiate the product. Additionally, Novo Nordisk revised the protocols to UT54 and UT59 but did not provide the revisions for FDA review prior to commencing with these studies.

Novo Nordisk provided the results of a summative usability study for the differentiation of the PDS290 (UT59) from other insulin products and a summative usability study for the handling of the PDS290 (UT54) with the original application on September 29, 2011. CDRH's human factors team provided comments for the results which were forwarded to the Novo Nordisk, December 23, 2011. In response to these comments, Novo Nordisk submitted a protocol for a supplemental summative handling study (UT86) for the PDS290 with modifications to the patient instructions for use and the additional of a training video to address the deficiencies identified by CDRH. DMEPA and CDRH provided comments for revisions to the protocol. However, Novo Nordisk proceeded with the summative study (UT86) without any input from the Agency and submitted the study results and report on April 24, 2012. As the Agency was unaware that the Applicant had planned to commence with the study without advice, the provided comments on the protocol were forwarded to the Applicant in an advice letter on May 3, 2012. Subsequently, Novo Nordisk provided responses to the Agency comments on May 16, 2012.

2 REVIEW METHODS AND MATERIALS

DMEPA evaluated the following submissions for this review:

- Supplemental Summative Usability Test Report for UT86 submitted April 24, 2012.
- Novo Nordisk's Risk Management Conclusions and Final Report submitted April 24, 2012.
- NDA Amendment: Response to May 3, 2012 General Advice Letter submitted May 16, 2012.

3 REVIEW RESULTS

The following sections describe DMEPA's resulting evaluation of the Supplemental Usability Test Report.

3.1 STUDY OBJECTIVES

The primary objective, as noted in the study protocol submitted February 15, 2012, is to collect data related to use errors, close calls, operational difficulties, and deviations with the PDS290. The study would also demonstrate that patients could safely and effectively use the PDS290 to administer these insulin products (Tresiba and Ryzodeg).

3.1.1 DMEPA Comments on Study Objective

DMEPA notes that Novo Nordisk made modifications to the training materials to mitigate use errors and deficiencies identified by CDRH in the Summative Handling Study UT54. These revised training materials were used by all the participants in UT86.

3.2 STUDY DESIGN

Participants included three user groups including both men and women of various ages, visual impairments (e.g. glasses or retinopathy), hearing impairments, range of dexterity, and educational background. The user groups were made up of Type 1 diabetes and Type 2 diabetes patients as per the sought indications for these products. However, the pediatric indication is not being requested in this initial application.

- 16 Children (eight pen naïve and eight pen users): all were trained.
- 17 Adults (eight pen naïve and nine pen users): Eleven Adult users received training, and the remaining six Adult users did not.
- 18 Elderly (ten pen naïve and eight pen users): Eight Elderly users received training, and the remaining ten Elderly users did not.

Training was provided by certified diabetic educators who covered the basics of pen-injector use, provided a detailed IFU review, a demonstration of the proper use of the PDS290, a presentation of the instructional video (added for this study), and a hands-on practice period. All trained participant were asked to perform two base line injections of 5 units. A total of 16 users consisting of Adult and Elderly users did not receive training. However, these participants were required to read the patient IFU prior to performing the hands-on tasks. In addition, the eight untrained participants who had prior pen-injector experience were also asked to perform two baseline injections with their current pen.

The IFU and instructional video were made available to all participants to refer to during the study as well as the ability to simulate a call to Novo Nordisk for assistance.

The tasks performed by the users are described in Appendix A. The participants used the same pen injector (Tresiba® 100 units/mL, Ryzodeg™ 100 units/mL, or Tresiba® 200 units/mL) for all tasks.

All use errors, close calls, operational difficulties, and deviations with the PDS290 were noted. A root cause analysis for all use errors and close calls were completed, and a root cause was identified.

3.2.1 DMEPA Comments on Study Design

DMEPA noted the fact that the untrained participants were required to read patient instruction for use during the familiarization periods which from our point of view constitutes a form of self-training. DMEPA also found that no inpatient nurses were studied in the use of this pen injector device.

Additionally, DMEPA notes that the number of participants in total for each age group appears to be representative of the numbers needed to validate the usability of the PDS290 configured for 200 units/mL insulin. We note that these users were divided among three PDS290 device Ryzodeg FlexTouch 100 unit/mL, Tresiba FlexTouch 100 units/ mL, and Tresiba FlexTouch 200 units/mL. (See Table 1 on page 5.) Furthermore, these participants were made of both prior insulin users and insulin naïve patients. Falkner[1] demonstrated that when testing for a usability problem, each category of users (insulin naïve trained, insulin naïve untrained as well as insulin users trained and insulin users untrained) should have at least 15 participants of each type in each category, to decrease the rate of variance and identify at least 90 percent of errors. It is likely that users of the Tresiba U200 pen would be prior insulin users and moved to the higher concentration due to the increased daily insulin requirements. Therefore, the Tresiba U200 participant size included in this study is inadequate.

However, DMEPA agrees the overall tasks included in this study should be able to adequately demonstrate that indicated users can safely and effective use the FlexTouch pen injectors with 100 units/mL insulin products. DMEPA agrees that the children participants would use the PDS290 with the 100 units/mL product only.

[1] Faulkner, Laura. Beyond the five-user assumption: Benefits of increased sample sizes in usability testing. (2003). *Behav. Research Methods, Instruments and Computers*. 35 (3): 379-383.

Table 1: Participants characteristic by drug concentration in the PDS290

Participants using the 200 unit/mL PDS290 in UT86				
	Participant groups by age	Insulin users	Insulin naïve	The total participants with the same training
Trained	Adults (age 18-64)	2	1	[redacted]
	Elderly (age 65 and over)	2	0	
	Total	**4**	**1**	**5**
Untrained	Adults (age 18-64)	1	0	[redacted]
	Elderly (age 65 and over)	2	2	
	Total	**3**	**2**	**5**
Participants using the 100 units/mL PDS290 in UT 86				
	Participant groups by age	Insulin users	Insulin naïve	The total participants with the same training
Trained	Children (age 10 to 17)	8	8	[redacted]
	Adults (age 18-64)	3	5	
	Elderly (age 65 and over)	3	3	
	Total	**14**	**16**	**30**
Untrained	Adults (age 18-64)	4	1	[redacted]
	Elderly (age 65 and over)	3	3	
	Total	**7**	**4**	**11**

3.3 STUDY RESULTS

A summary of use errors committed by the participants and a summary of the close calls in which the participants caught themselves before committing use errors appear in Appendix B and Appendix C, respectively. The report noted a root cause for each of these events.

Additionally, the report also included any participant operational difficulties, any deviations in the proper use of the pen, and the instances where the participants simulated a call to a 1-800 number for assistance.

3.3.1 DMEPA's Comments on Study Results

DMEPA noted the use errors occurred more frequently with the Elderly user group (five elderly vs. two adults) and with those participant who were considered untrained (five untrained vs. two trained). Additionally, we noted that one participant (E6) repeated the same error more than once. This previous insulin user (both pen and syringe) misunderstood the statement in the IFU which explained how the device measured

Tresiba 200 unit/mL at 2 unit increments and mistakenly believed that the dose of insulin delivered would be twice the dose that was set on the pen injector dial.

DMEPA noted that the close calls were divided almost evenly among trained and untrained users (five vs. four). Three untrained participants (E3, E6, and A7) committed close calls that would have resulted in the same use errors they had committed. Participant E6 repeatedly committed or nearly committed the same error of setting the dose based on the noted misinterpretation of the instructions in three of his five tasks. Furthermore, an elder participant's (E3) reported close call actually resulted in an under dose as the spring release when using a block needle causes the dose to set on the dial to decrease. After replacing the needle, the dose dialed by the participant was not the requested dose (36 units) but rather the dose the participant saw on the dial (26 units) when he noted the needle was defective.

DMEPA noted that several of the root causes of the errors were attributed to the device or the instructions for use. The causes related to the instructions for use appeared for untrained participants (e.g. appearance of and misinterpretation the priming instructions and the dose counter increment information). The causes related to the device were identified for both the trained and untrained participants (e.g. dose counter behavior due to internal pen injector compression and pen-injector feedback when delivering a dose). The root causes of the close calls were primarily user related (e.g. habit, inattention, or forgetfulness). However, one cause was identified as the misinterpretation of the training that the participant had received. Another cause was identified as unclear dose button behavior with an untrained participant as she did not realize she needed to hold the dose button down until the counter returned to "0."

4 DISCUSSION

The overall number of use errors recorded in UT86 was low. In addition, most of the errors identified in this study are expected since they are reported with the use of insulin pen injectors (e.g., omission or incorrectly priming the needle, the needle not left in place for the instructed amount of time, and needle sticks). In addition, the majority of participants used the PDS290 with the 100 unit/mL presentations of Tresiba or Ryzodeg which have the same interactions with users. However, the Tresiba FlexTouch 200 units/mL strength includes different interactions with the user, for example, in the way a user perceives the higher concentration and the way the dose is presented on the dial of the counter. DMEPA recognizes that most of the use errors identified in the study are related to the use of the pen injector overall and independent of the strength presentation of the product.

The directions for priming were either overlooked or confused with the directions for setting the dose in the instructions for use. Although the instructions for use direct patients to prime the needle each time to ensure insulin flow with each injection, when a blocked or defective needle is attached to this pen injector, the PDS behaves in a different manner (the dose counter does not return "0") and thus provides a secondary means to identify this problem. In addition, DMEPA finds the instructions for priming the FlexTouch pen (i.e., 2. Check the insulin flow) are clear. However, this step appears to be similar to the next and adjacent step "3. Setting the Dose" due to the fact that each of these tasks have similar initial steps when these tasks are completed correctly. When

"Step 2." is skipped, a patient may receive an under dose of as much as 2 units of insulin due the dead space in the needle. However, whether this error results in symptomatic hyperglycemia would depend on the patient's prescribed insulin dose. Therefore, the clinical significance of this error is dose dependant.

Two participants committed the use error of not holding the needle in place subcutaneously for at least one second after the counter returns to "0." This error occurs commonly with all pen injector devices and has lead to under dosing and overdosing (when patients readminister the dose) which results in hyperglycemia and hypoglycemia, respectively. Novo Nordisk submitted data that demonstrated 90% of the dose is delivered when the counter returns to "0" and the injector makes an audible click. The instructions for use direct the user to keep the needle in place for six seconds which is noted in the Risk Management Assessment that this step is to ensure the entire insulin dose is delivered.[2] While an ideal device would include feed back to the user when dose delivery is completed, DMEPA defers the mechanical justification of medication delivery to CDRH.

The needle stick error appears to be related to the design of the marketed Novo Nordisk needle used in the study rather than the pen injector as the user was not aware of the fact that there was an unseen end of the needle where the needle connects to the pen injector as well as the visible end that is injected into the patient. Thus, the mishandling of the needle led to the error rather than using the pen-injector PDS290.

However, one of the remaining use errors identified the fact that the use of the PDS290 with insulin products at a higher concentration (e.g. 200 units/mL) has additional inherent risks. These risks stem the fact that marketed insulin pen injectors are all available in 100 units/mL concentrations and the dose is usually set in one unit increments. Additionally, the intended patient population for using the higher concentration insulin products has insulin resistance and thus requires higher doses of insulin to meet daily needs. Some of these patients are likely to have used U-500 insulin in the United States. The fact that the risk of the error identified in this usability study have not been fully evaluated for methods of mitigation raises concern and thus is discussed further in Section 4.1.

The final use error resulted from the fact the device releases the compression spring and the dose counter decrease even if the needle is blocked or defective. We discuss this further in Section 4.2. Also, DMEPA provides further discussion of the comments we provided regarding the protocol for UT86 in the May 3 advice letter and whether these were addressed by Novo Nordisk as well as the risk of reusing of needles identified in the reported deviations.

[2] Risk Management Analysis Input to Usability Test, PDS290 pen-injector Insulin Degludec 100 U/ml, Insulin Degludec 200 U/ml, and Insulin Degludec/Insulin Aspart 100 U/ml included in Original submission September 29. 2011.

4.1 PRESENTATION OF A CONCENTRATED INSULIN (200 UNITS/ML) IN A PEN INJECTOR

The introduction of a novel concentration of insulin in a pen injector device provides the opportunity for dosing errors. Novo Nordisk notes the benefit of this concentration presentation as "allows the users to inject up to 160 units per injection…..decreasing the number of injections for those in need of higher doses."[3] DMEPA acknowledges that the PDS290 would be useful to patients who need to deliver doses of insulin of a higher concentration (> 100 units/mL) to patients. However, DMEPA believes Tresiba FlexTouch 200 units/mL pen injector has usability problems related to dosing based on the data from UT86 and our post-marketing experience with Humulin R U500 medication errors.[4] Healthcare providers and patients experienced with the use of Humulin R U-500 insulin have created practices or work-arounds to help them explain and administer correct dosing of this product converting U500 insulin doses to U100 doses (i.e., divide the dose by five) which contributes to this risk. This conversion has resulted in confusion and wrong dose errors with U-500 insulin. This manipulation of the dose was created out of necessity due to an incongruence between the strength of the higher strength insulin product (U-500) and the insulin syringes available to administer them (U-100).

We believe experienced healthcare practitioners who routinely prescribe or educate patients on the use of the concentrated U-500 insulin may also be at risk to make calculation errors when teaching to administer Tresiba FlexTouch 200 units/mL. And patients may make calculation errors when dialing the appropriate dose of insulin with the Tresiba FlexTouch 200 unit/mL pen-injector. This was demonstrated in the UT86 study by participant E6 who from prior syringe use was in the habit of calculating the volume of the dose prior to drawing up the dose of insulin. Thus, this participant converted the dose to volume and split the dose in half.

Understandably, it may seem difficult to rely on the performance of one individual to predict the problems with a product. However, in this case, DMEPA also has the benefit of experience with U-500 insulin to provide context to this finding. Also, we bear in mind that the Human Factors studies are not meant to characterize the extent of the problem we would expect to see but rather, the purpose of these studies are meant to identify problems along with the appropriate corrective actions to reduce the risk of error. The applicant has proposed no corrective actions to address this risk.

Finally, the labeling for Tresiba FlexTouch 200 units/mL could potentially be modified to provide instructions to users that no dose conversion is needed when using this product. However, a similar approach has been used with other drug products and was not successful in resolving this type of dosing errors.[5] Also, based on the data submitted, it is not clear whether or not the unique dialing mechanism (in increments of 2 units) is partly

[3] Risk Management Conclusions, Final Report from Novo Nordisk, Section 7.3.1, p. 45.

[4] OSE review #2008-434, Review of MedMARX Medication Error Reports for Humulin R U-500, September 18, 2008, Griffis, M.

[5] OSE review #2010-571; Fosphenytoin Sodium Injection and Phenytoin Sodium Injection Mediation Error Review, October 1, 2010. Tobenkin, A.

responsible. Therefore, without additional data, DMEPA is uncertain that labeling or possibly some other means would adequately address the risk of dose confusion with the Tresiba FlexTouch 200 unit/mL.

4.1.1 Dose dialing mechanism

All currently marketed insulin pen injectors are only available in a 100 units/mL concentration. The dose counters for the majority of the marketed insulin products are marked to deliver doses in one unit increments. However, the dose counter for Tresiba FlexTouch 200 units/mL is calibrated to dial doses in two unit increments which may also contribute to the risk of wrong dosing with this product. DMEPA acknowledges that the dose counter displays the numeric dose to the user and the IFU notes this difference in incremental dose. However, prior pen users or visually impaired users who rely on the clicking noise the dial makes to set the dose may lead to overdoses of Tresiba.

Also, patients are unable to deliver an odd numbered dose (e.g. 55 units, 77 units, or 101 units) with Tresiba FlexTouch 200 units/mL pen injector as each marking represents two units of insulin. DMEPA acknowledges that the instructions for use state that the dose counter reflects 2 unit increments. However, similar to the 100 unit/mL FlexTouch pens, the dose counter of the Tresiba FlexTouch 200 unit/mL pen is marked every other unit (4, 8, 12, etc.) The patients may mistakenly believe that the unmarked dash above or below the numbered dash may represent an odd numbered dose leading to a wrong dose error. We further note that the summative studies (UT54 or UT86) did not include such a task involving the Tresiba 200 units/mL pen injector requesting the patient to dial an odd numbered dose. However, DMEPA acknowledges that the resulting incorrect dose should this error occur would be one unit more or less than the prescribed dose and likely not to result in an adverse event.

4.1.2 Intended Patient Population for the Tresiba FlexTouch 200 units/mL Pen Injector

Tresiba is indicated to improve glycemic control in adults with diabetes mellitus. Among the indicated population, the likely users of Tresiba FlexTouch 200 units/mL are those patients who are insulin resistant and require insulin in higher doses as noted previously. It is unclear from the data provided that participants from this insulin resistant patient group were included. These intended patients have a recall bias related to any prior use insulin in a pen injector which was considered and included in these studies. But prior use of concentrated U-500 insulin was not fully considered and adds to the risk. Thus, the use handling studies (UT54 and UT86) lacked a complete evaluation of the Tresiba 200 unit/mL with the intended patient user of the product.

In addition, the study UT86 included only 10 participants who completed tasks with the Tresiba 200 units/mL PDS290. We note that seven of these participants were insulin users. This number is inadequate to demonstrate that the PDS290 in the higher concentration is safe and effective as this size population is likely to identify a minimum of 55% of use errors.[6] Furthermore, no data on the daily doses of insulin were included

[6] Faulkner, p 381.

to demonstrate these patients required higher doses. In fact, the patient who committed the use error of setting the wrong dose was one of the two prior insulin use participants that noted the use of a syringe previously. But, the participant was the only prior syringe user who was in the untrained group. The fact that one participant in such a small sub set of user groups committed the same use error repeatedly suggests the bias that adds risk associated with using the 200 unit/mL PDS290. This risk has been inadequately studied due to the fact that Novo Nordisk saw no difference in risk in the use of the different strengths and therefore did made not attempt to provide adequate numbers of users with this strength presentation of the PDS290. Thus, patients currently using insulin with a full range of insulin doses including those with insulin resistance (20 units to at least 120 units daily insulin requirement) should be evaluated in adequate numbers (15 trained and 15 untrained) to demonstrate adequate mitigation of all risks associated with the 200 unit/mL presentation.

4.2 POTENTIAL FOR UNDER DOSING

The study identified a root cause to misinterpreting the dose delivered after detecting a blocked needled as the behavior of the dose counter due to internal pen-injector compression. Novo Nordisk noted that the resultant under dosing of insulin by this use error as being non-serious and would result in mild transient hyperglycemia. However, the risk of hyperglycemia depends on the patient's usual dose and the difference between the dose the patient should have received and the dose delivered. We noted from the described use errors and close calls that the lower the dose the less change on the dose counter when the button was pressed to deliver the dose with a blocked or defective needle attached to the device. Conversely, a higher dose dialed on the counter results in a greater change on the dial when the dosing button on the pen is pressed. It appears to be proportional. Thus, DMEPA believes that this 20-25% decrease in the intended dose may be clinically significant depending on the patient's dose and how often blood glucose is monitored and disagrees that the outcome would be non-serious in all cases. However, DMEPA acknowledges this use error and close call involved the same untrained participant (E3) and that the instructions for use state that a blocked or defective needle "will not inject any insulin, even though the counter may move." DMEPA will discuss with the patient labeling reviewer in OMP to determine if this warning in the If's can be stated more clearly.

4.3 PREVIOUS DMEPA COMMENTS ON PARTICIPANTS INCLUDED IN THE STUDY

DMEPA's comments regarding the protocol for this study included the identified issues of studying both trained and untrained participants in which the untrained participants should not be required to read the instructions for use and the fact that the study did not include a previously unidentified user group, inpatient nurses. Our Comments were forwarded to the Applicant in the Advice Letter May 3, 2012.

4.3.1 Trained vs. Untrained Participants

We noted in our comments for the protocol for UT86 that the "untrained" participants were required to read the instructions for use as part of the product familiarization period. The fact that these participants were required to read the IFU provided for self-training of the pen-injector. Novo Nordisk noted in the response to the May 3, 2012 advice letter

that the American Diabetes Association recommends adherence to the National Standard for Diabetes Self-Management Education including training in the handling of the injection device. In addition, they noted that the summative study UT54 included untrained participants with the option to read the IFU. They further noted that UT54 demonstrated training had a positive effect on use errors. DMEPA acknowledges that training positively affects the way users interact with this device. However, DMEPA believes a more realistic approach to evaluating the untrained participant was that used in UT54 where these participants were given the option of using any training materials provided in the study. Although we noted some root causes related to the IFU, the prominence of some of the warnings will be discussed in the Labels and Labeling review for the FlexTouch Pen presentations of these products.

4.3.2 Inpatient Nurse Users

DMEPA also commented that the participants did not include inpatient nurses. Novo Nordisk's May 16, 2012 response noted that healthcare providers, including nurses, were participants in summative study UT54. They further noted that that study showed no appreciable difference in the type and frequency of use errors between healthcare providers and caregivers versus adult users. DMEPA acknowledges the fact that three nurses were included in the UT54 study. However, these nurse practice in a physician office or outpatient setting rather than an acute inpatient setting. Therefore, the practice-base and the experiential backgrounds differ for inpatient nurses compared to the included nurses and could affect their use of the pen. Furthermore, the nurses only completed tasks with either the (b) (4) 100 unit/mL (Ryzodeg FlexTouch) or the (b) (4) 100 unit/mL (Tresiba FlexTouch) PDS290 pen injector. Thus, nurses have not been evaluated in the use or the Tresiba FlexTouch pen injector in the 200 unit/mL strength presentation.

4.4 REUSE OF NEEDLES ON THE PEN INJECTOR

Finally, DMEPA noted that one user reused the same needle when completing the task to split the dose between two pen injector devices. This user removed the needle from the empty pen injector and attached it to a new pen. This deviation is actually a use error as the reuse of a needle could contaminate the new pen. DMEPA notes that the user that committed this use error was an untrained prior pen user. The use error is likely an artifact from her 2 year prior experience with the SoloSTAR pen device as it is an inherent risk with the use of pen injectors. Additionally, the instructions for use include the warning to "always use a new needle with each injection" as part of the preparation instructions.

5 CONCLUSIONS

The use errors and close calls were few and distributed between both the trained and untrained participants using the PDS290 with the insulin in the 100 units/mL presentation. Furthermore, many of the use errors are not specific to the PDS290 and generally managed adequately in other pen devices via labeling. Overall, DMEPA finds from a medication error perspective that the summative study adequately demonstrates

patients can safety and effectively use the FlexTouch Pen to administer Ryzodeg and Tresiba in the 100 units/mL presentations and thus are acceptable.

However, the safety risks associated with the use of the PDS290 Tresiba 200 units/mL have not been adequately assessed and mitigated based on the data available. In addition, because the type of confusion posed by Tresiba FlexTouch 200 units/mL is novel, we have little positive post-marketing experience to help guide us and Novo Nordisk to correct these risks. As such, we believe that the firm fully evaluate the dosing risk (particularly among insulin-experienced users) and nurses (who happen to be involved in a number of errors reported with other pens and U500) to identify the appropriate mitigation strategy for the dosing error risk. Potential actions may include training, labeling changes (to the IFU or container labels), and possibly device modification if the dose dialing mechanism is identified as the source of confusion.

Additional studies with the intended user participants in appropriate number are necessary to demonstrate safety and efficacy of the Tresiba FlexTouch 200 units/mL pen injector prior to the approval of this strength presentation. The numbers of participants using this strength in UT54 and UT86 were too small. Due to the small numbers of participants using the 200 units/mL presentation of the PDS290 in each user group in the completed studies also means that there may be additional user problems that have yet to be addressed. Given the serious potential for harm that insulin products pose when dosed incorrectly and the likelihood that this product and IFU as currently designed is prone to such dosing errors, we recommend that Novo Nordisk demonstrate to our satisfaction that they have thoroughly evaluated the risk and implemented appropriate corrective actions to prevent patient harm.

Finally, we note that the warning in the instructions for use (IFU) may need some changes to improve the prominence of the fact no insulin is delivered with blocked or defective needle. Therefore, DMEPA will review the Instructions for Use with the patient labeling reviewer and provide recommendations fro improvements in the DMEPA Label and Labeling Review for the FlexTouch pen presentation for these products.

6 RECOMMENDATIONS

DMEPA provides the following recommendations with regards to the supplemental summative usability study for the use of PDS290 for NDAs 203313 (Ryzodeg FlexTouch) and 203314 (Tresiba FlexTouch.)

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

6.1 COMMENTS TO THE DIVISION

Based on the data submitted in the Supplemental summative usability study, the PDS290 is safe for use with NDA 203313 Ryzodeg FlexTouch (70% Insulin Degludec and 30% Insulin Aspart [rDNA origin]) 100 units/mL pen injector and with NDA 203314, the 100 units/mL presentation of Tresiba FlexTouch (Insulin Degludec [rDNA origin]) pen injector from a medication error perspective.

However, the data for Tresiba FlexTouch 200 units/mL (Insulin Degludec [rDNA origin]) pen injector is not adequate to demonstrate safety in the intended population and should not be approved without further usability assessment by the Applicant.

Unfortunately, in reviewing the study report, it seems that Novo Nordisk could have more fully evaluated these aspects in UT86 had they waited for comments on the human factors protocol before proceeding.

6.2 COMMENTS TO THE APPLICANT (NDA 203314)

Upon review of the report for UT86 in support of your Application 203314, DMEPA is concerned that there is additional risk associated with the use of Tresiba FlexTouch 200 units/mL pen injector. One user experienced errors in setting the dose with this device which leads us to believe your product is prone to dosing errors and additional risks are associated with this strength of Tresiba. Our evaluation of the submitted data noted the number of users completing tasks with Tresiba FlexTouch 200 units/mL were inadequate (10 total users, 5 trained and 5 untrained) to clearly identify all the risks and thus demonstrate the product is safe and effective with all the intended users. Additionally, the Human Factors studies are not meant to characterize the extent of the problem we would expect to see but rather, the purpose of these studies are meant to identify problems along with the appropriate corrective actions to reduce the risk. Thus, DMEPA believes a further evaluation is necessary of the Tresiba FlexTouch 200 units/mL pen injector and should include:

- The intended adult and elderly patients who require larger daily doses of insulins (from 50 units to at least 120 units daily insulin requirement) who are likely to make up the majority of your potential users. Also, since the patient users of Tresiba FlexTouch 200 unit/ mL will be prior insulin users (pen injector or syringe and vial); therefore, insulin naïve patients do not need to be included. If naïve patients are included, please ensure they are a separate user group. Lastly, patients with prior Humulin U-500 experience must be noted do not need to be excluded from the study.
- Both trained (15 participants) and untrained (15 participants) patients who have prior insulin experience should be evaluated. The untrained group should have the option to read the instructions for use rather than required to read it to better simulate "real use" untrained scenario. All participants should be informed during the training and/or familiarization period that the strength of the insulin is "200 units/mL."
- If visually impaired participants are not included in this study, the tasks for patient user groups should include visual impairment simulation.
- Finally, include both trained (15 participants) and untrained (15 participants) inpatient nurses as healthcare providers that use the Tresiba FlexTouch 200 units/mL as this user group has not been assessed in any of the prior studies.

7 REFERENCES

OSE review 2008-434 Postmarketing Medication Error Review, Humulin U-500 Injection; Griffis, M; June 24, 2008.

APPENDICES

Appendix A: The hands on tasks performed by the participants in UT86

All participants performed the five tasks listed below, with the following two exceptions:

- Eight pen-injector naïve children only performed Tasks 1 – 4 (per the protocol). (CH2, CH4, CH7, CH9, CH13, CH14, CH15, CH16)
- 4 participants performed Task 1 (normal injection) and Task 2 (normal injection) with different dose amounts (CH2, CH3, E1, E2).

Each participant performed Task 1 (normal injection) first, and then performed the remaining three or four tasks in a counterbalanced order pre-determined by the test personnel. Although the instructions below list all three insulin types, each participant performed all tasks using one, randomly-assigned insulin type, as described above.

Task 1 (normal injection)

Deliver 24 units of insulin using the pen injector containing Tresiba® 100 U/mL / Ryzodeg™ 100 U/mL or 64 units of insulin using the pen injector containing Tresiba® 200 U/mL.

Task 2 (normal injection)

Deliver 30 units of insulin using the pen injector containing Tresiba® 100 U/mL / Ryzodeg™ 100 U/mL or 52 units of insulin using the pen injector containing Tresiba® 200 U/mL.

Task 3 (blocked needle)

Deliver 18 units of insulin using the pen injector containing Tresiba® 100 U/mL / Ryzodeg™ 100 U/mL or 36 units of insulin using the pen injector containing Tresiba® 200 U/mL.

Note: The test administrator attached a blocked needle to the pen-injector and provided the pen injector to the participant without a pen-injector cap attached. If the participant said s/he would replace the needle, the test administrator said, "During this particular task, we would like you to proceed with the simulated injection and see how things go using the currently attached needle," so that the participant encountered the blocked needle scenario.

Task 4 (dose reversal)

Deliver 41/27 units of insulin using the pen injector containing Tresiba® 100 U/mL / Ryzodeg™ 100 U/mL or 42/28 units of insulin using the pen injector containing Tresiba® 200 U/mL.

Task 5 (end of content)

Deliver 50 units of insulin using the pen injector containing Tresiba® 100 U/mL / Ryzodeg™ 100 U/mL / Tresiba® 200 U/mL (no pen-injector-naïve children performed this task, per the protocol).

Note: The test administrator provided a pen-injector containing 32 units (i.e., less than the requested dose).

Appendix B: Summary of reported use errors from UT86.

	Number of:			
Use error description	Participants who committed the use error	Use errors	Opportunities to commit the use error [4]	Use error rate
Pen is not primed before first injection (200 U/mL)	1 / 10[5] (10.0%)	1 Trained: 0 Untrained: 1	25	1 / 25 (4.0%)
Initially misinterpreted priming instructions	1/51 (2.0%)	1 Trained: 0 Untrained: 1	N/A	N/A
Dose not set correctly	1 / 51 (2.0%)	2 Trained: 0 Untrained: 2	281	2 / 281 (0.7%)
Misinterpreted the dose delivered after detecting blocked needle	1 / 51 (2.0%)	1 Trained: 0 Untrained: 1	51	1 / 51 (2.0%)
Needle is not held in the skin at least 1 second after the scale is back to "0"	2 / 51 (3.9%)	2 Trained: 1 Untrained: 1	281	2 / 281 (0.7%)
Needle stick injury	1 / 51 (2.0%)	1 Trained: 1 Untrained: 0	N/A	N/A

Appendix C: Summary of reported close calls from UT86.

	Number of:			
Close call description (i.e., description of the use error that almost occurred)	**Participants who encountered the close call**	**Close calls**	**Opportunities to encounter close call**	**Close call rate**
Blocked needle is not detected	2 / 51 (3.9%)	2 Trained: 1 Untrained: 1	51	2 / 51 (3.9%)
Pen is not primed before first injection	1 / 10 (10.0%)	1 Trained: 1 Untrained: 0	25	1 / 25 (4.0%)
Needle is attached after dose is set and dose is altered	1 / 51 (2.0%)	1 Trained: 0 Untrained: 1	298	1 / 298 (0.3%)
Dose initially not dialled	2 / 51 (3.9%)	2 Trained: 1 Untrained: 1	281	2 / 281 (0.7%)
Dose not set correctly	1 / 51 (2.0%)	2 Trained: 0 Untrained: 2	281	2 / 281 (0.7%)
Dose button is not held down until dose counter is back to "0"	1 / 51 (2.0%)	1 Trained: 0 Untrained: 1	281	1 / 281 (0.4%)
Miscalculates second dose amount when splitting dose between nearly empty and new pen	1 / 43 (2.3%)	1 Trained: 1 Untrained: 0	43	1 / 43 (2.3%)
Device cap is not mounted after use	1 / 51 (2.0%)	1 Trained: 1 Untrained: 0	281	1 / 281 (0.4%)

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

/s/

KELLIE A TAYLOR on behalf of RICHARD A ABATE
06/26/2012

KELLIE A TAYLOR
06/26/2012

CAROL A HOLQUIST
06/26/2012

1 05/31/12

Memo

Date: March 14, 2012

Revised April 5, April 25, May 25, and May 30,2012

From: Fred Mills, Staff Scientist, DTP

To: Daniela Verthelyi, Chief, Laboratory of Immunology, DTP, OBP

FDA designation: NDA 203314, original NDA submission

Sponsor: Novo Nordisk

Product: insulin degludec (IDeg, generic name insulin 454), for treatment of diabetes

Subject of Review: RadioImmunoAssay (RIA) for detection of anti-insulin 454 antibodies

Table of Contents

Comments to the File:

The sponsor provided the validation for a screening and confirmatory assays/ there is no neutralizing assay report, but this may be acceptable since there is no precedent for neutralizing antibodies to insulin. The screening is a radio immunoanalysis (RIA) and the confirmatory assay is a subtraction RIA (cold competition). The control antibody specific for IDeg is low affinity creating some uncertainty as to the quality of the assay. In addition, the assay seems to be sensitive to concentrations of insulin (both IDeg and endogenous insulin) that are expected to be present in the patients at the time of testing therefore the sensitivity of the assay is uncertain.
Therefore, even though the clinical data they have provided suggests that there was no change in the level of IDeg (Insulin 454) specific antibodies or cross-reacting antibodies from baseline to the end of the trial, these results are questionable until they can demonstrate appropriate sensitivity in the presence of on-board product and endogenous insulin In the target population.

Comments to the Sponsor:

The Agency has three major comments, regarding your assays for anti-insulin 454, anti-insulin aspart, and anti-insulin antibodies:

1. The Agency is concerned about the effects of both on-board insulin 454 product and endogenous insulin may have on the sensitivity of your antibody assay due to the following considerations:

You have provided data demonstrating a significant effect of on-board insulin 454 product on the sensitivity of the insulin antibody screening assay at concentrations above 200 pM. This is a concern because in your PK/PD study (NN1250-1988), a single dose of 0.4 U/kg (2.4 nmol/kg) gave mean serum concentrations from 45 to 2100 pmol/L over a 120 hour sampling interval, with a mean half life of 19 hours. Also, a dose-response study in T1D patients (NN1250-1993) showed that for the maximum study dose (0.8 U/kg =4.8 nmol/kg), a Cmax of 9731 pmol/L was achieved at steady-state, with a mean 26 hour mean terminal half life after multiple doses. Therefore, it is reasonable to expect serum insulin 454 product concentrations significantly above the threshold that you have determined for on-board product interference with your assay.

Furthermore, subjects with type 2 diabetes who will be receiving this product are expected to have high endogenous insulin levels. Although insulin levels will vary considerably from subject to subject depending on insulin resistance and glycemic control, most type 2 diabetes patients are expected to have endogenous fasting insulin levels at or above the normal range (145 pmol/L) and fed levels ~ 3 times this concentration. In addition, some patients with extreme insulin resistance could have much higher levels. Thus endogenous insulin levels may also be high enough to interfere with your assay. For these reasons, unless you can demonstrate sufficient sensitivity in the presence of onboard drug and/or

expected insulin levels, you need to modify the current assay or develop an alternative assay format that minimizes interference from on-board insulin 454 product as well as endogenous insulin. The cutpoint for the assay needs to be determined using sera of treatment-naive patients.

In this regard, the FDA also notes that you have tested the effects of 200, 2000, and 20,000 pM insulin 454, with no intermediate steps- testing for interference at intermediate concentrations between 200 and 2000 pM may reveal that your assay is tolerant of product concentrations higher than 200 pM.

2. In summarizing your antibody testing, you state that there was no change in the level of IDeg (Insulin 454) specific antibodies or cross-reacting antibodies from baseline to the end of the trial. You also state that for all subjects, the change from baseline in antibodies to your product as well as those cross-reacting with human insulin were low and similar in data from 7 trials with IDeg. However, unless you can demonstrate appropriate sensitivity in the presence of on-board product and endogenous insulin, it is difficult to evaluate the significance of the immunogenicity data you have submitted. **Therefore, once you have optimized you're assay and confirmed the cutpoint in** treatmetn-naïve patients you may need to re-analyze patient sera and submit these data to the FDA for evaluation.

3. You state that the differences in sensitivity observed using the control antibodies are due to low affinity of your antibody specific for IDeg. Without a high affinity control antibody that will enable appropriate validation of the anti-IDeg antibody assay it is difficult to have confidence as to what the true sensitivity of the anti-Deg assay is and what the levels of anti-IDeg antibody are. Therefore, please develop a suitable control and provide assay validation demonstrating an appropriate level of sensitivity.

In addition, please address the following issues:

a. Report nn960358 on the crossreactivity of antibodies to IDEG to the human insulin, insulin X14, and insulin NN304 antibody assays describes the effects of -20 ^{0}C storage and freeze-thaw cycles on antibody controls. Please provide data from stability and freeze-thaw studies for control antibody solutions specific for the insulin 454 antibody assay.

b. While it may be true that inter assay variation is low and well within the 15% acceptance limits, a more general consideration is the need for system suitability specifications to ensure reproducibility between assay runs. Therefore please implement system suitability controls with appropriate specifications for this assay. The low positive quality control for this purpose should have a concentration that is close to the limit of detection for the assay to ensure that the assay has a reproducible sensitivity. Your low positive quality control should be designed to produce a signal above the cut point (positive) 99% of the time (failing in $\leq$1% of the time). A high positive quality control will ensure that the

range of the assay remains consistent and should be used at a concentration that falls within the linear range of the dose-response curve.

c. Validation of your antibody assays indicates that there is no effect of lysed red blood cells at the dilutions studied, which are $\geq$ 1/200. Please clarify how you will treat samples that are contaminated with larger amounts of RBCs.

d. Regarding other potential matrix effects, in your previous validation of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997), you also investigated the effects of bilirubin, lipid, Human Serum Albumin (HSA), and pH. Bilirubin had no effect in the range studied, but lipid, HSA, and pH change significantly altered the signal for one or more of the antibodies. Please provide data that assesses the effects of these factors on your anti-insulin 454 antibody assay.

Executive Summary

Product description

NDA 203314 is for Novo Nordisk's insulin degludec (IDeg, generic name insulin 454) which is an ultra-long acting insulin for once-daily subcutaneous administration in patients with diabetes. IDeg is a modified insulin, or insulin analogue, in which the threonine at position B30 of human insulin has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid (palmitic acid) via a glutamic acid spacer. This structure allows IDeg to form soluble, stable multi-hexamers, resulting in accumulation in the subcutaneous tissue after injection. A gradual dissociation of IDeg monomers from the multi-hexamers provides a slow and continuous delivery of IDeg from the s.c. injection site into the circulation, leading to long pharmacokinetic and pharmacodynamic profiles. In addition, binding of the palmitic acid (b) (4) of IDeg to albumin contributes to extending the half life. IDeg monomers bind to and activate insulin receptors triggering glucose uptake.

For reference, the following tabulation of other insulin analogues may also be helpful

Insulin aspart (X14): substitution of the B28 threonine with aspartic acid, *fast acting*

NN304 insulin (insulin detemir): similar to insulin 454, but with myristic acid conjugated at lysine B29, instead of pamitic acid. *Long acting via fatty acid binding to albumin*

Insulin glargine : glycine substituted for asparagine at position A21, two arginines added C terminal of B chain, *long acting due to aggregate formation*

Clinical trials

This NDA contains data from 7 clincial trials, including one Phase 3 trial (Trial NN9068-3632) that was completed January 31, 2011. This study was a single-center, single-dose, randomized, double-blind, double-dummy, four-period crossover trial in healthy male subjects to investigate the safety and tolerability of IDegLira compared to simultaneous, separate dose administration of liraglutide *(long-acting glucagon-like peptide-1 analog)* and IDeg, as well as single dose administration of liraglutide and single dose administration of IDeg on separate occasions. In total, 46 subjects were screened for this trial and as planned, 24 subjects were randomized and included in both the safety analysis set and the full analysis set. All 24 subjects completed the trial.

No samples were positive for liraglutide antibodies. The sponsor states that there was no change in the level of IDeg specific antibodies or cross-reacting antibodies from baseline to the end of the trial. For all subjects, the change from baseline in antibodies cross-reacting with human insulin was low and similar in data from 7 trials with IDeg (Figure 3–1). **Also, the change from baseline in specific** insulin analogue antibodies was low and similar in all 7 trials with IDeg.

Reviewer comments
Data for cross-reacting antibodies to insulin and insulin analogues other than IDeg/ insulin 454 have been obtained using antibody assays that have appropriate sensitivity (≤ 500 ng/ ml antibody, as per FDA draft guidance, 2009), and are therefore interpretable. This is reassuring since (1) for human insulin, antibodies cross-reacting with the endogenous insulin of patients could pose serious safety concerns. (2) antibodies cross-reacting with insulin analogues would have the potential to render patients resistant to standard of care treatments.

However, validation of the antibody assay for the IDeg/ insulin 454 product itself (discussed more fully below) gave a sensitivity in the range of 1800 ng/ml. The sponsor states this result is due to the low affinity of the control anti-IDeg antibody (a monoclonal) used to validate the assay. However, without a high affinity control antibody that will enable appropriate validation of the anti-IDeg antibody assay, it is difficult to have confidence as to what the true levels of anti-IDeg antibody are. Therefore, the sponsor should develop a high affinity control and provide assay validation demonstrating an appropriate level of sensitivity.
Further, high degree of on-board drug interference was noted suggesting that the assay may be less sensitive than stated. the cutpoint has not been validated in the patient population and therefore it is unclear that the sensitivity of the assay is as claimed.

A related issue is the lack of a neutralizing antibody assay, which is necessary to assess the physiological significance of observed antibody levels. The sponsor should develop and validate such an assay.

Assay validation
Assay description
The sponsor's antibody assay is a RadioImmunoPrecipitation (RIA). This method has previously been validated for determination of antibodies to human insulin, and insulin analogues insulin aspart (insulin X14), NN304 and NN344. Briefly, the assay is a subtraction radioimmunoassay. The samples were incubated with ^{125}I labeled tracer ± excess insulin/insulin analogue. After incubation overnight the immunoglobulin was precipitated together with any antigen that may have bound. The precipitate was counted in a gamma counter and the amount of radioactivity was expressed in percent of the total amount of added radioactivity (%B *(bound)* /T*(total)*).

Reagents and stability

As described in previous studies in report nn960358 for the human insulin, insulin X14, and insulin NN304 antibody assays, the effects of -20 ^{0}C storage and five freeze-thaw cycles were assessed .
Reviewer comment
Similar stability and freeze-thaw studies should be performed for the reagents specific for the insulin 454 antibody assay

Assay sensitivity.
Assay sensitivity was determined as the concentration of antibody that produced a %B/T

equal to the upper 95 % limit of 150 normal serum samples.

Sensitivities were:
1800 ng/ ml for insulin 454
(similar low sensitivity was observed in a subsequent validation of method transfer)
35 ng/ml for insulin aspart
20 ng/ml for cross-reacting insulin antibodies

Reviewer comments
The sponsor notes the poor assay sensitivity for insulin 454 (1800 ng/ ml), stating that this is probably due to the low affinity of the insulin 454 specific monoclonal antibody. This level of sensitivity is over three times higher than the current recommendation (FDA 2009 draft guidance), making the assay of little or no utility for detecting anti-insulin 454 antibodies. However, the assay is of utility in detecting antibodies for insulin aspart (35 ng/ml) and insulin activities (20 ng/ ml). It is particularly important to have appropriate detection of anti-insulin antibodies, since ***antibodies raised to a patient's endogenous*** *insulin (if neutralizing) could have serious safety effects.*

Range of signals in normal sera
150 plasma samples from healthy donors were analyzed. The 95 % percentiles were calculated for insulin aspart insulin 454 specific (F-E, F'-E) and cross-reacting antibodies (A-C or D-F). The 95% percentile values are shown in Table 8

Table 8 95 % upper limit (%B/T)

Antibody	95 % percentile %B/T
Insulin aspart specific Ab (C-B)	4.4
Insulin 454 specific Ab (F'-E)	0.6
Cross-reacting Ab (A-C)	0.8
Insulin 454 specific Ab (F-E)	0.6
Cross-reacting Ab (D-F)	0.5

Reviewer comment
The background for anti-product signal (Insulin 454 ab) appears to be quite low. However, any signal above this background will be difficult to interpret because, as discussed in the section on assay sensitivity, the low affinity of the anti-insulin 454 control antibody makes the anti-insulin 454 assay appear to be very insensitive.

Drift during assay runs
Drifting was determined by analyzing the control samples 6 times in duplicate in the beginning and in the end of the assay. No significant difference between control samples analyzed in the beginning and in the end of the assay was seen for insulin 454 specific antibodies nor for cross reacting antibodies. There was a modest difference between results insulin aspart specific antibodies analyzed first and last in the assay, although this the sponsor did not consider this important for their analysis.

Reviewer comment
I agree with the sponsor that the insulin aspart measurements that were taken first and those that were taken last are similar, since the mean of the first series is 41.7, with a standard deviation of 1.8, while the mean of the last series is 40 with a standard deviation of 0.98. Therefore, there is a substantial overlap in these distributions, and a t test says there is p=0.016 that their means are the same, which is still above the p=0.01 level of statistical significant.

Repeatability and Intermediate variation
Repeatability and intermediate variation were investigated by analyzing in two double determinations in eight independent assays four control antibody samples designed to yield levels of insulin aspart antibodies, insulin X-14 antibodies, and cross reactive (anti-insulin) antibodies. Both the repeatability and the intermediary variation were below 10 % , which is within the acceptance limits of %CVs below 15%. The sponsor takes this to mean that antibody samples taken at various time points from the same patient do not need to be analyzed in same assay set-up.

Reviewer comments
While it may be true that inter assay variation is low and well within the 15% acceptance limits, a more general consideration is the need for system suitability specifications to ensure reproducibility between assay runs. These should be provided by the sponsor

Determination of Cut Point
Reviewer comment
Determination of a sensitivity as the concentration of antibody that produces a %B/T equal to the upper 95% limit of 150 normal serum samples is conceptually similar to setting a cutpoint equal to a 5% false positive rate for normal serum samples, as per Mire-Sluis 2004;i.e. the sponsor is classifying samples as positive that have signals equivalent to the upper 5% of normal serum samples.
Therefore the sponsor has in effect set an appropriate cutpoint for the anti-human insulin an anti-insulin aspart assays.
Sensitivity as the equivalent of cutpoint for the anti insulin 454 assay may also be acceptable, but only if appropriate sensitivity can be demonstrated.

Drug Tolerance
The interference from insulin aspart and insulin 454 in the antibody analysis was first investigated by addition of insulin aspart and insulin 454 to the four control antibody samples The control samples were divided in two and either insulin aspart or insulin 454 was added to the following final concentrations during incubation with tracer: 0, 50, 150, 450, 1350, 4050, 12150, 36450, 109350, 328050 pM. Each sample was analyzed in duplicate. Recovery of $\geq$ 80% of the no added drug signal was taking as indicating no interference.

Taking the polyclonal Guinea Pig anti-insulin antibody as a surrogate for patient antibodies, with no competitor, there was a detectable signal above background at 0.140 µg/ ml= 140 ng/ ml, well within the FDA-recommended sensitivity of 500 ng/ ml.

However, at the lowest competitor insulin 454 concentration of 200 pM, signal is lost 0.41 mg/ ml= 410 ng/ ml, with a faint signal retained at 1.2 mg/ml =1200 ng/ ml. The sponsor concluded that 200 pM insulin 454 is the highest allowable on-board product concentration. Dilution of samples did not improve the drug tolerance of the assay

The signal for monoclonal anti-Insulin 454 antibody was only weakly competed by **Insulin 454, consistent with the sponsor's statement** that this is a low affinity antibody.

Reviewer comments
There is concern regarding the potential for interference from both on-board insulin 454 product, as well as endogenous insulin. Following discussion with Dr. Vetheyli, I requested input from both the Pharm/Tox reviewer for this NDA (Dr. Manoj Khurana) and the Clinical Reviewer (Dr. Jean-Marc Guettier). Dr Khurana stated that from a pK study, serum concentrations can range from 45 to 2100 pmole/ l over a sampling duration of 120 hours, and in a steady state study on Type 1 diabetics, a mean Cmax of 9731 pmol/L was achieved. Furthermore, Dr. Guettier noted that most Type 2 diabetics are expected to have fasting levels of endogenous insulin at or above normal (145 pmol/ L) with fed levels increasing about 3 fold. Some patients with insulin resistance can have much higher levels.

Therefore, it is reasonable to expect serum insulin 454 product concentrations significantly above the 200 pM threshold that the sponsor has determined for on-board product interference. In addition, patients can also have substantial endogenous insulin levels, which may interfere with the assay.

I also note that the sponsor only tested the effect of 200, 2000, and 20,000 pM insulin 454, and the sponsor should explore intermediate steps between 200 and 2000 pM, since it is possible that there may be a value for adequate drug tolerance above 200 pM that would allow the sponsor to reliably detect patient antibodies in many cases.

Matrix effects
The effect of hemolysis on the antibody measurement was investigated by measuring control samples with or without addition of erythrocytes. This study was performed because in a previous validation study of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997) increases in the range 5.5%-7% were seen upon addition of dilute lysed RBCs.
Reviewer comments
There appeared to be no effect of lysed RBS at the dilutions studied, which are $\geq$ 1/200 (20 µl of packed erythrocytes in 380 µl control samples, followed by at least a 1/10 dilution). There should be a specification to avoid contaminating patient serum samples with larger amounts of RBCs.

Furthermore, in the previous validation study of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997), the sponsor also investigated the effects of bilirubin, lipid, Human Serum Albumin (HSA), and pH. Bilirubin had no effect in the rage studied, but lipid, HSA, and pH change all had

significant effects for one or more of the antibodies.

Reviewer comment
Given the effects observed on the readings for insulin or other insulin analogue antibodies, the sponsor should assess the effects of lipid, HSA, and pH on the assay for anti-insulin 454 antibodies.

Extended Discussion of NDA 203314 Immunogenicity, including tables and figures

Product Background

Insulin degludec (IDeg, generic name insulin 454) is an ultra-long acting basal insulin for once-daily (OD) subcutaneous (s.c.) administration in patients with diabetes mellitus. IDeg is modified such that the amino acid (b) (4) threonine in position B30 of human insulin has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid (palmitic acid) via a glutamic acid spacer. This structure allows IDeg to form soluble and stable multi-hexamers, resulting in a depot in the subcutaneous tissue after injection. The gradual separation of IDeg monomers from the multi-hexamers results in a slow and continuous delivery of IDeg from the s.c. injection site into the circulation, leading to the observed ultra-long pharmacokinetic and pharmacodynamic profiles. Furthermore, binding of the fatty acid moiety of IDeg to albumin contributes to some extent to the protraction mechanism. At the target tissues, IDeg monomers bind to and activate insulin receptors triggering the same cellular effects as human insulin such as promoting glucose uptake.

Summary of Immunogenicity Results

In the IDegLira clinical development program, one clinical pharmacology trial (Trial NN9068- 3632) was completed as of 31 January 2011. In addition, one phase 3 trial was ongoing as of 31 January 2011. Trial NN9068-3632 was a single-centre, single-dose, randomized, double-blind, double-dummy, four-period crossover trial in healthy male subjects to investigate the safety and tolerability of IDegLira compared to simultaneous, separate dose administration of liraglutide *(long-acting glucagon-like peptide-1 analog)* and IDeg, as well as single dose administration of liraglutide and single dose administration of IDeg on separate occasions. In total, 46 subjects were screened for this trial and as planned, 24 subjects were randomized and included in both the safety analysis set and the full analysis set. All 24 subjects completed the trial.

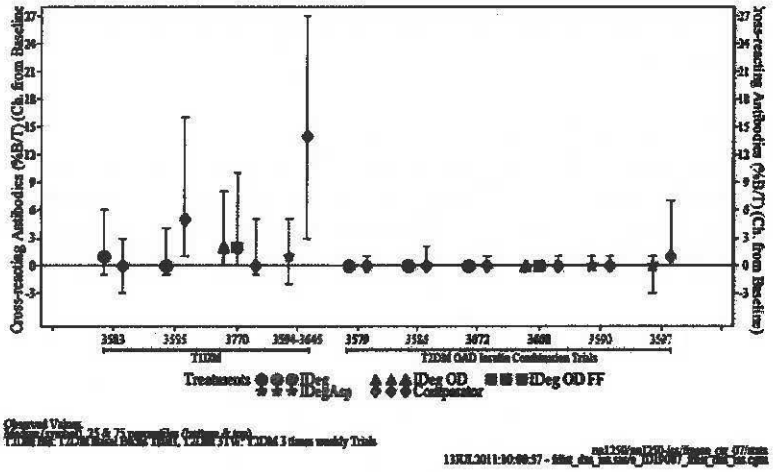
No samples were positive for liraglutide antibodies. There was no change in the level of IDeg specific antibodies or cross-reacting antibodies from baseline to the end of the trial For all subjects, the change from baseline in antibodies cross-reacting with human insulin was low and similar in all 7 trials with IDeg (Figure 3–1). As was the change from baseline in specific insulin analogue antibodies was low and similar in all 7 trials with IDeg

Comparison across Trials

Cross-reacting Antibodies

For all subjects, the mean change from baseline to follow-up visit in antibodies cross-reacting with human insulin was low in both the IDeg and the comparator group, and there was no difference between the treatment groups. The mean value of antibodies cross-reacting with human insulin at baseline and at the end of the trial (after 27 or 53 weeks of treatment) was similar in the IDeg and the comparator group. The majority of

subjects in both treatment groups had no or little change in antibodies cross-reacting with human insulin.

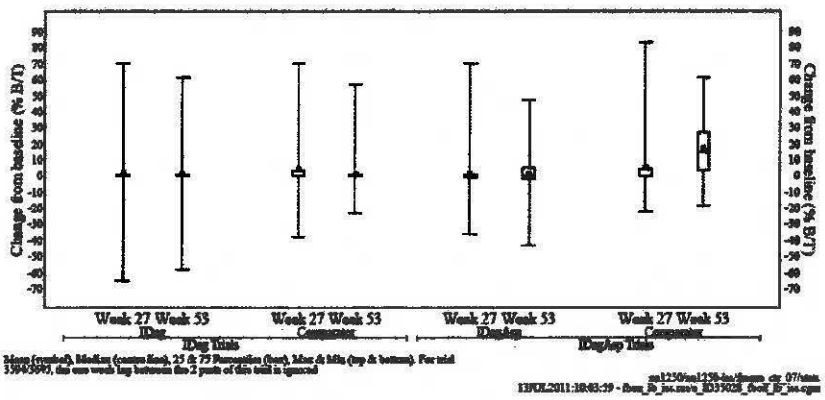


Cross-reference: Appendix 1.20, Figure 3

Figure 3–1 Cross Reacting Antibodies at Week 27/53 – Change from Baseline – All Therapeutic Confirmatory Trials – All Subjects – IDeg and IDegAsp vs. Comparator – Distribution by Trial – Safety Analysis Set

Cross-reacting Antibodies

For all subjects, the mean change from baseline to follow-up visit in antibodies cross-reacting with human insulin was low in both the IDeg and the comparator group, and there was no difference between the treatment groups (Figure 3–2). The mean value of antibodies cross-reacting with human insulin at baseline and at the end of the trial (after 27 or 53 weeks of treatment) was similar in the IDeg and the comparator group The majority of subjects in both treatment groups had no or little change in antibodies cross-reacting with human insulin



Cross-reference: Appendix 1.20, Figure 6

Figure 3–2 Cross-reacting Antibodies – Change from Baseline – All Therapeutic Confirmatory Trials – All Subjects – IDeg and IDegAsp vs. Comparator – Safety Analysis Set

Specific Insulin Analogue Antibodies
For all subjects, the mean values of specific insulin analogue antibodies showed no or very little change after 27 and 53 weeks of treatment with no difference between the IDeg and the comparator group (The majority of subjects in the IDeg group had no or little change in specific IDeg antibodies

Adverse Events and Increase in Antibodies
For all subjects, 220 (5%) subjects in the IDeg group and 145 (6%) subjects in the comparator group had an increase of 10% B/T (absolute value) or more in antibodies cross-reacting with human insulin or an increase in specific insulin analogue antibodies of 5% B/T or more

RIA Assay Validation

Overview of Method

The aim of this study was to validate a method for determination of antibodies against insulin 454 (insulin Degludec) in human serum. The method has previously been validated for determination of antibodies to human insulin, insulin aspart (insulin X14), NN304 and NN344. Briefly, the assay is a subtraction radioimmunoassay. The samples were incubated with ^{125}I labeled tracer ± excess insulin/insulin analogue. After incubation overnight the immunoglobulin was precipitated together with any antigen that may have bound. The precipitate was counted in a gamma counter and the amount of radioactivity was expressed in percent of the total amount of added radioactivity (%B *(bound)* /T*(total)*).

The complete assay setup was as follows:

Series	Assay mixture	Result represent the sum of
A	Sample + Buffer + X-14 tracer	Background, X-14 specific and cross reacting antibodies
B	Sample + Cold X-14 + X-14 tracer	Background
C	Sample + Cold 0454 + X-14 tracer	Background, X-14 specific antibodies
D	Sample + Buffer + 0454 tracer	Background, 0454 specific and cross reacting antibodies
E	Sample + Cold 0454 + 0454 tracer	Background
F	Sample + Cold insulin + 0454 tracer	Background, 0454 specific antibodies
F'	Sample + Cold X-14 + 0454 tracer	Background, 0454 specific antibodies

For each sample the following was calculated:
The amount of specific X-14 antibodies = C-B
The amount of specific 0454 antibodies = F-E, (F´-E)
The amount of cross- reacting antibodies = D-F, (D-F') (or A-C)
In practice only the necessary series will be included. This means that in clinical trials series A will often be deleted and only series F or F' will be included.

Important reagents

insulin analogue tracers

^{125}I-(Tyr A14) - X14 Batch: 57B and 63B
^{125}I- NN454 Batch: 11A, 14A, 18B and 20B

Control antibodies

The assay sensitivity was measured by dilution of the following antibodies:

polyclonal guinea pig anti-insulin antibody

3.1.2.3 Polyclonal antibodies for determination of cross-reacting antibodies

ID	Polyclonal anti-insulin
Host	Guinea pig
Antigen	Bovine and porcine insulin
Source	Novo Nordisk A/S
Lot/Batch No.	01D19E2512-1
Physical Form	Solution (PBS + 0.05% Sodium acid)
Content	7.15 mg/mL
Expiry Date	Apr-2011
Storage Conditions	5°C

monoclonal insulin 454 specific antibody

3.1.2.2 Monoclonal antibodies specific for insulin 454

ID	NN454-1 F46
Source	Novo Nordisk A/S
Lot/Batch No.	04K17J3127-4
Physical Form	Solution
Concentration	1.16 mg/mL
Expiry Date	Oct-2014
Storage Conditions	5°C

monoclonal anti-insulin aspart (insulin X14) antibody

3.1.2.1 Monoclonal antibodies specific for insulin aspart

ID	X14-6 F34
Source	Novo Nordisk A/S
Lot/Batch No.	8J13H1842-1
Physical Form	Solution
Concentration	0.26 mg/mL
Expiry Date	Oct-2008
Storage Conditions	5°C

Antibody Solutions

C2: X14-6 F34 (batch 8J13H1842-1) diluted 1:371 ~ 0.56 µg/ml
C3: GPα Insulin (batch Mix 1) diluted 1:1200 ~ 6.8 µg/ml
C8: NN454-1 F46 (batch 04K17J3127-4) diluted 1:20 ~ 58 µg/ml
C9: GPα Insulin (batch 01D19E2512-1) diluted 1:500 ~ 14.3 µg/ml

Reviewer comments

The sponsor has previously assessed stability of the reagents for measuring anti-insulin and anti-insulin aspart antibodies. Similar stability evaluation of reagents specific for the anti-insulin 454 antibody determination should be performed (^{125}I- NN454, cold NN454 solution, and anti-insulin 454)

Assay sensitivity.

The assay sensitivity was measured by dilution of the three control antibodies:
polyclonal guinea pig anti-insulin antibody
monoclonal insulin 454 specific antibody
monoclonal anti-insulin aspart antibody

Assay sensitivity was determined as the concentration of antibody that produced a %B/T equal to the upper 95 % limit of 150 normal serum samples.

Sensitivities were:
1800 ng/ ml for insulin 454
(similar low sensitivity was observed in a subsequent validation of method transfer from Novo Nordisk to (b) (4) report nn208156)
35 ng/ml for insulin aspart
20 ng/ml for cross-reacting insulin antibodies

Reviewer comments
The sponsor notes the poor assay sensitivity for insulin 454 (1800 ng/ ml), stating that this is probably due to the low affinity of the insulin 454 specific monoclonal antibody. This level of sensitivity is over three times higher than the current recommendation (FDA 2009 draft guidance), making the assay of little or no utility for detecting anti-insulin 454 antibodies. However, the assay is of utility in detecting antibodies for insulin aspart (35 ng/ml) and insulin activities (20 ng/ ml). It is particularly important to have appropriate detection of anti-insulin antibodies, since antibodies raised to a patient's endogenous insulin (if neutralizing) could have serious safety effects.

Range of signals in normal sera
150 plasma samples from healthy donors were analyzed. The 95 % percentiles were calculated for insulin aspart (X-14) specific **(C-B), insulin 454 specific (F-E, F'-E) and** cross-reacting antibodies (A-C or D-F). The 95% percentile values are shown in Table 8

Table 8 95 % upper limit (%B/T)

Antibody	95 % percentile %B/T
Insulin aspart specific Ab (C-B)	4.4
Insulin 454 specific Ab (F'-E)	0.6
Cross-reacting Ab (A-C)	0.8
Insulin 454 specific Ab (F-E)	0.6
Cross-reacting Ab (D-F)	0.5

Reviewer comment
The background for anti-product signal (Insulin 454 ab) appears to be quite low. However, any signal above this background will be difficult to interpret because, as discussed in the section on assay sensitivity, the low affinity of the anti-insulin 454 control antibody makes the anti-insulin 454 assay appear to be very insensitive.

Drift during assay runs

Drifting was determined by analyzing the control samples 6 times in duplicate in the beginning and in the end of the assay. The values obtained in the beginning and in the end of the assay were compared by a paired t-test using excel. The values are shown in Table 3. No significant difference between control samples analyzed in the beginning and in the end of the assay was seen for insulin 454 specific antibodies (C8) nor for cross reacting antibodies (C3). Some difference between insulin aspart specific antibodies (C2) analyzed first and last in the assay was, however, seen. The mean difference between C2 analyzed first and last in the assay was below 2 %B/T which is less than 5 % of mean %B/T of C2. The sponsor did not consider this difference to be important.

Table 3 Drifting
(Set-up ID: 25, 26 and 31-Jan-2006/BSka)

C2 % B/T Series C-B		C8 % B/T Series F-E		C3 % B/T Series A-C		C3 % B/T Series D-F	
first	last	first	last	first	last	first	last
43.1	40.2	31.6	31.7	19.7	18.6	7.4	7.7
40.7	39.2	29.5	31.6	20.1	18.8	8.3	7.9
41.3	41.0	30.8	32.4	19.3	19.6	8.0	8.0
38.8	38.4	32.4	31.9	19.2	19.8	7.8	8.1
43.0	40.6	32.1	32.8	19.6	20.0	7.6	6.1
43.3	40.4	30.8	33.8	19.1	19.3	7.8	7.6

Reviewer comment

I agree with the sponsor that the C2 measurements that were taken first and those that were taken last are similar, since the mean of C2 first series is 41.7, with a standard deviation of 1.8, while the mean of C2 last series is 40 with a standard deviation of 0.98. Therefore, there is a substantial overlap in these distributions, and a t test says there is p=0.016 that their means are the same, which is still above the p=0.01 level of statistical significant.

Repeatability and intermediate variation

The repeatability and intermediate variation was investigated by analyzing the four control antibody samples (C2, C3, C8 and C9) in two double determinations in eight independent assays. Repeatability and intermediary variation was calculated for insulin X-14 (insulin aspart) specific antibodies (C-B)(Control 2), insulin 454 specific antibodies (F-E) (Control 8) and cross-reacting antibodies (A-C or D-F) (Control 3 and 9). Since outliers were detected in assay set-up 1 it was decided to leave out assay 1 from the calculation of the variation. The results are shown in Table 1 and Table 2:

Table 1 Repeatability

Insulin Aspart antibodies C2 (C-B)			Cross-reacting antibodies C3 and C9 (A-C)			Cross-reacting antibodies C3 and C9 (D-F)			Insulin 454 specific antibodies C8 (F-E)		
Mean % B/T		%CV	Mean %B/T		%CV	Mean %B/T		%CV	Mean %B/T		%CV
C2	42.1	4.2	C3	19.3	2.8	C3	7.6	3.6	C8	32.6	6.4
-		-	C9	88.2	2.5	C9	84.3	1.2			

Table 2 Intermediary variation

Insulin Aspart antibodies C2 (C-B)			Cross-reacting antibodies C3 and C9 (A-C)			Cross-reacting antibodies C3 and C9 (D-F)			Insulin 454 specific antibodies C8 (F-E)		
Mean % B/T		%CV	Mean %B/T		%CV	Mean %B/T		%CV	Mean %B/T		%CV
C2	42.1	9.0	C3	19.3	5.3	C3	7.6	6.2	C8	32.6	6.4
-		-	C9	88.2	4.2	C9	84.3	3.4	-		-

Both the repeatability and the intermediary variation were below 10 % , which is within the acceptance limits of %CVs below 15%. The sponsor takes this to mean that antibody samples taken at various time points from the same patient do not need to be analyzed in same assay set-up.

Reviewer comments
While it may be true that inter assay variation is low and well within the 15% acceptance limits, a more general consideration is the need for specifications for system suitability to ensure reproducibility between assay runs. These should be provided by the sponsor.

Determination of Cut Point
Reviewer comment
Determination of a sensitivity as the concentration of antibody that produces a %B/T equal to the upper 95% limit of 150 normal serum samples is conceptually similar to setting a cutpoint equal to a 5% false positive rate for normal serum samples, as per Mire-Sluis 2004;i.e. the sponsor is classifying samples as positive that have signals equivalent to the upper 5% of normal serum samples.
Therefore the sponsor has in effect set an appropriate cutpoint for the anti-human insulin an anti-insulin aspart assays. The cutpoint for the anti insulin 454 assay may also be adequate if appropriate sensitivity can be demonstrated.

Drug Tolerance
The interference from insulin aspart and insulin 454 in the antibody analysis was first investigated by addition of insulin aspart and insulin 454 to the four control antibody samples
The control samples were divided in two and either insulin aspart or insulin 454 was added to the following final concentrations during incubation with tracer: 0, 50, 150, 450, 1350, 4050, 12150, 36450, 109350, 328050 pM. Each sample was analyzed in duplicate.

C3 *(Guinea Pig α Insulin ~ 6.8 µg/ml)* and C9 *(GPα Insulin ~ 14.3 µg/ml)* were measured using both insulin aspart and insulin 454 as tracers, whereas C2*(X14-6 F34)* was only measured using insulin aspart as tracer and C8 (NN454-1) only with insulin 454 as tracer. An overview of the results can be seen below in Table 4 and Table 5. Recovery of ≥ 80% of the no added drug signal was taking as indicating no interference.

Table 4 Interference from insulin aspart

Insulin aspart pM	C2 (560 ng/ml X14-6 F34) Insulin aspart specific antibodies %B/T	C3 (6.8 µg/ml guinea pig anti-insulin total IgG) Crossreacting antibodies %B/T	C9 (14.3 µg/ml guinea pig anti-insulin total IgG) Crossreacting antibodies %B/T
0	**47.1**	**18.0**	**89.3**
50	**47.8**	**16.3**	**88.6**
150	46.6	11.9	**85.1**
450	**44.9**	**8.5**	**76.3**
1350	**34.3**	**4.3**	**27.3**
4050	**22.5**	**2.5**	**11.0**
12150	**9.7**	0.6	**5.3**
36450	3.9	**0.2**	**2.4**
109350	1.1	-0.1	1.1
328050	0.1	**-0.2**	0.2
80%=	**37.7**	**14.4**	**71.4**

Bold = no interference

Table 5 Interference from insulin 454

Insulin 454 pM	C8 (58 µg/ml NN454-1 F46) Insulin 454 specific antibodies %B/T	C3 (6.8 µg/ml guinea pig anti-insulin total IgG) Crossreacting antibodies %B/T	C9 (14.3 µg/ml guinea pig anti-insulin total IgG Crossreacting antibodies %B/T
0	**31.0**	**7.4**	**79.1**
50	**30.4**	**6.4**	**80.9**
150	**30.6**	**5.4**	**75.4**
450	**30.9**	3.4	55.1
1350	**30.3**	2.2	16.3
4050	**30.6**	**0.9**	7.5
12150	**30.0**	0.2	3.7
36450	**28.7**	0.0	**1.3**
109350	**23.9**	**-0.1**	0.9
328050	12.7	-0.2	0.6
80%=	**24.8**	**5.92**	**63.28**

Bold = no interference

Reviewer comment

In Table 5, the C8 signal for monoclonal anti-Insulin 454 antibody is only weakly competed by Insulin 454, consistent with the sponsor's statement that this is a low affinity antibody.

In an attempt to enhance the drug tolerance of the assay to insulin 454, the sponsor performed experiments with several sample dilutions:

Table 6 Interference from insulin 454 and effect of sample dilution
Normal range for cross-reacting antibodies (insulin 454/human insulin) = 0.5%B/T. Numbers in italics are below normal range.

Concentration of insulin 454	Target purified GP anti-insulin µg/ml	Cross-reacting antibodies in %B/T		
		Undiluted	Diluted 1:5	Diluted 1:10
20.000 pM	100	1.5	1.6	1.4
	33	0.5	0.6	0.5
	11	*0.2*	*0.2*	*0.2*
	3.7	*0.3*	*0.1*	*0.0*
	1.2	*0.0*	*0.1*	*0.0*
	0.41	*0.0*	*0.0*	*0.1*
	0.14	*0.0*	*-0.1*	*0.2*
2000 pM	100	9.6	8.6	8.1
	33	3.4	3.2	2.9
	11	1.2	1.2	1.1
	3.7	0.6	0.6	*0.2*
	1.2	*0.3*	*0.4*	*0.2*
	0.41	*0.3*	*0.2*	*0.1*
	0.14	*0.2*	*0.0*	*0.2*
200 pM	100	89.1	78.7	61.2
	33	20.1	16.8	14.3
	11	6.5	6.3	4.7
	3.7	2.5	2.0	1.7
	1.2	0.8	0.8	0.6
	0.41	*0.2*	*0.4*	*0.2*
	0.14	*0.1*	*0.1*	*0.1*
0 pM	100	96.6	97.8	94.9
	33	96.5	94.6	93.5
	11	95.6	91.7	77.6
	3.7	90.8	59.3	27.8
	1.2	81.0	19.3	8.8
	0.41	25.6	5.6	2.7
	0.14	5.8	1.9	0.8

Taking the polyclonal Guinea Pig anti-insulin antibody as a surrogate for patient antibodies, one can see that with no competitor, there is a detectable signal above background at 0.140 µg/ ml= 140 ng/ ml, well within the FDA-recommended sensitivity of 500 ng/ ml. However, at the lowest competitor insulin 454 concentration of 200 pM, signal is lost 0.41 mg/ ml= 410 ng/ ml, with a faint signal retained at 1.2 mg/ml =1200 ng/ ml. The sponsor concludes that 200 pM insulin 454 is the highest allowable on-board product concentration. Dilution of samples did not improve the drug tolerance of the assay

Reviewer comments
There is concern regarding the potential for interference from both on-board insulin 454 product, as well as endogenous insulin. Following discussion with Dr. Vetheyli, I requested input from both the Pharm/Tox reviewer for this NDA (Dr. Manoj Khurana) and the Clinical Reviewer (Dr. Jean-Marc Guettier). Their comments are inserted below:

Subject: RE: Finalized - NDA 203314 General Consult Request (FRM-CONSULT-01)
Date: Tuesday, April 10, 2012 10:06:31 AM ET
From: Khurana, Manoj
To: Mills, Frederick, Jain, Ritesh
CC: Verthelyi, Daniela I, Calis, Karim, Hartford, Rachel, Vaidyanathan, Jayabharathi

Hi Mills,
Based on the PKPD study (NN1250-1988) a single dose of 0.4 U/kg (equivalent to 2.4 nmol/kg from 600 nmol/mL formulation) is expected to provide mean concentrations that range from 45 to 2100 pmol/L over the sampling duration from 0-120h, mean half-life was 19 hours. Dose-response study in subjects with Type 1 DM (1250-1993) showed mean Cmax value of 9731 pmol/L (range: 6260 - 13900 pmol/L) at steady-state from 0.8 U/kg (4.8 nmol/kg), the maximum dose evaluated in this study; mean terminal half life after multiple dose was 26 hours. Does that answer your questions. Also for my curiosity, can you let me know the reference for the following statement -"The sponsor has found the assay is sensitive to on-board insulin 454 product above 200 pM concentrations." in the e-mail thread below, and which assay is referred here.
Thanks
Manoj

-----Original Message-----
From: Mills, Frederick
Sent: Tuesday, April 10, 2012 9:40 AM
To: Khurana, Manoj; Jain, Ritesh
Cc: Verthelyi, Daniela I; Calis, Karim; Hartford, Rachel
Subject: FW: Finalized - NDA 203314 General Consult Request (FRM-CONSULT-01)

On 4/6/12 1:54 PM, "Guettier, Jean-Marc" <Jean-Marc.Guettier@fda.hhs.gov> wrote:

> Hello All,
>
> I am the clinical reviewer and team leader for this application. Please see my answers to your questions below. I have also cced the clinical pharmacology reviewers who may have additional comments.
>
> 1. Will the patient population be expected to produce significant levels of endogenous insulin, and if so, at what concentration range?
>
> Yes, subjects with type 2 diabetes who will be receiving this product are expected to have high endogenous insulin levels. Insulin levels will vary considerably from subject to subject depending on insulin resistance and glycemic control. For each individual subject endogenous insulin levels will also vary; due to insulin resistance and depending on whether they are fasting or fed. Most type 2 DM patient are expected to have endogenous fasting insulin levels at or above the normal range (145 pmol/L) and fed levels ~ 3 times this concentration. Again some patients

with extreme insulin resistance can have much higher levels.

2. What are the expected serum concentrations of insulin 454? The sponsor has found the assay is sensitive to on-board insulin 454 product above 200 pM concentrations.

This may best be answered by the clinical pharmacology reviewers; Dr. Khurana and Jain who have looked at PK data. What I will say is that there are really no "expected" serum concentrations since insuslin 454 will be individualized to meet the patient's need. In type 2 DM a "typical" dose would be 360-600 nmol delivered subcutaneously; I am not sure what that would translate to in terms of plasma concentration.

Best,

Jean-Marc

Therefore, it is reasonable to expect serum insulin 454 product concentrations significantly above the 200 pM threshold that the sponsor has determined for on-board product interference. In addition, patients may also have substantial endogenous levels, which may also interfere with the assay.

I also note that the sponsor only tested the effect of 200, 2000, and 20,000 pM insulin 454, and therefore should explore intermediate steps between 200 and 2000 pM, since it is possible that there may be a value for adequate drug tolerance above 200 pM that would allow the sponsor to reliably detect patient antibodies in many cases

Matrix effects

Hemolysis
The effect of hemolysis on the antibody measurement was investigated by measuring control samples with or without addition of erythrocytes. This study was performed because in a previous validation study of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997) increases in the range 5.5%-7% were seen upon addition of dilute lysed RBCs.

The following samples were prepared:
A stock lysed red blood cell (dilution E) was prepared by adding 20 µl of packed erythrocytes from a healthy donor to 380 µl control samples (C2,3,8, or 9), and then adding aliquots of these dilutions to control samples (2, 3, 8 or 9) in the following proportions:

Grade 3: 450 µl Control samples (2, 3, 8 or 9) +50 µl dilution E (C 2, 3, 8 or 9)
Grade 2: 475 µl Control samples (2, 3, 8 or 9) +25 µl dilution E (C2, 3, 8 or 9)
Grade 1: 490µl Control samples (2, 3, 8 or 9) +10 µl dilution E (C2, 3, 8 or 9)
The hemolyzed samples were compared to non-hemolyzed Control samples (2, 3, 8 or 9) For control 3 and 9 twice the amount described above were made since these controls were measured in two series. The samples were frozen at -20°C and analyzed twice in duplicate. No interference from hemolysis was seen as the values of the hemolyzed control samples were within 85-115 % of the mean value for non-hemolyzed control samples. The results are shown below:

Table 7 Effect of haemolysis on control samples
The results are shown in %B/T for the non-haemolysed control samples the mean +/- 15% is shown.

Control sample	%B/T	Control Sample	%B/T
C8 non-haemolysed F-E	33.9 (28.8-39.0)	C2 non-haemolysed C-B	40.8 (34.7-46.7)
C8 grade 1	33.4	C2 grade 1	40.7
C8 grade 2	31.9	C2 grade 2	42.1
C8 grade 3	32.3	C3 grade 3	43.5
C3 non-haemolysed D-F	7.6 (6.5-8.8)	C9 non-haemolysed D-F	81.2 (69.0-93.4)
C3 grade 1	7.7	C9 grade 1	82.3
C3 grade 2	7.6	C9 grade 2	82.2
C3 grade 3	7.6	C9 grade 3	82.1
C3 non-haemolysed A-C	18.9 (16.1-21.7)	C9 non-haemolysed A-C	85.7 (72.8-98.6)
C3 grade 1	18.4	C9 grade 1	88.0
C3 grade 2	18.4	C9 grade 2	89.1
C3 grade 3	17.3	C9 grade 3	86.1

Reviewer comments
There appears to be no effect of lysed RBS at the dilutions studied, which are ≥ 1/200 (1/20 x 1/10). There should be a specification to avoid contaminating patient serum samples with larger amounts of RBCs.

Other matrix effects
In the previous validation study of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997), the sponsor also investigated the effects of bilirubin, lipid, Human Serum Albumin (HSA), and pH. Bilirubin had no effect in the rage studied, but lipid, HSA, and pH change all had significant effects for one or more of the antibodies.

Reviewer comment
Given the effects observed on the readings for insulin or other insulin analogue antibodies, the sponsor should assess the effects of lipid, HSA, and pH on the assay for anti-insulin 454 antibodies.

Reagent stability

This was assessed in report nn960358 for the human insulin, insulin X14, and insulin NN304 antibody assays for -20 ^{0}C storage and five freeze-thaw cycles.

Reviewer comment

Similar stability and freeze-thaw studies should be performed for the reagents specific for the insulin 454 antibody assay.

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/s/

FREDERICK C MILLS
05/31/2012

DANIELA I VERTHELYI
05/31/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE:	June 15, 2012
FROM:	QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID
THROUGH:	Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID
CC:	Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID
TO:	Rachel Hartford, Senior Regulatory Project Manager, CDER/OND/ODEII/DMEP
SUBJECT:	**NDA 203313/203314** **Applicant: Novo Nordisk** **Device Constituent: Ryzodeg and Tresiba PDS290 Pen Injector** **Intended Treatment: Diabetes**

QuynhNhu Nguyen, Combination Products Human Factors Specialist — 6/18/2012 Date

Molly F. Story, for Ron Kaye

Ron Kaye, Human Factors and Device Use-Safety Team Leader — 6/18/12 Date

Review Memo – Table of Content

CDRH Human Factors Review

Overview

The Division of Metabolism and Endocrinology requested a Human Factors consultative review of the NDAs 203313 and 203314 submitted by Novo Nordisk. This review provides CDRH's review and recommendations on the Human Factors related information contained in both of the NDAs.

This review is conducted on the Human Factors/usability re-validation study (UT86) that Novo Nordisk submitted under the NDAs. Previously, CDRH Human Factors team has reviewed the Human Factors/usability validation study (UT54) and did not find adequate evidence to support safe and effective use. The Agency issued an advice letter dated December 23, 2012 requesting Novo Nordisk to address the issues identified from the 1st study. Novo Nordisk then submitted their response to the information request, made changes to the Instructions for Use, and provided a supplemental Human Factors/usability validation study protocol based on the IFU changes. The Agency then issued another advice letter dated May 3, 2012 requesting for a rationale or evidence that the proposed IFU changes will adequately address the use-related issues observed in the previous study. However, Novo Nordisk seemed to have conducted the revalidation study prior to incorporating the comments/advice that the Agency issued on May 3, 2012.

Please see the recommendation section (page 7-9) for questions to be transmitted to Novo Nordisk.

Review Materials

EDR Location: \\CDSESUB1\EVSPROD\NDA203313\203313.enx
Supporting Document Number: 17
eCTD Sequence Number: 0016
Letter Date: 04/24/2012
Stamp Date: 4/24/2012

EDR Location: \\CDSESUB1\EVSPROD\NDA203314\203314.enx
Supporting Document Number: 17
eCTD Sequence Number: 0016
Letter Date: 04/24/2012
Stamp Date: 4/24/2012

CDRH Human Factors Review

Combination Product Device Information

Submission Number: NDAs 203313 and 203314
Applicant: Novo Nordisk
Drug Constituent: Insulin degludec
Device Constituent: PDS290 pen injectors

Intended treatment: Diabetes

CDRH Human Factors Involvement History

- 8-DEC-2012: CDRH HF provided a review of the Human Factors report contained in the NDA (See Appendix 1) – A General Advice letter was issued on 23-DEC-2012.
- 19-JAN-2012: CDRH HF was requested to provide a review on the Applicant's response to Human Factors request, and on a supplemental validation protocol – A General Advice letter was issued on 3-MAY-2012
- 1-MAY-2012: CDRH HF was requested to provide a review of the results of the supplemental validation protocol

Review of Human Factors Related Information

The re-validation study was conducted with 51 participants (17 adult users, 18 elderly users, and 16 child users). Novo Nordisk indicated that based on the FDA feedback received on 23 December 2011, the following use errors were identified as requiring further mitigation:

- Dose not set correctly
- Miscalculating the second dose when splitting the intended dose between two pens
- Dose button is not held down until dose counter is back to "0"
- Needle not held in skin for appropriate amount of time
- Needle stick injuries
- Remove the needle/Reuse of needle
- Not detecting a blocked needle

Novo Nordisk performed further human factors/usability evaluation that determined the following mitigations should be implemented before the UT86 handling test to address the specific use errors cited by the FDA:

- Improvements to the IFU
- Improvements to the training – ancillary instructional video available to the users

The improvements to the IFU include:

- (b) (4)
- (b) (4)
  d
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

Of the 51 participants, 36 participants received training and 16 did not receive training. Training sessions for the "trained" participant group included the following modules:

- Describing the basics of pen-injector use
- Reviewing in detail each step and warning presented in the IFU and explaining the importance of each step
- Demonstrating proper PDS290 pen-injector use
- Showing the ancillary instructional video

Hands-on practice period

- Administering a "question and answer" period and answering any participant questions
- Delivering supplemental training as needed past the pre-planned 30 minutes
- Test participants participated in training sessions during which they (1) received 15–30 minutes of one-on-one, hands-on training by a diabetes educator, and (2) watched the ancillary instructional video. A delay period between training and the actual test (2–32 hours) was also incorporated.

The study results are summarized in the following table:

		Number of:			
Use error description	Potential medical impact of the observed use errors	Participants who committed the use error	Use errors	Opportunities to commit the use error	Use error rate**
Pen is not primed before first injection (U200)	Minor transient hyperglycaemia	1 / 10* (10.0%)	1 Trained: 0 Untrained: 1	25 Trained: 14 Untrained: 11	1 / 25 (4.0%) Trained: (0%) Untrained: (9.1%)
Initially misinterpreted priming instructions	Minor transient hyperglycaemia	1 / 51 (2.0%)	1 Trained: 0 Untrained: 1	N/A	N/A
Dose not set correctly	Minor transient hyperglycaemia	1 / 51 (2.0%)	2 Trained: 0 Untrained: 2	281 Trained: 184 Untrained: 97	2 / 281 (0.7%) Trained: (0%) Untrained: (2.1%)
Misinterprets the dose delivered after detecting blocked needle	Minor transient hyperglycaemia	1 / 51 (2.0%)	1 Trained: 0 Untrained: 1	51 Trained: 35 Untrained: 16	1 / 51 (2.0%) Trained: (0%) Untrained: (0.3%)
Needle is not held in the skin at least 1 second after the scale is back to "0"	Minor transient hyperglycaemia	2 / 51 (3.9%)	2 Trained: 1 Untrained: 1	281 Trained: 184 Untrained: 97	2 / 281 (0.7%) Trained: (0.5%) Untrained: (0.5%)
Needle stick injury	Transient minor pain	1 / 51 (2.0%)	1 Trained: 1 Untrained: 0	N/A	N/A

*Per the protocol, approximately one third of the adult and elderly test participants used a pen-injector labelled as one of the three insulin types: Tresiba® 100 U/ml, Tresiba® 200 U/ml, and Ryzodeg® 100 U/ml. 10 (10) out of the 35 adult and elderly participants used a Tresiba® 200 U/ml pen-injector

The study results showed that the use error rates have been reduced. However, based on the analysis provided by Novo Nordisk on all use errors, this reviewer remains concerned with the following use errors:

- 1 participant did not set dose correctly

  This participant was an elderly, pen-experienced, and untrained participant. The participant was on basal–bolus insulin therapy with Lantus® vial and syringe as basal insulin and NovoLog® FlexPen® as bolus insulin. It should be noted that the Novolog® FlexPen® delivers 1 unit increments of insulin when dialled. When using his vial and syringe, he has to convert number of units tc the correct volume.

  He was tested with a PDS290 pen-injector for insulin degludec 200 U/ml, for which the dose is dialled in 2-unit increments. Despite the different concentrations, all the user had to do was to set PDS290 to the correct units to be deliver, which is shown on the dose counter, and the pen-injection delivers the exact amount of units indicated by the dose counter without performing any dose conversion. However, in this case, the participant dialled and administered an incorrect dose during two different tasks during normal injection and during end-of content/split dose between two pens. The medical consequence would be underdosing.

  Novo Nordisk also reported that one participant experienced close call with this step. Because this type of use error can result incorrect dosing in actual use and while Novo Nordisk has taken helpful measures to reduce the potential of use errors, they do not directly address the potential of users converting the number of units required based on the prescribed dose. The reviewer recommends that Novo Nordisk implement further mitigation via modifying the IFU to inform the users that regardless of the concentration of insulin used, the PDS290 pen-injectors are designed to deliver the specified number of insulin units as prescribed, and that the users do not need to perform any dose conversion.

- 1 participant misinterpret the dose delivered after detecting blocked needle

  This participant was an elderly, pen-experienced and untrained participant. The participant set the dose correctly (instructed dose - 36 units of 200 U/ml Tresiba®) and attempted to administer the injection. The participant removed the needle from the cushion and noticed that the dose counter showed "26", thereby providing visual feedback that the dose counter did not return to zero and that the intended dose was not delivered. The participant incorrectly concluded that he had delivered 10 units, and that he needed to deliver 26 additional units to administer the full 36 unit dose. The participant replaced the needle on the pen-injector and administered 26 units, rather than 36 units.

  Novo Nordisk also reported that two participants experienced close call with this step. Because this type of use error can result incorrect dosing in actual use and while Novo Nordisk has taken helpful measures to reduce the potential of use errors, they do not directly address the potential of users misinterpreting that some insulin has been delivered when in actuality, no insulin has been delivered. As discussed in previous review memo, this finding indicated that users were not aware of the potential for dose

counter malfunction associated with blocked needles i.e. the device dose counter may wrongly report that up to a maximum of 7 units have been delivered. This could result in clinically significant dosing errors after the user discovers that the needle on the device is blocked.

This reviewer believes that the dose counter, which serves as a visual feedback to the users, is not optimally designed as it can mislead users and cause confusion with regards to dosing after the device problem (i.e. blocked needle) is discovered. If there are no design alternatives to reduce this risk further, the reviewer recommends that Novo Nordisk implement further mitigation via modifying the IFU to inform the users that in case of a blocked needle, the dose counter will display a value that is different from the original dose that the user has set. In addition, the IFU should provide specific instructions for use to resolve a blocked needle situation.

- 2 participants did not hold the needle at the injection site for the specified time

One participant was an elderly, pen-experienced and trained participant committed one use error during her fifth task (blocked needle). The other participant was an adult, pen-naïve and untrained participant committed one use error during the first task (normal injection). The participants both set the dose correctly and administered the injection, but held the needle in the cushion for less than one second after the dose counter had returned to"0".

Novo Nordisk stated that the IFU that the needle should be held in the skin for 6 seconds, yet dose accuracy testing has demonstrated that a full dose can be delivered after 1 second after the dose counter returns to "0". As previously communicated, the reviewer is not clear about instructing patients to hold the needle for 6 seconds, and then defining that it is only a use error if the participant did not keep the needle in the skin for at least 1 second after the dose counter returns to "0." If proper injection is defined as holding the needle for 6 seconds, then the study should demonstrate that users can hold the device for 6 seconds.

Novo Nordisk also reported that one participant experienced close call with this step. Because this type of use error can result wet injection and/or incorrect dosing in actual use and while Novo Nordisk has taken helpful measures to reduce the potential of use errors, they do not directly address the potential of users pulling the needle out within the specified time.

CDRH Human Factors Review Recommendations

The reviewer recommends that Novo Nordisk address the use errors identified in the UT86 report. Please transmit the following questions to Novo Nordisk.

The UT86 report, while demonstrating that through improving IFU and training materials, the use errors can be reduced, we are concerned with the results of the study continue to show use

errors that can result in incorrect dosing that require further mitigations. We are most concerned with the following findings:

- 1 participant did not set dose correctly and committed use error

  You reported that this participant was an elderly, pen-experienced, and untrained participant. The participant was on basal–bolus insulin therapy with Lantus® vial and syringe as basal insulin and NovoLog® FlexPen® as bolus insulin. It should be noted that the Novolog® FlexPen® delivers 1 unit increments of insulin when dialled. When using his vial and syringe, he has to convert number of units to the correct volume. The test reslts reported that this participant dialled and administered an incorrect dose during two different tasks during normal injection and during end-of content/split dose between two pens. You also reported that one participant experienced close call with this step. Because this type of use error can result incorrect dosing in actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential of risk of users converting the number of units required based on the prescribed dose. We recommends that you implement further mitigation via modifying the IFU to inform the users that regardless of the concentration of insulin used, the PDS290 pen-injectors are designed to deliver the specified number of insulin units as prescribed, and that the users do not need to perform any dose conversion.

- 1 participant misinterpret the dose delivered after detecting blocked needle

  You reported that this participant was an elderly, pen-experienced and untrained participant. The participant set the dose correctly (instructed dose - 36 units of 200 U/ml Tresiba®) and attempted to administer the injection. However, due the block needle scenario, the participant incorrectly concluded that he had delivered 10 units, and that he needed to deliver 26 additional units to administer the full 36 unit dose. The participant replaced the needle on the pen-injector and administered 26 units, rather than 36 units. Because this type of use error can result incorrect dosing in actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential of risk of users misinterpreting that some insulin has been delivered when in actuality, no insulin has been delivered in situation where the needle is blocked. You also reported that tww participants experienced close call with this step. As previously communicated in our General Advice letter dated May 3, 2012, this finding indicated that user might not be aware of the potential for dose counter malfunction associated with blocked needles i.e. the device dose counter may wrongly report that up to a maximum of 7 units have been delivered. This could result in clinically significant dosing errors after the user discovers that the needle on the device is blocked. We conclude that the dose counter, which serves as a visual feedback to the users, is not optimally designed as it can mislead users and cause confusion with regards to dosing after the device problem (i.e. blocked needle) is discovered. If there are no design alternatives to reduce this risk further, we recommend that you implement further mitigation via modifying the IFU to inform the users that in case of a blocked needle, the dose counter will display a value that is different from the original dose that the user has set. In addition, the IFU should provide specific instructions for use to resolve a blocked needle situation.

- 2 participants did not hold the needle at the injection site for the specified time

You reported that one participant was an elderly, pen-experienced and trained participant committed one use error during her fifth task (blocked needle). The other participant was an adult, pen-naïve and untrained participant committed one use error during the first task (normal injection). The participants both set the dose correctly and administered the injection, but held the needle in the cushion for less than one second after the dose counter had returned to"0". You also reported that one participant experienced close call with this step. As previously communicated in our General Advice letter dated May 3, 2012, we are concerned that you instruct patients to hold the needle for 6 seconds. However, in the study, you defined that it is only a use error if the participant did not keep the needle in the skin for at least 1 second after the dose counter returns to "0." If proper injection is defined as holding the needle for 6 seconds, then the study should demonstrate that users can hold the device for 6 seconds.

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/s/

RACHEL E HARTFORD
06/21/2012
On behalf of
QuynhNhu Nguyen
Biomedical Engineer/Human Factors Reviewer CDRH/ODE/DAGID

06/14/12

Memo

Date: March 14, 2012

Revised April 5, April 25, May 25, May 30,2012, June 13, 2012

From: Fred Mills, Staff Scientist, DTP

To: Daniela Verthelyi, Chief, Laboratory of Immunology, DTP, OBP

FDA designation: NDA 203314, original NDA submission

Sponsor: Novo Nordisk

Product: insulin degludec (IDeg, generic name insulin 454), for treatment of diabetes

Subject of Review: RadioImmunoAssay (RIA) for detection of anti-insulin 454 antibodies

Table of Contents

Comments to the File:

The sponsor provided the validation for a screening and confirmatory assays. There is no neutralizing assay report, but this may be acceptable since there is no precedent for neutralizing antibodies to insulin. The screening is a radio immunoanalysis (RIA) and the confirmatory assay is a subtraction RIA (cold competition). The control antibody specific for IDeg is low affinity creating some uncertainty as to the quality of the assay. In addition, the assay seems to be sensitive to concentrations of insulin (both IDeg and endogenous insulin) therefore the sensitivity of the assay is uncertain. The sponsor has provided patient antibody data obtained after at least a 7 day washout period, so on board IDeg interference is unlikely. However, the effect of endogenous insulin has not been addressed.Therefore, even though the clinical data they have provided suggests that there was no change in the level of IDeg (Insulin 454) specific antibodies or cross-reacting antibodies from baseline to the end of the trial, these results are questionable until they can demonstrate appropriate sensitivity in the presence of endogenous insulin In the target population.

Comments to the Sponsor:

The Agency has three major comments, regarding your assays for anti-insulin 454, anti-insulin aspart, and anti-insulin antibodies:

1. The Agency is concerned about the effects endogenous insulin may have on the sensitivity of your antibody assay due to the following considerations:

Interference from insulin 454 is unlikely to have had an effect on the antibody results reported in your submission, because you reported data at 26 and 52 weeks that included at least a 7 day washout, and your PK/PD studies have shown a mean half-life of 19 hours. However, subjects with type 2 diabetes who will be receiving this product are expected to have high endogenous insulin levels. Although insulin levels will vary considerably from subject to subject depending on insulin resistance and glycemic control, most type 2 diabetes patients are expected to have endogenous fasting insulin levels at or above the normal range (145 pmol/L) and fed levels ~ 3 times this concentration. In addition, some patients with extreme insulin resistance could have much higher levels. Thus endogenous insulin levels may be high enough to interfere with your assay. For these reasons, unless you can demonstrate sufficient sensitivity in the presence of expected insulin levels, you may need to modify the current assay or develop an alternative assay format that minimizes interference from endogenous insulin. The cutpoint for the assay needs to be determined using sera of treatment-naive patients.

As a related comment, the FDA notes that you have tested the effects of 200, 2000, and 20,000 pM insulin 454, with no intermediate steps- testing for interference at intermediate concentrations between 200 and 2000 pM may reveal that your assay is tolerant of product concentrations higher than 200 pM, and thus could possibly be used

with a reduced washout period

2. In summarizing your antibody testing, you state that there was no change in the level of IDeg (Insulin 454) specific antibodies or cross-reacting antibodies from baseline to the end of the trial. You also state that for all subjects, the change from baseline in antibodies to your product as well as those cross-reacting with human insulin were low and similar in data from 7 trials with IDeg. However, unless you can demonstrate appropriate sensitivity in the presence of endogenous insulin, it is difficult to evaluate the significance of the immunogenicity data you have submitted. Therefore, once you have optimized your assay and confirmed the cutpoint in treatment-naïve patients you may need to re-analyze patient sera and submit these data to the FDA for evaluation.

3. You state that the differences in sensitivity observed using the control antibodies are due to low affinity of your antibody specific for IDeg. Without a high affinity control antibody that will enable appropriate validation of the anti-IDeg antibody assay it is difficult to have confidence as to what the true sensitivity of the anti-Deg assay is and what the levels of anti-IDeg antibody are. Therefore, please develop a suitable control and provide assay validation demonstrating an appropriate level of sensitivity.

In addition, please address the following issues:

a. Report nn960358 on the crossreactivity of antibodies to IDEG to the human insulin, insulin X14, and insulin NN304 antibody assays describes the effects of -20 ^{0}C storage and freeze-thaw cycles on antibody controls. Please provide data from stability and freeze-thaw studies for control antibody solutions specific for the insulin 454 antibody assay.

b. While it may be true that inter assay variation is low and well within the 15% acceptance limits, a more general consideration is the need for system suitability specifications to ensure reproducibility between assay runs. Therefore please implement system suitability controls with appropriate specifications for this assay. The low positive quality control for this purpose should have a concentration that is close to the limit of detection for the assay to ensure that the assay has a reproducible sensitivity. Your low positive quality control should be designed to produce a signal above the cut point (positive) 99% of the time (failing in $\leq$ 1% of the time). A high positive quality control will ensure that the range of the assay remains consistent and should be used at a concentration that falls within the linear range of the dose-response curve.

c. Validation of your antibody assays indicates that there is no effect of lysed red blood cells at the dilutions studied, which are $\geq$ 1/200. Please clarify how you will treat samples that are contaminated with larger amounts of RBCs.

d. Regarding other potential matrix effects, in your previous validation of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997), you also investigated the effects of bilirubin, lipid, Human

Serum Albumin (HSA), and pH. Bilirubin had no effect in the range studied, but lipid, HSA, and pH change significantly altered the signal for one or more of the antibodies. Please provide data that assesses the effects of these factors on your anti-insulin 454 antibody assay.

Executive Summary

Product description

NDA 203314 is for Novo Nordisk's insulin degludec (IDeg, generic name insulin 454) which is an ultra-long acting insulin for once-daily subcutaneous administration in patients with diabetes. IDeg is a modified insulin, or insulin analogue, in which the threonine at position B30 of human insulin has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid (palmitic acid) via a glutamic acid spacer. This structure allows IDeg to form soluble, stable multi-hexamers, resulting in accumulation in the subcutaneous tissue after injection. A gradual dissociation of IDeg monomers from the multi-hexamers provides a slow and continuous delivery of IDeg from the s.c. injection site into the circulation, leading to long pharmacokinetic and pharmacodynamic profiles. In addition, binding of the palmitic acid (b) (4) of IDeg to albumin contributes to extending the half life. IDeg monomers bind to and activate insulin receptors triggering glucose uptake.

For reference, the following tabulation of other insulin analogues may also be helpful

Insulin aspart (X14): substitution of the B28 threonine with aspartic acid, *fast acting*

NN304 insulin (insulin detemir): similar to insulin 454, but with myristic acid conjugated at lysine B29, instead of pamitic acid. *Long acting via fatty acid binding to albumin*

Insulin glargine : glycine substituted for asparagine at position A21, two arginines added C terminal of B chain, *long acting due to aggregate formation*

Clinical trials

This NDA contains data from 7 clincial trials, including one Phase 3 trial (Trial NN9068-3632) that was completed January 31, 2011. This study was a single-center, single-dose, randomized, double-blind, double-dummy, four-period crossover trial in healthy male subjects to investigate the safety and tolerability of IDegLira compared to simultaneous, separate dose administration of liraglutide *(long-acting glucagon-like peptide-1 analog)* and IDeg, as well as single dose administration of liraglutide and single dose administration of IDeg on separate occasions. In total, 46 subjects were screened for this trial and as planned, 24 subjects were randomized and included in both the safety analysis set and the full analysis set. All 24 subjects completed the trial.

Interference from insulin 454 is unlikely to have had an effect on the antibody results reported in your submission, because you reported data at 26 and 52 weeks that included at least a 7 day washout, and your PK/PD studies have shown a mean half-life of 19 hours.

No samples were positive for liraglutide antibodies. The sponsor states that there was no

change in the level of IDeg specific antibodies or cross-reacting antibodies from baseline to the end of the trial. For all subjects, the change from baseline in antibodies cross-reacting with human insulin was low and similar in data from 7 trials with IDeg (Figure 3–1). Also, the change from baseline in specific insulin analogue antibodies was low and similar in all 7 trials with IDeg.

Reviewer comments
Data for cross-reacting antibodies to insulin and insulin analogues other than IDeg/ insulin 454 have been obtained using antibody assays that have appropriate sensitivity (≤ 500 ng/ ml antibody, as per FDA draft guidance, 2009), and are therefore interpretable. This is reassuring since (1) for human insulin, antibodies cross-reacting with the endogenous insulin of patients could pose serious safety concerns. (2) antibodies cross-reacting with insulin analogues would have the potential to render patients resistant to standard of care treatments.

However, validation of the antibody assay for the IDeg/ insulin 454 product itself (discussed more fully below) gave a sensitivity in the range of 1800 ng/ml. The sponsor states this result is due to the low affinity of the control anti-IDeg antibody (a monoclonal) used to validate the assay. However, without a high affinity control antibody that will enable appropriate validation of the anti-IDeg antibody assay, it is difficult to have confidence as to what the true levels of anti-IDeg antibody are. Therefore, the sponsor should develop a high affinity control and provide assay validation demonstrating an appropriate level of sensitivity.
Further, high degree of on-board drug interference was noted suggesting that the assay may be less sensitive than stated. the cutpoint has not been validated in the patient population and therefore it is unclear that the sensitivity of the assay is as claimed.

Assay validation
Assay description
The sponsor's antibody assay is a RadioImmunoPrecipitation (RIA). This method has previously been validated for determination of antibodies to human insulin, and insulin analogues insulin aspart (insulin X14), NN304 and NN344. Briefly, the assay is a subtraction radioimmunoassay. The samples were incubated with ^{125}I labeled tracer ± excess insulin/insulin analogue. After incubation overnight the immunoglobulin was precipitated together with any antigen that may have bound. The precipitate was counted in a gamma counter and the amount of radioactivity was expressed in percent of the total amount of added radioactivity (%B *(bound)* /T*(total)*).

Reagents and stability

As described in previous studies in report nn960358 for the human insulin, insulin X14, and insulin NN304 antibody assays, the effects of -20 ^{0}C storage and five freeze-thaw cycles were assessed .
Reviewer comment
Similar stability and freeze-thaw studies should be performed for the reagents specific for the insulin 454 antibody assay

Assay sensitivity.
Assay sensitivity was determined as the concentration of antibody that produced a %B/T equal to the upper 95 % limit of 150 normal serum samples.

Sensitivities were:
1800 ng/ ml for insulin 454
(similar low sensitivity was observed in a subsequent validation of method transfer)
35 ng/ml for insulin aspart
20 ng/ml for cross-reacting insulin antibodies

Reviewer comments
The sponsor notes the poor assay sensitivity for insulin 454 (1800 ng/ ml), stating that this is probably due to the low affinity of the insulin 454 specific monoclonal antibody. This level of sensitivity is over three times higher than the current recommendation (FDA 2009 draft guidance), making the assay of little or no utility for detecting anti-insulin 454 antibodies. However, the assay is of utility in detecting antibodies for insulin aspart (35 ng/ml) and insulin activities (20 ng/ ml). It is particularly important to have appropriate detection of anti-insulin antibodies, since antibodies raised to a patient's endogenous insulin (if neutralizing) could have serious safety effects.

Range of signals in normal sera
150 plasma samples from healthy donors were analyzed. The 95 % percentiles were calculated for insulin aspart insulin 454 specific (F-E, F'-E) and cross-reacting antibodies (A-C or D-F). The 95% percentile values are shown in Table 8

Table 8 95 % upper limit (%B/T)

Antibody	95 % percentile %B/T
Insulin aspart specific Ab (C-B)	4.4
Insulin 454 specific Ab (F'-E)	0.6
Cross-reacting Ab (A-C)	0.8
Insulin 454 specific Ab (F-E)	0.6
Cross-reacting Ab (D-F)	0.5

Reviewer comment
The background for anti-product signal (Insulin 454 ab) appears to be quite low. However, any signal above this background will be difficult to interpret because, as discussed in the section on assay sensitivity, the low affinity of the anti-insulin 454 control antibody makes the anti-insulin 454 assay appear to be very insensitive.

Drift during assay runs
Drifting was determined by analyzing the control samples 6 times in duplicate in the beginning and in the end of the assay. No significant difference between control samples analyzed in the beginning and in the end of the assay was seen for insulin 454 specific

antibodies nor for cross reacting antibodies. There was a modest difference between results insulin aspart specific antibodies analyzed first and last in the assay, although this the sponsor did not consider this important for their analysis.

Reviewer comment
I agree with the sponsor that the insulin aspart measurements that were taken first and those that were taken last are similar, since the mean of the first series is 41.7, with a standard deviation of 1.8, while the mean of the last series is 40 with a standard deviation of 0.98. Therefore, there is a substantial overlap in these distributions, and a t test says there is p=0.016 that their means are the same, which is still above the p=0.01 level of statistical significant.

Repeatability and Intermediate variation
Repeatability and intermediate variation were investigated by analyzing in two double determinations in eight independent assays four control antibody samples designed to yield levels of insulin aspart antibodies, insulin X-14 antibodies, and cross reactive (anti-insulin) antibodies. Both the repeatability and the intermediary variation were below 10 % , which is within the acceptance limits of %CVs below 15%. The sponsor takes this to mean that antibody samples taken at various time points from the same patient do not need to be analyzed in same assay set-up.

Reviewer comments
While it may be true that inter assay variation is low and well within the 15% acceptance limits, a more general consideration is the need for system suitability specifications to ensure reproducibility between assay runs. These should be provided by the sponsor

Determination of Cut Point
Reviewer comment
Determination of a sensitivity as the concentration of antibody that produces a %B/T equal to the upper 95% limit of 150 normal serum samples is conceptually similar to setting a cutpoint equal to a 5% false positive rate for normal serum samples, as per Mire-Sluis 2004;i.e. the sponsor is classifying samples as positive that have signals equivalent to the upper 5% of normal serum samples.
Therefore the sponsor has in effect set an appropriate cutpoint for the anti-human insulin an anti-insulin aspart assays.
Sensitivity as the equivalent of cutpoint for the anti insulin 454 assay may also be acceptable, but only if appropriate sensitivity can be demonstrated.

Drug Tolerance
The interference from insulin aspart and insulin 454 in the antibody analysis was first investigated by addition of insulin aspart and insulin 454 to the four control antibody samples The control samples were divided in two and either insulin aspart or insulin 454 was added to the following final concentrations during incubation with tracer: 0, 50, 150, 450, 1350, 4050, 12150, 36450, 109350, 328050 pM. Each sample was analyzed in duplicate. Recovery of $\geq$ 80% of the no added drug signal was taking as indicating no interference.

Taking the polyclonal Guinea Pig anti-insulin antibody as a surrogate for patient antibodies, with no competitor, there was a detectable signal above background at 0.140 µg/ ml= 140 ng/ ml, well within the FDA-recommended sensitivity of 500 ng/ ml. However, at the lowest competitor insulin 454 concentration of 200 pM, signal is lost 0.41 mg/ ml= 410 ng/ ml, with a faint signal retained at 1.2 mg/ml =1200 ng/ ml. The sponsor concluded that 200 pM insulin 454 is the highest allowable on-board product concentration. Dilution of samples did not improve the drug tolerance of the assay

The signal for monoclonal anti-Insulin 454 antibody was only weakly competed by Insulin 454, consistent with the sponsor's statement that this is a low affinity antibody.

Reviewer comments
There is concern regarding the potential for interference from both on-board insulin 454 product, as well as endogenous insulin. Following discussion with Dr. Vetheyli, I requested input from both the Pharm/Tox reviewer for this NDA (Dr. Manoj Khurana) and the Clinical Reviewer (Dr. Jean-Marc Guettier). Dr Khurana stated that from a pK study, serum concentrations can range from 45 to 2100 pmole/ l over a sampling duration of 120 hours, and in a steady state study on Type 1 diabetics, a mean Cmax of 9731 pmol/L was achieved. Furthermore, Dr. Guettier noted that most Type 2 diabetics are expected to have fasting levels of endogenous insulin at or above normal (145 pmol/ L) with fed levels increasing about 3 fold. Some patients with insulin resistance can have much higher levels.

A priori, it is reasonable to expect serum insulin 454 product concentrations significantly above the 200 pM threshold that the sponsor has determined for on-board product interference. In actual fact on board product is unlikely to have affected these data, since the sponsor only reported antibody data taken after at least a 7 day washout,and mean insulin 454 half-life was found to be 19 hours, However, a further complication in interpreting the patient antibody stems from the fact that patients can have substantial endogenous insulin levels, which may also interfere with the assay.

I also note that the sponsor only tested the effect of 200, 2000, and 20,000 pM insulin 454, and the sponsor should explore intermediate steps between 200 and 2000 pM, since it is possible that there may be a value for adequate drug tolerance above 200 pM that would allow the sponsor to reliably detect patient antibodies in many cases.

Matrix effects
The effect of hemolysis on the antibody measurement was investigated by measuring control samples with or without addition of erythrocytes. This study was performed because in a previous validation study of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997) increases in the range 5.5%-7% were seen upon addition of dilute lysed RBCs.
Reviewer comments
There appeared to be no effect of lysed RBS at the dilutions studied, which are ≥ 1/200 (20 µl of packed erythrocytes in 380 µl control samples, followed by at least a 1/10 dilution). There should be a specification to avoid contaminating patient serum samples

with larger amounts of RBCs.

Furthermore, in the previous validation study of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997), the sponsor also investigated the effects of bilirubin, lipid, Human Serum Albumin (HSA), and pH. Bilirubin had no effect in the rage studied, but lipid, HSA, and pH change all had significant effects for one or more of the antibodies.

Reviewer comment
Given the effects observed on the readings for insulin or other insulin analogue antibodies, the sponsor should assess the effects of lipid, HSA, and pH on the assay for anti-insulin 454 antibodies.

Extended Discussion of NDA 203314 Immunogenicity, including tables and figures

Product Background

Insulin degludec (IDeg, generic name insulin 454) is an ultra-long acting basal insulin for once-daily (OD) subcutaneous (s.c.) administration in patients with diabetes mellitus. IDeg is modified such that the amino acid (b) (4) threonine in position B30 of human insulin has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid (palmitic acid) via a glutamic acid spacer. This structure allows IDeg to form soluble and stable multi-hexamers, resulting in a depot in the subcutaneous tissue after injection. The gradual separation of IDeg monomers from the multi-hexamers results in a slow and continuous delivery of IDeg from the s.c. injection site into the circulation, leading to the observed ultra-long pharmacokinetic and pharmacodynamic profiles. Furthermore, binding of the fatty acid moiety of IDeg to albumin contributes to some extent to the protraction mechanism. At the target tissues, IDeg monomers bind to and activate insulin receptors triggering the same cellular effects as human insulin such as promoting glucose uptake.

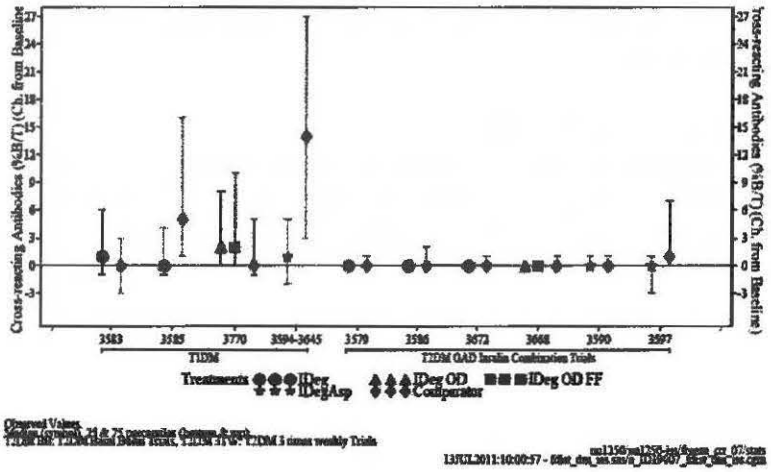
Summary of Immunogenicity Results

In the IDegLira clinical development program, one clinical pharmacology trial (Trial NN9068- 3632) was completed as of 31 January 2011. In addition, one phase 3 trial was ongoing as of 31 January 2011. Trial NN9068-3632 was a single-centre, single-dose, randomized, double-blind, double-dummy, four-period crossover trial in healthy male subjects to investigate the safety and tolerability of IDegLira compared to simultaneous, separate dose administration of liraglutide *(long-acting glucagon-like peptide-1 analog)* and IDeg, as well as single dose administration of liraglutide and single dose administration of IDeg on separate occasions. In total, 46 subjects were screened for this trial and as planned, 24 subjects were randomized and included in both the safety analysis set and the full analysis set. All 24 subjects completed the trial.

No samples were positive for liraglutide antibodies. There was no change in the level of IDeg specific antibodies or cross-reacting antibodies from baseline to the end of the trial For all subjects, the change from baseline in antibodies cross-reacting with human insulin was low and similar in all 7 trials with IDeg (Figure 3–1). As was the change from baseline in specific insulin analogue antibodies was low and similar in all 7 trials with IDeg

Comparison across Trials
Cross-reacting Antibodies
For all subjects, the mean change from baseline to follow-up visit in antibodies cross-reacting with human insulin was low in both the IDeg and the comparator group, and there was no difference between the treatment groups. The mean value of antibodies cross-reacting with human insulin at baseline and at the end of the trial (after 27 or 53 weeks of treatment) was similar in the IDeg and the comparator group. The majority of

subjects in both treatment groups had no or little change in antibodies cross-reacting with human insulin.

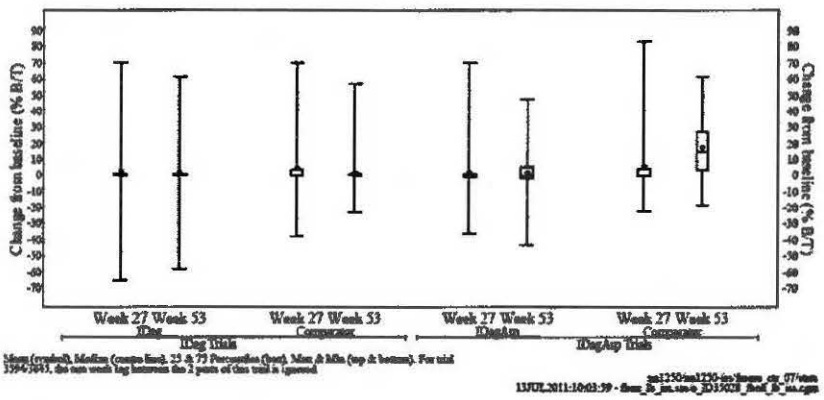


Cross-reference: Appendix 1.20, Figure 3

Figure 3–1 Cross Reacting Antibodies at Week 27/53 – Change from Baseline – All Therapeutic Confirmatory Trials – All Subjects – IDeg and IDegAsp vs. Comparator – Distribution by Trial – Safety Analysis Set

Cross-reacting Antibodies

For all subjects, the mean change from baseline to follow-up visit in antibodies cross-reacting with human insulin was low in both the IDeg and the comparator group, and there was no difference between the treatment groups (Figure 3–2). The mean value of antibodies cross-reacting with human insulin at baseline and at the end of the trial (after 27 or 53 weeks of treatment) was similar in the IDeg and the comparator group The majority of subjects in both treatment groups had no or little change in antibodies cross-reacting with human insulin



Cross-reference: Appendix 1.20, Figure 6

Figure 3–2 Cross-reacting Antibodies – Change from Baseline – All Therapeutic Confirmatory Trials – All Subjects – IDeg and IDegAsp vs. Comparator – Safety Analysis Set

Specific Insulin Analogue Antibodies
For all subjects, the mean values of specific insulin analogue antibodies showed no or very little change after 27 and 53 weeks of treatment with no difference between the IDeg and the comparator group (The majority of subjects in the IDeg group had no or little change in specific IDeg antibodies

Adverse Events and Increase in Antibodies
For all subjects, 220 (5%) subjects in the IDeg group and 145 (6%) subjects in the comparator group had an increase of 10% B/T (absolute value) or more in antibodies cross-reacting with human insulin or an increase in specific insulin analogue antibodies of 5% B/T or more

RIA Assay Validation

Overview of Method

The aim of this study was to validate a method for determination of antibodies against insulin 454 (insulin Degludec) in human serum. The method has previously been validated for determination of antibodies to human insulin, insulin aspart (insulin X14), NN304 and NN344. Briefly, the assay is a subtraction radioimmunoassay. The samples were incubated with ^{125}I labeled tracer ± excess insulin/insulin analogue. After incubation overnight the immunoglobulin was precipitated together with any antigen that may have bound. The precipitate was counted in a gamma counter and the amount of radioactivity was expressed in percent of the total amount of added radioactivity (%B *(bound)* /T*(total)*).

The complete assay setup was as follows:

Series	Assay mixture	Result represent the sum of
A	Sample + Buffer + X-14 tracer	Background, X-14 specific and cross reacting antibodies
B	Sample + Cold X-14 + X-14 tracer	Background
C	Sample + Cold 0454 + X-14 tracer	Background, X-14 specific antibodies
D	Sample + Buffer + 0454 tracer	Background, 0454 specific and cross reacting antibodies
E	Sample + Cold 0454 + 0454 tracer	Background
F	Sample + Cold insulin + 0454 tracer	Background, 0454 specific antibodies
F'	Sample + Cold X-14 + 0454 tracer	Background, 0454 specific antibodies

For each sample the following was calculated:
The amount of specific X-14 antibodies = C-B
The amount of specific 0454 antibodies = F-E, (F'-E)
The amount of cross- reacting antibodies = D-F, (D-F') (or A-C)
In practice only the necessary series will be included. This means that in clinical trials series A will often be deleted and only series F or F' will be included.

Important reagents

insulin analogue tracers

^{125}I-(Tyr A14) - X14 Batch: 57B and 63B
^{125}I- NN454 Batch: 11A, 14A, 18B and 20B

Control antibodies

The assay sensitivity was measured by dilution of the following antibodies:

polyclonal guinea pig anti-insulin antibody

3.1.2.3 Polyclonal antibodies for determination of cross-reacting antibodies

ID	Polyclonal anti-insulin
Host	Guinea pig
Antigen	Bovine and porcine insulin
Source	Novo Nordisk A/S
Lot/Batch No.	01D19E2512-1
Physical Form	Solution (PBS + 0.05% Sodium acid)
Content	7.15 mg/mL
Expiry Date	Apr-2011
Storage Conditions	5°C

monoclonal insulin 454 specific antibody

3.1.2.2 Monoclonal antibodies specific for insulin 454

ID	NN454-1 F46
Source	Novo Nordisk A/S
Lot/Batch No.	04K17J3127-4
Physical Form	Solution
Concentration	1.16 mg/mL
Expiry Date	Oct-2014
Storage Conditions	5°C

monoclonal anti-insulin aspart (insulin X14) antibody

3.1.2.1 Monoclonal antibodies specific for insulin aspart

ID	X14-6 F34
Source	Novo Nordisk A/S
Lot/Batch No.	8J13H1842-1
Physical Form	Solution
Concentration	0.26 mg/mL
Expiry Date	Oct-2008
Storage Conditions	5°C

Antibody Solutions

C2: X14-6 F34 (batch 8J13H1842-1) diluted 1:371 ~ 0.56 µg/ml
C3: GPα Insulin (batch Mix 1) diluted 1:1200 ~ 6.8 µg/ml
C8: NN454-1 F46 (batch 04K17J3127-4) diluted 1:20 ~ 58 µg/ml
C9: GPα Insulin (batch 01D19E2512-1) diluted 1:500 ~ 14.3 µg/ml

Reviewer comments

The sponsor has previously assessed stability of the reagents for measuring anti-insulin and anti-insulin aspart antibodies. Similar stability evaluation of reagents specific for the anti-insulin 454 antibody determination should be performed (^{125}I- NN454, cold NN454 solution, and anti-insulin 454)

Assay sensitivity.

The assay sensitivity was measured by dilution of the three control antibodies:
polyclonal guinea pig anti-insulin antibody
monoclonal insulin 454 specific antibody
monoclonal anti-insulin aspart antibody

Assay sensitivity was determined as the concentration of antibody that produced a %B/T equal to the upper 95 % limit of 150 normal serum samples.

Sensitivities were:
1800 ng/ ml for insulin 454
(similar low sensitivity was observed in a subsequent validation of method transfer from Novo Nordisk to (b) (4) report nn208156)
35 ng/ml for insulin aspart
20 ng/ml for cross-reacting insulin antibodies

Reviewer comments
The sponsor notes the poor assay sensitivity for insulin 454 (1800 ng/ ml), stating that this is probably due to the low affinity of the insulin 454 specific monoclonal antibody. This level of sensitivity is over three times higher than the current recommendation (FDA 2009 draft guidance), making the assay of little or no utility for detecting anti-insulin 454 antibodies. However, the assay is of utility in detecting antibodies for insulin aspart (35 ng/ml) and insulin activities (20 ng/ ml). It is particularly important to have appropriate detection of anti-insulin antibodies, since antibodies raised to a patient's endogenous insulin (if neutralizing) could have serious safety effects.

Range of signals in normal sera
150 plasma samples from healthy donors were analyzed. The 95 % percentiles were calculated for insulin aspart (X-14) specific (C-B), insulin 454 specific (F-E, F'-E) and cross-reacting antibodies (A-C or D-F). The 95% percentile values are shown in Table 8

Table 8 95 % upper limit (%B/T)

Antibody	95 % percentile %B/T
Insulin aspart specific Ab (C-B)	4.4
Insulin 454 specific Ab (F'-E)	0.6
Cross-reacting Ab (A-C)	0.8
Insulin 454 specific Ab (F-E)	0.6
Cross-reacting Ab (D-F)	0.5

Reviewer comment
The background for anti-product signal (Insulin 454 ab) appears to be quite low. However, any signal above this background will be difficult to interpret because, as discussed in the section on assay sensitivity, the low affinity of the anti-insulin 454 control antibody makes the anti-insulin 454 assay appear to be very insensitive.

Drift during assay runs

Drifting was determined by analyzing the control samples 6 times in duplicate in the beginning and in the end of the assay. The values obtained in the beginning and in the end of the assay were compared by a paired t-test using excel. The values are shown in Table 3. No significant difference between control samples analyzed in the beginning and in the end of the assay was seen for insulin 454 specific antibodies (C8) nor for cross reacting antibodies (C3). Some difference between insulin aspart specific antibodies (C2) analyzed first and last in the assay was, however, seen. The mean difference between C2 analyzed first and last in the assay was below 2 %B/T which is less than 5 % of mean %B/T of C2. The sponsor did not consider this difference to be important.

Table 3 Drifting
(Set-up ID: 25, 26 and 31-Jan-2006/BSka)

C2 % B/T Series C-B		C8 % B/T Series F-E		C3 % B/T Series A-C		C3 % B/T Series D-F	
first	last	first	last	first	last	first	last
43.1	40.2	31.6	31.7	19.7	18.6	7.4	7.7
40.7	39.2	29.5	31.6	20.1	18.8	8.3	7.9
41.3	41.0	30.8	32.4	19.3	19.6	8.0	8.0
38.8	38.4	32.4	31.9	19.2	19.8	7.8	8.1
43.0	40.6	32.1	32.8	19.6	20.0	7.6	6.1
43.3	40.4	30.8	33.8	19.1	19.3	7.8	7.6

Reviewer comment

I agree with the sponsor that the C2 measurements that were taken first and those that were taken last are similar, since the mean of C2 first series is 41.7, with a standard deviation of 1.8, while the mean of C2 last series is 40 with a standard deviation of 0.98. Therefore, there is a substantial overlap in these distributions, and a t test says there is p=0.016 that their means are the same, which is still above the p=0.01 level of statistical significant.

Repeatability and intermediate variation

The repeatability and intermediate variation was investigated by analyzing the four control antibody samples (C2, C3, C8 and C9) in two double determinations in eight independent assays. Repeatability and intermediary variation was calculated for insulin X-14 (insulin aspart) specific antibodies (C-B)(Control 2), insulin 454 specific antibodies (F-E) (Control 8) and cross-reacting antibodies (A-C or D-F) (Control 3 and 9). Since outliers were detected in assay set-up 1 it was decided to leave out assay 1 from the calculation of the variation. The results are shown in Table 1 and Table 2:

Table 1 Repeatability

Insulin Aspart antibodies C2 (C-B)			Cross-reacting antibodies C3 and C9 (A-C)			Cross-reacting antibodies C3 and C9 (D-F)			Insulin 454 specific antibodies C8 (F-E)		
Mean % B/T		%CV	Mean %B/T		%CV	Mean %B/T		%CV	Mean %B/T		%CV
C2	42.1	4.2	C3	19.3	2.8	C3	7.6	3.6	C8	32.6	6.4
-		-	C9	88.2	2.5	C9	84.3	1.2			

Table 2 Intermediary variation

Insulin Aspart antibodies C2 (C-B)			Cross-reacting antibodies C3 and C9 (A-C)			Cross-reacting antibodies C3 and C9 (D-F)			Insulin 454 specific antibodies C8 (F-E)		
Mean % B/T		%CV	Mean %B/T		%CV	Mean %B/T		%CV	Mean %B/T		%CV
C2	42.1	9.0	C3	19.3	5.3	C3	7.6	6.2	C8	32.6	6.4
-		-	C9	88.2	4.2	C9	84.3	3.4	-		-

Both the repeatability and the intermediary variation were below 10 % , which is within the acceptance limits of %CVs below 15%. The sponsor takes this to mean that antibody samples taken at various time points from the same patient do not need to be analyzed in same assay set-up.

Reviewer comments
While it may be true that inter assay variation is low and well within the 15% acceptance limits, a more general consideration is the need for specifications for system suitability to ensure reproducibility between assay runs. These should be provided by the sponsor.

Determination of Cut Point
Reviewer comment
Determination of a sensitivity as the concentration of antibody that produces a %B/T equal to the upper 95% limit of 150 normal serum samples is conceptually similar to setting a cutpoint equal to a 5% false positive rate for normal serum samples, as per Mire-Sluis 2004;i.e. the sponsor is classifying samples as positive that have signals equivalent to the upper 5% of normal serum samples.
Therefore the sponsor has in effect set an appropriate cutpoint for the anti-human insulin an anti-insulin aspart assays. The cutpoint for the anti insulin 454 assay may also be adequate if appropriate sensitivity can be demonstrated.

Drug Tolerance
The interference from insulin aspart and insulin 454 in the antibody analysis was first investigated by addition of insulin aspart and insulin 454 to the four control antibody samples
The control samples were divided in two and either insulin aspart or insulin 454 was added to the following final concentrations during incubation with tracer: 0, 50, 150, 450, 1350, 4050, 12150, 36450, 109350, 328050 pM. Each sample was analyzed in duplicate.

C3 *(Guinea Pig α Insulin ~ 6.8 µg/ml)* and C9 *(GPα Insulin ~ 14.3 µg/ml)* were measured using both insulin aspart and insulin 454 as tracers, whereas C2*(X14-6 F34)* was only measured using insulin aspart as tracer and C8 (NN454-1) only with insulin 454 as tracer. An overview of the results can be seen below in Table 4 and Table 5. Recovery of ≥ 80% of the no added drug signal was taking as indicating no interference.

Table 4 Interference from insulin aspart

Insulin aspart pM	C2 (560 ng/ml X14-6 F34) Insulin aspart specific antibodies %B/T	C3 (6.8 µg/ml guinea pig anti-insulin total IgG) Crossreacting antibodies %B/T	C9 (14.3 µg/ml guinea pig anti-insulin total IgG) Crossreacting antibodies %B/T
0	47.1	18.0	89.3
50	47.8	16.3	88.6
150	46.6	11.9	85.1
450	44.9	8.5	76.3
1350	34.3	4.3	27.3
4050	22.5	2.5	11.0
12150	9.7	0.6	5.3
36450	3.9	0.2	2.4
109350	1.1	-0.1	1.1
328050	0.1	-0.2	0.2
80% =	37.7	14.4	71.4

Bold = no interference

Table 5 Interference from insulin 454

Insulin 454 pM	C8 (58 µg/ml NN454-1 F46) Insulin 454 specific antibodies %B/T	C3 (6.8 µg/ml guinea pig anti-insulin total IgG) Crossreacting antibodies %B/T	C9 (14.3 µg/ml guinea pig anti-insulin total IgG Crossreacting antibodies %B/T
0	31.0	7.4	79.1
50	30.4	6.4	80.9
150	30.6	5.4	75.4
450	30.9	3.4	55.1
1350	30.3	2.2	16.3
4050	30.6	0.9	7.5
12150	30.0	0.2	3.7
36450	28.7	0.0	1.3
109350	23.9	-0.1	0.9
328050	12.7	-0.2	0.6
80% =	24.8	5.92	63.28

Bold = no interference

Reviewer comment

In Table 5, the C8 signal for monoclonal anti-Insulin 454 antibody is only weakly competed by Insulin 454, consistent with the sponsor's statement that this is a low affinity antibody.

In an attempt to enhance the drug tolerance of the assay to insulin 454, the sponsor performed experiments with several sample dilutions:

Table 6 Interference from insulin 454 and effect of sample dilution
Normal range for cross-reacting antibodies (insulin 454/human insulin) = 0.5%B/T. Numbers in italics are below normal range.

Concentration of insulin 454	Target purified GP anti-insulin ng/ml	Cross-reacting antibodies in %B/T		
		Undiluted	Diluted 1:5	Diluted 1:10
20.000 pM	100	1.5	1.6	1.4
	33	0.5	0.6	0.5
	11	*0.2*	*0.2*	*0.2*
	3.7	*0.3*	*0.1*	*0.0*
	1.2	*0.0*	*0.1*	*0.0*
	0.41	*0.0*	*0.0*	*0.1*
	0.14	*0.0*	*-0.1*	*0.2*
2000 pM	100	9.6	8.6	8.1
	33	3.4	3.2	2.9
	11	1.2	1.2	1.1
	3.7	0.6	0.6	*0.2*
	1.2	*0.3*	*0.4*	*0.2*
	0.41	*0.3*	*0.2*	*0.1*
	0.14	*0.2*	*0.0*	*0.2*
200 pM	100	89.1	78.7	61.2
	33	20.1	16.8	14.3
	11	6.5	6.3	4.7
	3.7	2.5	2.0	1.7
	1.2	0.8	0.8	0.6
	0.41	*0.2*	*0.4*	*0.2*
	0.14	*0.1*	*0.1*	*0.1*
0 pM	100	96.6	97.8	94.9
	33	96.5	94.6	93.5
	11	95.6	91.7	77.6
	3.7	90.8	59.3	27.8
	1.2	81.0	19.3	8.8
	0.41	25.6	5.6	2.7
	0.14	5.8	1.9	0.8

Taking the polyclonal Guinea Pig anti-insulin antibody as a surrogate for patient antibodies, one can see that with no competitor, there is a detectable signal above background at 0.140 µg/ ml= 140 ng/ ml, well within the FDA-recommended sensitivity of 500 ng/ ml. However, at the lowest competitor insulin 454 concentration of 200 pM, signal is lost 0.41 mg/ ml= 410 ng/ ml, with a faint signal retained at 1.2 mg/ml =1200 ng/ ml. The sponsor concludes that 200 pM insulin 454 is the highest allowable on-board product concentration. Dilution of samples did not improve the drug tolerance of the assay

Reviewer comments
There is concern regarding the potential for interference from both on-board insulin 454 product, as well as endogenous insulin. Following discussion with Dr. Vetheyli, I requested input from both the Pharm/Tox reviewer for this NDA (Dr. Manoj Khurana) and the Clinical Reviewer (Dr. Jean-Marc Guettier). Their comments are inserted below:

Subject: RE: Finalized - NDA 203314 General Consult Request (FRM-CONSULT-01)
Date: Tuesday, April 10, 2012 10:06:31 AM ET
From: Khurana, Manoj
To: Mills, Frederick, Jain, Ritesh
CC: Verthelyi, Daniela I, Calis, Karim, Hartford, Rachel, Vaidyanathan, Jayabharathi

Hi Mills,
Based on the PKPD study (NN1250-1988) a single dose of 0.4 U/kg (equivalent to 2.4 nmol/kg from 600 nmol/mL formulation) is expected to provide mean concentrations that range from 45 to 2100 pmol/L over the sampling duration from 0-120h, mean half-life was 19 hours. Dose-response study in subjects with Type 1 DM (1250-1993) showed mean Cmax value of 9731 pmol/L (range: 6260 - 13900 pmol/L) at steady-state from 0.8 U/kg (4.8 nmol/kg), the maximum dose evaluated in this study; mean terminal half life after multiple dose was 26 hours. Does that answer your questions. Also for my curiosity, can you let me know the reference for the following statement -"The sponsor has found the assay is sensitive to on-board insulin 454 product above 200 pM concentrations." in the e-mail thread below, and which assay is referred here.
Thanks
Manoj

-----Original Message-----
From: Mills, Frederick
Sent: Tuesday, April 10, 2012 9:40 AM
To: Khurana, Manoj; Jain, Ritesh
Cc: Verthelyi, Daniela I; Calis, Karim; Hartford, Rachel
Subject: FW: Finalized - NDA 203314 General Consult Request (FRM-CONSULT-01)

On 4/6/12 1:54 PM, "Guettier, Jean-Marc" <Jean-Marc.Guettier@fda.hhs.gov> wrote:

> Hello All,
>
> I am the clinical reviewer and team leader for this application. Please see my answers to your questions below. I have also cced the clinical pharmacology reviewers who may have additional comments.
>
> 1. Will the patient population be expected to produce significant levels of endogenous insulin, and if so, at what concentration range?
>
> Yes, subjects with type 2 diabetes who will be receiving this product are expected to have high endogenous insulin levels. Insulin levels will vary considerably from subject to subject depending on insulin resistance and glycemic control. For each individual subject endogenous insulin levels will also vary; due to insulin resistance and depending on whether they are fasting or fed. Most type 2 DM patient are expected to have endogenous fasting insulin levels at or above the normal range (145 pmol/L) and fed levels ~ 3 times this concentration. Again some patients

with extreme insulin resistance can have much higher levels.

2. What are the expected serum concentrations of insulin 454? The sponsor has found the assay is sensitive to on-board insulin 454 product above 200 pM concentrations.

This may best be answered by the clinical pharmacology reviewers; Dr. Khurana and Jain who have looked at PK data. What I will say is that there are really no "expected" serum concentrations since insuslin 454 will be individualized to meet the patient's need. In type 2 DM a "typical" dose would be 360-600 nmol delivered subcutaneously; I am not sure what that would translate to in terms of plasma concentration.

Best,

Jean-Marc

Therefore, it is reasonable to expect serum insulin 454 product concentrations significantly above the 200 pM threshold that the sponsor has determined for on-board product interference. In addition, patients may also have substantial endogenous levels, which may also interfere with the assay.

I also note that the sponsor only tested the effect of 200, 2000, and 20,000 pM insulin 454, and therefore should explore intermediate steps between 200 and 2000 pM, since it is possible that there may be a value for adequate drug tolerance above 200 pM that would allow the sponsor to reliably detect patient antibodies in many cases

Matrix effects

Hemolysis

The effect of hemolysis on the antibody measurement was investigated by measuring control samples with or without addition of erythrocytes. This study was performed because in a previous validation study of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997) increases in the range 5.5%-7% were seen upon addition of dilute lysed RBCs.

The following samples were prepared:
A stock lysed red blood cell (dilution E) was prepared by adding 20 µl of packed erythrocytes from a healthy donor to 380 µl control samples (C2,3,8, or 9), and then adding aliquots of these dilutions to control samples (2, 3, 8 or 9) in the following proportions:

Grade 3: 450 µl Control samples (2, 3, 8 or 9) +50 µl dilution E (C 2, 3, 8 or 9)
Grade 2: 475 µl Control samples (2, 3, 8 or 9) +25 µl dilution E (C2, 3, 8 or 9)
Grade 1: 490µl Control samples (2, 3, 8 or 9) +10 µl dilution E (C2, 3, 8 or 9)
The hemolyzed samples were compared to non-hemolyzed Control samples (2, 3, 8 or 9) For control 3 and 9 twice the amount described above were made since these controls were measured in two series. The samples were frozen at -20°C and analyzed twice in duplicate. No interference from hemolysis was seen as the values of the hemolyzed control samples were within 85-115 % of the mean value for non-hemolyzed control samples. The results are shown below:

Table 7 Effect of haemolysis on control samples
The results are shown in %B/T for the non-haemolysed control samples the mean +/- 15% is shown.

Control sample	%B/T	Control Sample	%B/T
C8 non-haemolysed F-E	**33.9 (28.8-39.0)**	**C2 non-haemolysed C-B**	**40.8 (34.7-46.7)**
C8 grade 1	33.4	C2 grade 1	40.7
C8 grade 2	31.9	C2 grade 2	42.1
C8 grade 3	32.3	C3 grade 3	43.5
C3 non-haemolysed D-F	**7.6 (6.5-8.8)**	**C9 non-haemolysed D-F**	**81.2 (69.0-93.4)**
C3 grade 1	7.7	C9 grade 1	82.3
C3 grade 2	7.6	C9 grade 2	82.2
C3 grade 3	7.6	C9 grade 3	82.1
C3 non-haemolysed A-C	**18.9 (16.1-21.7)**	**C9 non-haemolysed A-C**	**85.7 (72.8-98.6)**
C3 grade 1	18.4	C9 grade 1	88.0
C3 grade 2	18.4	C9 grade 2	89.1
C3 grade 3	17.3	C9 grade 3	86.1

Reviewer comments
There appears to be no effect of lysed RBS at the dilutions studied, which are ≥ 1/200 (1/20 x 1/10). There should be a specification to avoid contaminating patient serum samples with larger amounts of RBCs.

Other matrix effects
In the previous validation study of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997), the sponsor also investigated the effects of bilirubin, lipid, Human Serum Albumin (HSA), and pH. Bilirubin had no effect in the rage studied, but lipid, HSA, and pH change all had significant effects for one or more of the antibodies.

Reviewer comment
Given the effects observed on the readings for insulin or other insulin analogue antibodies, the sponsor should assess the effects of lipid, HSA, and pH on the assay for anti-insulin 454 antibodies.

Reagent stability

This was assessed in report nn960358 for the human insulin, insulin X14, and insulin NN304 antibody assays for -20 ^{0}C storage and five freeze-thaw cycles.

Reviewer comment

Similar stability and freeze-thaw studies should be performed for the reagents specific for the insulin 454 antibody assay.

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

/s/

FREDERICK C MILLS
06/14/2012
Addendum to May 31, 2012 DTP review

DANIELA I VERTHELYI
06/14/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 11, 2012

TO: Rachel E. Hartford, Regulatory Project Manager
Jean-Marc Guettier, M.D., Medical Officer
Hylton Joffe, M.D., Clinical Team Leader
Division of Metabolism and Endocrinology Products

FROM: Jean Mulinde, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Lauren Iacono-Connors, Ph.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 203313

APPLICANT: Novo Nordisk, Inc.

DRUG: Ryzodeg™ (70% insulin degludec and 30% insulin aspart [rDNA origin] injection) solution for subcutaneous injection

NME: Yes

REVIEW PRIORITY: Standard Review

INDICATION: To improve glycemic control in adults with Type 1 and Type 2 diabetes mellitus.

CONSULTATION REQUEST DATE: December 6, 2011
INSPECTION SUMMARY GOAL DATE: June 30, 2012
DIVISION ACTION GOAL DATE: July 29, 2012
PDUFA DATE: July 29, 2012

I. BACKGROUND:

Ryzodeg™ (70% insulin degludec and 30% insulin aspart [rDNA origin] injection) solution for subcutaneous injection is a co-formulated soluble insulin analogue product for the treatment of patients with diabetes mellitus (Type 1 and Type 2) (b) (4). Insulin degludec/insulin aspart (IDegAsp) is composed of a new molecular entity, insulin degludec, an ultra-long-acting human insulin analog and insulin aspart, a rapid-acting human insulin analog found in NovoLog® (NDA 20-986, approved June 7, 2000). The co-formulated product is intended for once or twice-daily dosing at any main meal. IDeg is a basal insulin analogue that has been modified such that soluble and stable multi-hexamers are formed upon injection, resulting in a depot in the subcutaneous tissue. The gradual separation of IDeg monomers from the multi-hexamers results in a slow and continuous delivery of IDeg from the subcutaneous injection site into the circulation, leading to ultra-long pharmacokinetic and pharmacodynamic profiles. Binding of the fatty acid moiety of IDeg to albumin contributes to some extent to the protraction mechanism. According to the Applicant, the formulation of IDegAsp has been optimized such that the individual components do not interact, with IAsp present as soluble and stable hexamers and IDeg as soluble and stable di-hexamers. Once injected into the subcutaneous tissue, the IAsp hexamers are immediately split into monomers that are rapidly absorbed into the circulation, while the IDeg di-hexamers form soluble multi-hexamers, which in themselves are of a molecular size too large to be absorbed, leading to a depot from which IDeg monomers are slowly and continuously absorbed into the circulation. In this manner, the Applicant states that it has been possible to obtain a clear separation between the effects of the basal (IDeg) and bolus (IAsp) components of IDegAsp. At the target tissues, IDeg and IAsp monomers bind to and activate insulin receptors, triggering the same cellular effects as human insulin such as promoting glucose uptake.

In support of the efficacy and safety of Ryzodeg™ (IDegAsp) for the treatment of adults with diabetes mellitus (b) (4), the Applicant has submitted data from six pivotal Phase 3 studies (NN5401-3590, NN5401-3592, NN5401-3593, NN5401-3597, NN5401-3594, and NN5401-3645, which is an extension study that followed on to NN5401-3594). Brief descriptions of these studies follow.

1. **Protocol NN5401-3590,** entitled "A 26-Week, Multinational, Multi-Centre, Open-Labelled, Two-Arm, Parallel, Randomised, Treat-To-Target, Efficacy and Safety Comparison of NN5401 Once Daily (OD) with Insulin Glargine (IGlar) OD, Both in Combination with Metformin in Insulin-Naïve Subjects with Type 2 Diabetes Inadequately Controlled on Oral Antidiabetic Drugs"

Study NN5401-3590 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target two-arm parallel group study that evaluated the safety and efficacy of IDegAsp OD + metformin with that of IGlar OD + metformin in insulin-naïve subjects diagnosed with type 2 diabetes. The total duration of the study was 28 weeks, including three treatment periods (1 week screening period, 26 week treatment period, and a 1 week follow-up period). Once determined to be eligible, subjects were randomized (Visit 2) in a 1:1 ratio: IDegAsp OD + metformin or IGlar OD + metformin. The study was conducted (subjects randomized) at 88 clinical investigator sites in eight countries: Austria (4 sites), India (7 sites), Republic of Korea (5 sites), Poland (6 sites), Russia (10 sites), Spain (11 sites), Turkey (5 sites), and United States (40 sites). A total of 813 subjects were screened and 530 subjects were randomized into the trial. Subjects were enrolled in the study from January 11, 2010 through October 26, 2010 (Date of final study report: May 27, 2011).

Novo Nordisk A/S, Denmark was responsible for the preparation of the protocol, electronic case report forms (eCRFs), supply of trial products and stated equipment, monitoring (frequency determined by outcome of remote monitoring of eCRFs, but interval between visits not to exceed 6-8 weeks), safety monitoring, data management, statistics, and the clinical trial report (CTR). The titration of insulin doses was monitored by (b) (4) and reviewed by an internal titration committee composed of members from Novo Nordisk, and any significant changes from the titration algorithm were to have been addressed. (b) (4) was responsible for data handling of Continuous Glucose Monitoring (CGM) and overall data management activities (after trial lock, source data shipped to Novo Nordisk). With the exception of insulin antibody analyses, all other laboratory analyses were provided by (b) (4) (multiple regional locations used). Insulin antibody analyses were provided by (b) (4). Electronic case report forms (eCRF) services were provided by (b) (4)). Site specific eCRF data (in an electronic readable format) was to be provided to the Investigator site and this data was to be retained by the site. [Of note, the following paper CRF forms were also used by sites: Safety Information Forms, Pregnancy Forms, hypoglycemic event questionnaires and the PRO questionnaires.] An interactive voice/web response system (IV/WRS), provided by (b) (4)), was used to perform enrollment, randomization, discontinuation of screening failures, withdrawals, allocation of trial product, drug accountability and document subject completion of the trial. An independent external Event Adjudication Committee (EAC) was constituted for the trial to perform ongoing adjudication, standardization and assessment of cardiovascular events in accordance with pre-defined classifications. The following events were to be evaluated and adjudicated by the EAC in an independent and blinded manner: acute coronary syndrome (including myocardial infarction), stroke, and cardiovascular death. Management of cardiovascular event adjudication was contracted by the sponsor to (b) (4)

The primary efficacy endpoint was defined as change from baseline in HbA1c (%) after 26 weeks of treatment (analyzed by central laboratory). Safety measurements included assessment of adverse events, number of hypoglycemic episodes (ADA definitions and minor episodes), clinical laboratory measurements (chemistry, hematology, lipids, cardiovascular risk markers, antibodies, and urinary albumin-to-creatinine ratio), 12-lead electrocardiograms (ECGs), vital signs, fundoscopy/fundo photography, and physical examinations. The following were designated as medical events of special interest: injection site reactions, severe hypoglycemia (by ADA definition), cardiovascular events (acute coronary syndrome, stroke, death), neoplasms, and immunogenicity reactions (events related to immune mechanisms to trial product).

2. **Protocol NN5401-3592**, entitled "A 26-Week, Randomised, Open-Labelled, Two-Arm, Parallel-Group, Treat-To-Target Trial Comparing Efficacy and Safety of NN5401 Twice Daily (BID) with Biphasic Insulin Aspart (BIAsp) 30 BID, with or without Metformin, with or without DPP-4 Inhibitor, with or without Pioglitazone in Subjects with Type 2 Diabetes in Inadequate Glycaemic Control On Once or Twice Daily Premixed or Self-Mixed Insulin Regimen with or without OADs"

   Study NN5401-3592 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target two-arm parallel group study that evaluated the safety and efficacy of IDegAsp BID ± metformin ± DPP-4 inhibitor ± pioglitazone (IDegAsp BID) with that of BIAsp 30 BID ± metformin ± DPP-4 inhibitor ± pioglitazone (BIAsp 30 BID) in subjects diagnosed with type 2 diabetes, not optimally controlled on once daily (OD) or BID premixed or self-mixed insulin regimen ± OADs. The total duration of the study was 28 weeks, including three treatment periods (1 week screening period, 26 week treatment period, and a 1 week follow-up period). Once determined to be eligible, subjects were randomized (Visit 2) in a 1:1 ratio to IDegAsp BID or BIAsp 30 BID. The study was conducted (subjects randomized) at 50 clinical investigator sites in ten countries: Australia (5 sites), Denmark (7 sites), Finland (5 sites), India (9 sites), Malaysia (3 sites), Poland (5 sites), Sweden (6 sites), Taiwan (3 sites), Thailand (3 sites), and Turkey (4 sites). A total of 661 subjects were screened and 447 subjects were randomized into the trial. Subjects were enrolled in the study from November 5, 2009 through August 23, 2010 (Date of final study report: May 30, 2011).

   The study was conducted by Novo Nordisk A/S, Denmark utilizing the same study conduct model and 3rd party vendors as were described for Study NN5401-3590, above.

   The primary efficacy endpoint is change from baseline in HbA1c (%) after 26 weeks of treatment (analyzed by central laboratory). Safety measurements were identical to those described for Study NN5401-3590, above.

3. **Protocol NN5401-3593**, entitled "A 26-Week, Randomised, Open-Labelled, Two-Armed, Parallel-Group, Treat-To-Target Study Comparing Efficacy and Safety of the NN5401 Once Daily (OD) with Insulin Glargine OD, Both in Combination with

Metformin ± Pioglitazone ± DPP-4 Inhibitors in Subjects with Type 2 Diabetes Inadequately Controlled with Basal Insulin OD + Oral Antidiabetic Drugs (OADs)"

Study NN5401-3593 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target two-arm parallel group study that evaluated the safety and efficacy of IDegAsp OD with IGlar OD, both in combination with metformin ± pioglitazone ± DPP-4 inhibitor in subjects with type 2 diabetes who were inadequately controlled with basal insulin OD + oral antidiabetic drugs (OADs). The total duration of the study was 28 weeks, including three treatment periods (1 week screening period, 26 week treatment period, and a 1 week follow-up period). Once determined to be eligible, subjects were randomized (Visit 2) in 1:1 ratio to IDegAsp OD + OADs or IGlar OD + OADs. The study was conducted (subjects randomized) at 61 clinical investigator sites in nine countries: Croatia (2 sites), France (4), India (8), Poland (4), South Africa (3), Republic of Korea (6), Sweden (5), Turkey (5) and United States (U.S.). A total of 717 subjects were screened and 465 subjects were randomized into the trial. Subjects were enrolled in the study from January 11, 2010 through October 25, 2010 (Date of final study report: May 27, 2011).

The study was conducted by Novo Nordisk A/S, Denmark utilizing the same study conduct model and 3rd party vendors as were described for Study NN5401-3590, above.

The primary efficacy endpoint is change from baseline in HbA1c (%) after 26 weeks of treatment (analyzed by central laboratory). Safety measurements were identical to those described for Study NN5401-3590, above.

4. **Protocol NN5401-3594**, entitled "A 26-Week, Multinational, Multi-Centre, Open-Labelled, Two-Arm, Parallel, Randomised, Treat-To-Target Trial Comparing Efficacy and Safety of NN5401 Once Daily Plus Meal-Time Insulin Aspart for the Remaining Meals vs. Basal-Bolus Treatment with Insulin Detemir Plus Meal-Time Insulin Aspart in Subjects with Type 1 Diabetes"

   Study NN5401-3594 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target two-arm parallel group study that evaluated the safety and efficacy of IDegAsp OD (meal time) + IAsp at the remaining meals or IDet OD + meal time IAsp in subjects diagnosed with type 1 diabetes mellitus. The total duration of the study was 28 weeks, including three treatment periods (1 week screening period, 26 week treatment period, and a 1 week follow-up period). Once determined to be eligible, subjects were randomized (Visit 2) in a 2:1 ratio to IDegAsp OD (meal time) + IAsp at the remaining meals or IDet OD + meal time IAsp. The study was conducted (subjects randomized) at 79 clinical investigator sites in nine countries: Denmark (3 sites), Poland (6 sites), Romania (8 sites), France (3 sites), United Kingdom (8 sites), Russian Federation (11 sites), Israel (4 sites), Australia (7 sites) and United States (29 sites). A total of 706 subjects were screened and 548 subjects were randomized into the trial. Subjects were enrolled in the study from August 25, 2009 through May 31, 2010 (Date of final study report: June 14, 2011).

The study was conducted by Novo Nordisk A/S, Denmark utilizing the same study conduct model and 3rd party vendors as were described for Study NN5401-3590, above.

The primary efficacy endpoint is change from baseline in HbA1c (%) after 26 weeks of treatment (analyzed by central laboratory). Safety measurements were identical to those described for Study NN5401-3590, above.

5. **Protocol NN5401-3597**, entitled "A 26-Week Trial, Randomised, Open-Label, Two-Arm, Parallel-Group, Treat-To-Target Study Comparing Efficacy and Safety of the NN5401 Twice Daily with Biphasic Insulin Aspart 30 Twice Daily, with or without Metformin in Subjects with Type 2 Diabetes in Inadequate Glycaemic Control on Once or Twice Daily Insulin Regimen with or without Metformin"

   Study NN5401-3597 was a Phase 3 multinational, multicenter, open-label, randomized treat-to-target, two-arm, parallel group study that evaluated the safety and efficacy of IDegAsp BID ± metformin with that of BIAsp 30 BID ± metformin subjects diagnosed with type 2 diabetes that were not optimally controlled on once daily (OD) or BID human or analogue basal insulin (basal insulin), premixed or self-mixed insulin regimen ± metformin. The total duration of the study was 28 weeks, including three treatment periods (1 week screening period, 26 week treatment period, and a 1 week follow-up period). Once determined to be eligible, subjects were randomized (Visit 2) in a 2:1 ratio to IDegAsp BID ± metformin or BIAsp 30 BID ± metformin.
   The study was conducted (subjects randomized) at 45 clinical investigator sites in five countries: Japan (16 sites), South Korea (16 sites), Hong Kong (1 site), Malaysia (8 sites), and Taiwan (4 sites). A total of 594 subjects were screened and 424 subjects were randomized into the trial. Subjects were enrolled in the study from February 1, 2010 through December 23, 2010 (Date of final study report: June 1, 2011).

   The study was conducted by Novo Nordisk A/S, Denmark utilizing the same study conduct model and 3rd party vendors as were described for Study NN5401-3590, above.

   The primary efficacy endpoint is change from baseline in HbA1c (%) after 26 weeks of treatment (analyzed by central laboratory). Safety measurements were identical to those described for Study NN5401-3590, above.

6. **Protocol NN5401-3645**, entitled "A 26-Week, Multinational, Multi-Centre, Open-Labelled, Two-Arm, Parallel, Treat-To-Target Extension Trial Comparing Safety and Efficacy of NN5401 Once Daily (OD) Plus Meal-Time Insulin Aspart for the Remaining Meals vs. Basal-Bolus Treatment with Insulin Detemir Plus Meal-Time Insulin Aspart in Subjects with Type 1 Diabetes"

   Study NN5401-3645 was an extension study to Study NN5401-3594. It was a Phase 3 multinational, multicenter, open-label, treat-to-target, two-arm, parallel group study

that evaluated the long term safety and tolerability of IDegAsp OD (meal time) + IAsp at the remaining meals or IDet OD + meal time IAsp in subjects diagnosed with type 1 diabetes mellitus. The extension trial included a screening visit to assess eligibility on the same day as the follow-up visit in the main trial. The total duration of the study was 27 weeks (add on to 28 weeks in Study NN5401-3594), including two treatment periods (26 week treatment period, and a 1 week follow-up period). Once determined to be eligible, subjects were continued on the same treatment that they had been randomized to in Study NN5401-3594. The study was conducted (subjects randomized) at 71 clinical investigator sites in nine countries: Denmark (3 sites), Poland (6 sites), Romania (7 sites), France (2 sites), United Kingdom (6 sites), Russian Federation (10 sites), Israel (4 sites), Australia (7 sites) and United States (26 sites). A total of 706 subjects were screened and 548 subjects were randomized into the trial. Subjects were enrolled in the study from March 15, 2010 through December 2, 2010 (Date of final study report: June 3, 2011).

The study was conducted by Novo Nordisk A/S, Denmark utilizing the same study conduct model and 3rd party vendors as were described for Study NN5401-3590, above.

The primary efficacy endpoint is change from baseline in HbA1c (%) after 26 weeks of treatment (analyzed by central laboratory). Safety measurements were identical to those described for Study NN5401-3590, above.

The clinical investigator sites were selected for inspection based on enrollment characteristics, impact of site data on efficacy outcomes, prior inspection history, and feasibility to review data for more than one study during an inspection at the site.

II. RESULTS (By Site)

Name of CI	Protocol # Site# Subject#	Inspection Date	Final Classification
Norwood, Paul 550 East Herndon Avenue, Suite 101 Fresno, CA 93720	Protocol: 3593 Site: #2332/314 Enrolled: 14	February 21-27, 2012	NAI
Wise, Jonathan K 3901 Houma Blvd, Suite 103 Metairie, Louisiana 70006-2930	Protocol: 3590 Site: #15195/834 Enrolled: 9	March 5-14, 2012	NAI
Cypryk, Katarzyna NZOZ OmniMed, ul. Rzgowska 281/289 Lodz, 93-338 Poland	Protocol: 3590 Site: #10049/401 Enrolled: 9 Protocol: 3594 Site: #10049/103 Enrolled: 19 Protocol: 3645 Site: #10049/103 Enrolled: 15	April 10-13, 2012	NAI

Name of CI	Protocol # Site# Subject#	Inspection Date	Final Classification
Murthy, Sreenivasa Life Care Clinic & Research Centre No 2253, MCN complex, Kodigehalli Main Road, Sahakarnagar Bangalore 560092 Karnataka, India	Protocol: 3593 Site: #15391/407 Enrolled: 25	April 2-5, 2012	NAI
Franek, Edward CSKMSWiA, Centrum Diabetologiczne Budynek "S", pokój 210, ul. Woloska 137 Warszawa, 02-507 Poland	Protocol: 3590 Site: #918/402 Enrolled: 17 Protocol: 3594 Site: #918/100 Enrolled: 16 Protocol: 3645 Site: #918/100 Enrolled: 14	April 16-19, 2012	NAI
Deerochanawong, Chaicharn Diabetes and Endocrinology Unit Department of Medicine Rajavithi Hospital Bangkok, 10400 Thailand	Protocol: 3592 Site: #377/200 Enrolled: 19	March 25-30, 2012	VAI
Wan Bebakar, Wan M School of Medical Sciences Hospital Universiti Sains Malaysia Kubang Kerian Kota Bharu, Kelantan 16150 Malaysia	Protocol: 3592 Site: #3022/601 Enrolled: 23 Protocol: 3597 Site: #3022/201 Enrolled: 9	April 1-5, 2012	VAI
Novo Nordisk A/S Vandtaarnsevej 114 DK 2860 Soeborg Denmark	Protocols NN5401-3590, NN5401-3592, NN5401-3593, NN5401-3594, NN5401-3597, NN5401-3645	April 16-30, 2012	Pending (Preliminary classification VAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 and preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **Paul, Norwood, M.D**.
   550 East Herndon Avenue, Suite 101
   Fresno, CA 93720
   Site #2332

a) What was inspected:

For Study NN5401-3593, at this site, 16 subjects were screened, 14 subjects were enrolled, and 14 subjects completed the study. All 14 enrolled subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, compliance with drug titration guidelines, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated the study related training received by site personnel from the sponsor/monitor, clinical laboratory report documentation, protocol deviation reports, concomitant medication usage, monitoring and sponsor correspondence with the site, IRB approvals and correspondence, and completion of financial disclosures by Dr. Norwood and his staff. There were no limitations to the inspection.

b) General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203313 were compared. Generally, the investigator's execution of Protocol NN5401-3593 was found to be adequate and a Form FDA 483 was not issued.

Of note, the ORA field investigator noted in the EIR that occasionally the CI did not follow the study drug titration guidelines provided in the protocol. When the CI deviated from titration guidelines, however, this was documented in source records and a comment was included as to the reason the CI deviated from the guidelines as was required by the Titration Guidelines that were present in the protocol.

c) Assessment of data integrity:

The data provided by Dr. Norwood's site for Study NN5401-3593 that was submitted to the Agency in support of NDA 203313 appear to be reliable and acceptable for use in support of the pending application.

2. Jonathan K. Wise, M.D.
3901 Houma Blvd, Suite 103
Metairie, Louisiana 70006-2930
Site #15195

a) What was inspected:
For Study NN5401-3590, at this site, 11 subjects were screened, 9 subjects were enrolled, and 8 subjects completed the study (1 subject withdrew prior to randomization). All 11 screened subjects' records were reviewed during the inspection. For each study, the record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, subject randomization procedures, inclusion/exclusion criteria compliance, compliance with drug titration guidelines, primary efficacy endpoint data, documentation and reporting of hypoglycemic events, subjects' diary entries, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated the study related training received by site personnel from the sponsor/monitor, the site's use of the electronic case report form system, clinical laboratory report documentation, protocol deviation reports, concomitant medication usage, monitoring and sponsor correspondence with the site, IRB approvals and correspondence, and completion of financial disclosures by Dr. Wise and his staff. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the sponsor to the Agency in NDA 203313 were compared. Generally, the investigator's execution of Protocol NN5401-3590 was found to be adequate and a Form FDA 483 was not issued. Of note, the ORA field investigator noted in the Establishment Inspection Report that the incidence of AE and concomitant medication usage reported by subjects appeared to be unexpectedly infrequent for enrolled subjects (as had been noted in the OSI Inspection Assignment), but there was no evidence identified in source documents reviewed at the site (i.e., clinic charts, subjects' diaries, source document worksheets) that the CI had failed to report AEs and concomitant medications for subjects enrolled in Study NN5401-3590. Whether this finding resulted from a true lack of AEs and concomitant medication usage in these subjects, or resulted from the site having not instructed subjects correctly on when and how to report AEs and concomitant medication usage, could not be determined during the inspection.

c) Assessment of data integrity:
Not withstanding the observation above, the data provided by Dr. Wise's site for Study NN5401-3590 that was submitted to the Agency in support of NDA 203313 appear to be reliable and acceptable for use in support of the pending application.

3. Katarzyna Cypryk, M.D.
NZOZ OmniMed, ul. Rzgowska 281/289
Lodz, Poland
Site #10049

a) What was inspected:
For Study NN5401-3590, at this site, 22 subjects were screened, 9 subjects were enrolled, and 9 subjects completed the study. Five enrolled subjects' records were reviewed during the inspection. For Study NN5401-3594, at this site, 24 subjects were screened, 19 subjects were enrolled, and 18 subjects completed the study. Ten enrolled subjects' records were reviewed during the inspection. For Study NN5401-3645, at this site, 15 subjects were screened, 15 subjects were enrolled, and 14 subjects completed the study. Nine enrolled subjects' records were reviewed during the inspection. For each study, the record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, randomization procedures, drug accountability, inclusion/exclusion criteria compliance, compliance with drug titration guidelines, primary efficacy endpoint data, concomitant medication usage, protocol deviations, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated the site's use of electronic case report forms, financial disclosure reporting, monitoring logs, monitoring and sponsor correspondence with the site, and Independent Ethics Committee approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203313 were compared and verified. Studies NN5401-3590, NN5401-3594, and NN5401-3645 were not conducted under IND at this site; therefore, Dr. Cypryk did not sign a Form FDA 1572. The investigator's execution of the protocols, however, was found to be adequate and a Form FDA 483 was not issued to the CI.

c) Assessment of data integrity:
The data provided by Cypryk's site for Study NN5401-3590, Study NN5401-3594, and Study NN5401-3645 that were submitted to the Agency in support of NDA 203313 appear to be reliable and acceptable for use in support of the pending application.

4. Sreenivasa Murthy, M.D.
Life Care Clinic & Research Centre
No 2253, MCN complex, Kodigehalli Main Road, Sahakarnagar
Bangalore 560092
Karnataka, India
Site #15391

a) What was inspected:
For Study NN5401-3593, at this site, 41 subjects were screened, 25 subjects were enrolled, and 23 subjects completed the study. Thirteen enrolled subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, randomization procedures, drug accountability, inclusion/exclusion criteria compliance, compliance with drug titration guidelines, primary efficacy endpoint data, concomitant medication usage, protocol deviations, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated the site's use of electronic case report forms, financial disclosure reporting, monitoring logs, monitoring and sponsor correspondence with the site, and Independent Ethics Committee approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203313 were compared and verified. Study NN5401-3593 was not conducted under IND at this site; therefore, Dr. Murthy did not sign a Form FDA 1572. The investigator's execution of the protocol, however, was found to be adequate and a Form FDA 483 was not issued to the CI.

c) Assessment of data integrity:
The data provided by Murthy's site for Study NN5401-3593 that were submitted to the Agency in support of NDA 203313 appear to be reliable and acceptable for use in support of the pending application.

5. Edward Franek, M.D.
CSKMSWiA, Centrum Diabetologiczne
Budynek "S", pokój 210, ul. Woloska 137
Warszawa, 02-507
Poland
Site #918

a) What was inspected:
For Study NN5401-3590, at this site, 22 subjects were screened, 17 subjects were enrolled, and 17 subjects completed the study. Ten enrolled subjects' records were

reviewed during the inspection. For Study NN5401-3594, at this site, 17 subjects were screened, 16 subjects were enrolled, and 14 subjects completed the study. Nine enrolled subjects' records were reviewed during the inspection. For Study NN5401-3645, at this site, 17 subjects were screened, 14 subjects were enrolled, and 14 subjects completed the study. Nine enrolled subjects' records were reviewed during the inspection. For each study, the record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, randomization procedures, drug accountability, inclusion/exclusion criteria compliance, compliance with drug titration guidelines, primary efficacy endpoint data, concomitant medication usage, protocol deviations, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated the site's use of electronic case report forms, financial disclosure reporting, monitoring logs, monitoring and sponsor correspondence with the site, and Independent Ethics Committee approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203313 were compared and verified. Studies NN5401-3590, NN5401-3594, and NN5401-3645 were not conducted under IND at this site; therefore, Dr. Franek did not sign a Form FDA 1572. The investigator's execution of the protocols, however, was found to be adequate and a Form FDA 483 was not issued to the CI.

c) Assessment of data integrity:
The data provided by Franek's site for Study NN5401-3590, Study NN5401-3594, and Study NN5401-3645 that were submitted to the Agency in support of NDA 203313 appear to be reliable and acceptable for use in support of the pending application.

6. Chaicharn Deerochanawong, M.D.
Diabetes and Endocrinology Unit
Department of Medicine
Rajavithi Hospital
Bangkok, 10400
Thailand
Site #377

a) What was inspected:
For Study NN5401-3592, at this site, 30 subjects were screened, 19 subjects were enrolled, and 19 subjects completed the study. All enrolled subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to

informed consent documentation, randomization procedures, drug accountability, inclusion/exclusion criteria compliance, primary efficacy endpoint data, concomitant medication usage, protocol deviations, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated the site's use of electronic case report forms, monitoring logs, monitoring and sponsor correspondence with the site, and Independent Ethics Committee approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:

Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203313 were compared and verified. Study NN5401-3592 was not conducted under IND at this site; therefore, Dr. Deerochanawong did not sign a Form FDA 1572. A Form FDA 483, Inspectional Observations, was issued to the CI for:

> Failure to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60].
>
> Specifically for enrollment of one subject (Subject #200006) who did not meet protocol eligibility criteria. Protocol NN5401-3592 exclusion criteria, exclude subjects that are receiving any concomitant medication that is being given for an off-label use. Subject #200006 was receiving amitriptyline throughout the study for treatment of diabetic neuropathy, an off-label use, based on review of the approved label for amitriptyline in Thailand.

During the inspection and in his subsequent response letter to the Form FDA 483 observation dated March 30, 2012, Dr. Deerochanawong stated that he did not consider use of amitriptyline for the treatment of diabetic neuropathy to be off-label use as it is recommended in broadly published guidelines for this indication. In his written Form FDA 483 response, he also stated that he was given the option by the study sponsor of either discontinuing the subject or continuing them on study as a protocol deviation; he chose to continue the subject on study and report the amitriptyline use as a protocol deviation.

c) Assessment of data integrity:

The data provided by Deerochanawong's site for Study NN5401-3592 that were submitted to the Agency in support of NDA 203313 appear to be reliable and acceptable for use in support of the pending application.

7. Wan M. Wan Bebakar, M.D.
School of Medical Sciences
Hospital Universiti Sains Malaysia
Kubang Kerian
Kota Bharu, Kelantan 16150
Malaysia
Site #3022

a) What was inspected:
For Study NN5401-3592, at this site, 42 subjects were screened, 23 subjects were enrolled, and 19 subjects completed the study. All enrolled subjects' records were reviewed during the inspection. For Study NN5401-3597, at this site, 24 subjects were screened, 9 subjects were enrolled, and 8 subjects completed the study. All enrolled subjects' records were reviewed during the inspection. For each study, the record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, randomization procedures, drug accountability, inclusion/exclusion criteria compliance, primary efficacy endpoint data, concomitant medication usage, protocol deviations, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated the site's use of electronic case report forms, monitoring logs, monitoring and sponsor correspondence with the site, and Independent Ethics Committee approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 203313 were compared and verified. Study NN5401-3592 and Study NN5401-3597 were not conducted under IND at this site; therefore, Dr. Wan Bebakar did not sign Form FDA 1572s for these studies. A Form FDA 483, Inspectional Observations, was issued to the CI for:

i. Failure to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically for:

a) Enrollment of one subject (Subject #601008) in Study NN5401-3592 who did not meet protocol eligibility criteria related to off-label use of medications. Protocol NN5401-3592 exclusion criteria, exclude subjects that are receiving any concomitant medication that is being given for an off-label use. Subject #601008 was receiving amitriptyline throughout the study for treatment of diabetic neuropathy, an off-label used, based on review of the approved label for amitriptyline in Malaysia.

b) Enrollment of one subject (Subject #601039) in Study NN5401-3592 who had not been on an insulin regimen for at least 3 months prior to enrollment as was required by the protocol inclusion criteria. When this violation of eligibility criteria was recognized the subject was withdrawn from the protocol.
c) Enrollment of one subject (Subject #201015) in Study NN5401-3597 who had a creatinine value ≥ 110 µmol/L, which was a protocol exclusion criterion. When this protocol violation was recognized the subject was withdrawn from the study.

ii. Failure to ensure Informed Consent was properly documented in that the written informed consent used in the study was not approved by the IRB/Ethics Committee [21CFR 50.27(a)]. Specifically, three subjects (Subject #601038, Subject #601039, and Subject #601040) signed an August 2009 version of the Informed Consent in January 2010, but a new version of the Informed Consent had been approved for use in December 2009. Two of the three subjects were re-consented with the correct version of the Informed Consent form at their next visit, and the third subject had withdrawn from the study prior to the site being able to obtain their signature on the most current version of the Informed Consent.

Dr. Wan Bebakar responded to the Form FDA 483 observations in a letter dated April 11, 2012. Dr. Wan Bebakar acknowledged errors in study conduct as listed on the Form FDA 483 and promised corrective actions to prevent the occurrence of similar deficiencies in future studies.

c) Assessment of data integrity:
Not withstanding the minor observations noted above, the data provided by Wan Bebakar's site for Study NN5401-3592 and Study NN5401-3597 that were submitted to the Agency in support of NDA 203313 appear to be reliable and acceptable for use in support of the pending application.

8. Novo Nordisk A/S
Vandtaarnsevej 114
DK 2860 Soeborg
Denmark
Sponsor Inspection

a) What was inspected:
The sponsor, Novo Nordisk A/S, was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. Studies NN5401-3590, NN5401-3592, NN5401-3593, NN5401-3594, NN5401-3597, and NN5401-3645 were conducted globally, and during this sponsor/monitor inspection clinical site records for the CI sites listed in the table above were focused on. In addition, the Investigator Trial File (ITF) for Site #14631/805 (Dr. Ekesbo,

Sweden) was reviewed during the inspection to follow-up on a statement in the NN5401-3593 Clinical Study Report submitted to the NDA, which stated that the Sponsor considered source data from this site to be unreliable. The record review included review of documents associated with the IRB approvals, site and investigator qualifications, monitoring activities, drug accountability records, serious adverse events, and the Sponsor's handling of protocol deviations and violations.

b) General observations/commentary:

Studies NN5401-3590, NN5401-3592, NN5401-3593, NN5401-3594, NN5401-3597, and NN5401-3645 were found to be generally well executed by the Sponsor, Novo Nordisk; however, a two item Form FDA 483 was issued at the inspection closeout with the following observations:

i. Failure to ensure that an investigator who did not comply with the general investigational plan was promptly brought into compliance [21 CFR 312.56(b)]. Specifically, for Site #14631/805 in Study NN5401-3593 monitors noted on numerous occasions that the CI was not appropriately documenting subjects' information in source records or eCRFs and the monitor called the Swedish Health Authorities to inform them of noncompliance at the site on May 3, 2010. In spite of these concerns with the site, an additional seven months went by with no further follow-up or correspondence being communicated to the investigator despite evidence of continued lack of compliance at the site (as evidenced by observations in monitoring reports).
ii. Failure to ensure proper monitoring of a study and ensure that the study was conducted in accordance with the investigational plan [21 CFR 312.50]. Specifically, for Site #834 (Dr. Wise, United States) in Study NN5401-3590 the Site Closure Monitoring Report stated that the Investigator Trial File (ITF) at the site was incomplete.

OSI Reviewer Comment: The Applicant identified concerns (late entry or missing source data) with data from Site #14631/805 in the Study NN5401-3593 study report and provided results of sensitivity analyses in which data for the seven subjects enrolled at this site were excluded. The Applicant concluded that results in sensitivity analyses were not substantially different from analyses in which data from Site #14631/805 were included and that trial conclusions were not impacted; therefore, the Applicant decided to keep all subject data from Site #14631/805 in the trial database. Given the nature of the deficiencies at this site by the Applicant it would be reasonable, even without FDA having inspected the site, to exclude data from this site from efficacy analyses. While it seems unlikely that removal of data from the 7 subjects entered at Site #14631/805 would significantly impact overall efficacy or safety conclusions, OSI recommends that the Review Division review sensitivity analyses to independently reach a conclusion regarding whether or not it is appropriate to retain these data in study analyses. Of note, based on the totality of information derived from inspections of other CI's for this NDA, as well as closely related NDA 203314, the findings at this site appear to be isolated.

Based on the FDA inspection of Site #15195/834, the data contributed by the site to Study NN5401-3590 was found to be reliable. Regarding the Form FDA 483 observation related to Site #15195/834, it seems unlikely that this finding would significantly impact the reliability of data submitted by the site.

The Applicant, Novo Nordisk, responded to the Form FDA 483 observations in a letter dated May 14, 2012. In their response they stated that corrective actions, including re-training of Sponsor staff on existing Standard Operating Procedures, are being implemented to prevent recurrence of these types of issues in future studies.

c) Assessment of data integrity:

The data generated, as it pertains to Studies NN5401-3590, NN5401-3592, NN5401-3593, NN5401-3594, NN5401-3597, and NN5401-3645 were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. Not withstanding the Form FDA 483 observations noted above, Studies NN5401-3590, NN5401-3592, NN5401-3593, NN5401-3594, NN5401-3597, and NN5401-3645 appear to have been conducted adequately by Novo Nordisk and the data submitted by the Applicant for these studies may be used in support of the pending Application.

Note: The EIR and associated exhibits for this inspection were not available at the time this CIS was written. The general observations described above are based on review of preliminary summary information provided by the ORA investigator. An inspection summary addendum will be generated if conclusions change upon final review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for the inspection of Novo Nordisk, as well as final review of inspectional findings for clinical investigators Dr. Norwood, Dr. Wise, Dr. Murthy, Dr. Deerochanawong, Dr. Wan Bebakar, Dr. Cypryk, and Dr. Franek the data submitted by the Applicant for Studies NN5401-3590, NN5401-3592, NN5401-3593, NN5401-3594, NN5401-3597, and NN5401-3645 appear reliable in support of NDA 203313.

The preliminary classification for the inspection of Novo Nordisk is Voluntary Action Indicated (VAI) based primarily on identification of one site (Site #14631/805 in Study NN5401-3593), which was self reported by the Applicant, at which corrective actions by the Sponsor/Monitor do not appear to have been promptly implemented. Due to concerns with data reliability, as reported by the Applicant, at Site #14631/805, OSI recommends that the Review Division review sensitivity analyses to independently reach a conclusion regarding whether or not it is appropriate to retain Site #14631/805 data in Study NN5401-3593 analyses.

The final classifications for the inspections of Dr. Deerochanawong (Site #377, Study

NN5401-3592) and Dr. Wan Bebakar (Site #3022, Study NN5401-3592 and Study NN5401-3597) are Voluntary Action Indicated (VAI). While regulatory violations occurred at these sites, as discussed above, they are considered minor in nature and unlikely to significantly impact primary safety or efficacy analyses, nor were they likely to have jeopardized subject safety.

The final classifications for the inspections of Dr. Franek (Site #918, Studies NN5401-3590, NN5401-3594, and NN5401-3645), Dr. Cypryk (Site #10049, Studies NN5401-3590, NN5401-3594, and NN5401-3645), Dr. Murthy (Site #15391, Study NN5401-3593), Dr. Norwood (Site #2332, Study NN5401-3593), and Dr. Wise (Site #15195, Study NN5401-3590) are No Action Indicated (NAI).

Note: All observations noted above related to the inspection of Novo Nordisk are based on the Form FDA 483, and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR for this inspection.

{See appended electronic signature page}

Jean Mulinde, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN M MULINDE
06/12/2012

LAUREN C IACONO-CONNORS
06/12/2012

Memo

Date: March 14, 2012

Revised April 5, April 25, May 25, and May 30,2012

From: Fred Mills, Staff Scientist, DTP

To: Daniela Verthelyi, Chief, Laboratory of Immunology, DTP, OBP

FDA designation: NDA 203314, original NDA submission

Sponsor: Novo Nordisk

Product: insulin degludec (IDeg, generic name insulin 454), for treatment of diabetes

Subject of Review: RadioImmunoAssay (RIA) for detection of anti-insulin 454 antibodies

Table of Contents

Comments to the File:

The sponsor provided the validation for a screening and confirmatory assays/ there is no neutralizing assay report, but this may be acceptable since there is no precedent for neutralizing antibodies to insulin. The screening is a radio immunoanalysis (RIA) and the confirmatory assay is a subtraction RIA (cold competition). The control antibody specific for IDeg is low affinity creating some uncertainty as to the quality of the assay. In addition, the assay seems to be sensitive to concentrations of insulin (both IDeg and endogenous insulin) that are expected to be present in the patients at the time of testing therefore the sensitivity of the assay is uncertain.
Therefore, even though the clinical data they have provided suggests that there was no change in the level of IDeg (Insulin 454) specific antibodies or cross-reacting antibodies from baseline to the end of the trial, these results are questionable until they can demonstrate appropriate sensitivity in the presence of on-board product and endogenous insulin In the target population.

Comments to the Sponsor:

The Agency has three major comments, regarding your assays for anti-insulin 454, anti-insulin aspart, and anti-insulin antibodies:

1. The Agency is concerned about the effects of both on-board insulin 454 product and endogenous insulin may have on the sensitivity of your antibody assay due to the following considerations:

You have provided data demonstrating a significant effect of on-board insulin 454 product on the sensitivity of the insulin antibody screening assay at concentrations above 200 pM. This is a concern because in your PK/PD study (NN1250-1988), a single dose of 0.4 U/kg (2.4 nmol/kg) gave mean serum concentrations from 45 to 2100 pmol/L over a 120 hour sampling interval, with a mean half life of 19 hours. Also, a dose-response study in T1D patients (NN1250-1993) showed that for the maximum study dose (0.8 U/kg =4.8 nmol/kg), a Cmax of 9731 pmol/L was achieved at steady-state, with a mean 26 hour mean terminal half life after multiple doses. Therefore, it is reasonable to expect serum insulin 454 product concentrations significantly above the threshold that you have determined for on-board product interference with your assay.

Furthermore, subjects with type 2 diabetes who will be receiving this product are expected to have high endogenous insulin levels. Although insulin levels will vary considerably from subject to subject depending on insulin resistance and glycemic control, most type 2 diabetes patients are expected to have endogenous fasting insulin levels at or above the normal range (145 pmol/L) and fed levels ~ 3 times this concentration. In addition, some patients with extreme insulin resistance could have much higher levels. Thus endogenous insulin levels may also be high enough to interfere with your assay. For these reasons, unless you can demonstrate sufficient sensitivity in the presence of onboard drug and/or

expected insulin levels, you need to modify the current assay or develop an alternative assay format that minimizes interference from on-board insulin 454 product as well as endogenous insulin. The cutpoint for the assay needs to be determined using sera of treatment-naive patients.

In this regard, the FDA also notes that you have tested the effects of 200, 2000, and 20,000 pM insulin 454, with no intermediate steps- testing for interference at intermediate concentrations between 200 and 2000 pM may reveal that your assay is tolerant of product concentrations higher than 200 pM.

2. In summarizing your antibody testing, you state that there was no change in the level of IDeg (Insulin 454) specific antibodies or cross-reacting antibodies from baseline to the end of the trial. You also state that for all subjects, the change from baseline in antibodies to your product as well as those cross-reacting with human insulin were low and similar in data from 7 trials with IDeg. However, unless you can demonstrate appropriate sensitivity in the presence of on-board product and endogenous insulin, it is difficult to evaluate the significance of the immunogenicity data you have submitted. Therefore, once you have optimized you're assay and confirmed the cutpoint in treatmetn-naïve patients you may need to re-analyze patient sera and submit these data to the FDA for evaluation.

3. You state that the differences in sensitivity observed using the control antibodies are due to low affinity of your antibody specific for IDeg. Without a high affinity control antibody that will enable appropriate validation of the anti-IDeg antibody assay it is difficult to have confidence as to what the true sensitivity of the anti-Deg assay is and what the levels of anti-IDeg antibody are. Therefore, please develop a suitable control and provide assay validation demonstrating an appropriate level of sensitivity.

In addition, please address the following issues:

a. Report nn960358 on the crossreactivity of antibodies to IDEG to the human insulin, insulin X14, and insulin NN304 antibody assays describes the effects of -20 ^{0}C storage and freeze-thaw cycles on antibody controls. Please provide data from stability and freeze-thaw studies for control antibody solutions specific for the insulin 454 antibody assay.

b. While it may be true that inter assay variation is low and well within the 15% acceptance limits, a more general consideration is the need for system suitability specifications to ensure reproducibility between assay runs. Therefore please implement system suitability controls with appropriate specifications for this assay. The low positive quality control for this purpose should have a concentration that is close to the limit of detection for the assay to ensure that the assay has a reproducible sensitivity. Your low positive quality control should be designed to produce a signal above the cut point (positive) 99% of the time (failing in $\leq$ 1% of the time). A high positive quality control will ensure that the

range of the assay remains consistent and should be used at a concentration that falls within the linear range of the dose-response curve.

c. Validation of your antibody assays indicates that there is no effect of lysed red blood cells at the dilutions studied, which are ≥ 1/200. Please clarify how you will treat samples that are contaminated with larger amounts of RBCs.

d. Regarding other potential matrix effects, in your previous validation of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997), you also investigated the effects of bilirubin, lipid, Human Serum Albumin (HSA), and pH. Bilirubin had no effect in the range studied, but lipid, HSA, and pH change significantly altered the signal for one or more of the antibodies. Please provide data that assesses the effects of these factors on your anti-insulin 454 antibody assay.

Executive Summary

Product description

NDA 203314 is for Novo Nordisk's insulin degludec (IDeg, generic name insulin 454) which is an ultra-long acting insulin for once-daily subcutaneous administration in patients with diabetes. IDeg is a modified insulin, or insulin analogue, in which the threonine at position B30 of human insulin has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid (palmitic acid) via a glutamic acid spacer. This structure allows IDeg to form soluble, stable multi-hexamers, resulting in accumulation in the subcutaneous tissue after injection. A gradual dissociation of IDeg monomers from the multi-hexamers provides a slow and continuous delivery of IDeg from the s.c. injection site into the circulation, leading to long pharmacokinetic and pharmacodynamic profiles. In addition, binding of the palmitic acid (b) (4) of IDeg to albumin contributes to extending the half life. IDeg monomers bind to and activate insulin receptors triggering glucose uptake.

For reference, the following tabulation of other insulin analogues may also be helpful

Insulin aspart (X14): substitution of the B28 threonine with aspartic acid, *fast acting*

NN304 insulin (insulin detemir): similar to insulin 454, but with myristic acid conjugated at lysine B29, instead of pamitic acid. *Long acting via fatty acid binding to albumin*

Insulin glargine : glycine substituted for asparagine at position A21, two arginines added C terminal of B chain, *long acting due to aggregate formation*

Clinical trials

This NDA contains data from 7 clincial trials, including one Phase 3 trial (Trial NN9068-3632) that was completed January 31, 2011. This study was a single-center, single-dose, randomized, double-blind, double-dummy, four-period crossover trial in healthy male subjects to investigate the safety and tolerability of IDegLira compared to simultaneous, separate dose administration of liraglutide *(long-acting glucagon-like peptide-1 analog)* and IDeg, as well as single dose administration of liraglutide and single dose administration of IDeg on separate occasions. In total, 46 subjects were screened for this trial and as planned, 24 subjects were randomized and included in both the safety analysis set and the full analysis set. All 24 subjects completed the trial.

No samples were positive for liraglutide antibodies. The sponsor states that there was no change in the level of IDeg specific antibodies or cross-reacting antibodies from baseline to the end of the trial. For all subjects, the change from baseline in antibodies cross-reacting with human insulin was low and similar in data from 7 trials with IDeg (Figure 3–1). Also, the change from baseline in specific insulin analogue antibodies was low and similar in all 7 trials with IDeg.

Reviewer comments
Data for cross-reacting antibodies to insulin and insulin analogues other than IDeg/ insulin 454 have been obtained using antibody assays that have appropriate sensitivity (≤ 500 ng/ ml antibody, as per FDA draft guidance, 2009), and are therefore interpretable. This is reassuring since (1) for human insulin, antibodies cross-reacting with the endogenous insulin of patients could pose serious safety concerns. (2) antibodies cross-reacting with insulin analogues would have the potential to render patients resistant to standard of care treatments.

However, validation of the antibody assay for the IDeg/ insulin 454 product itself (discussed more fully below) gave a sensitivity in the range of 1800 ng/ml. The sponsor states this result is due to the low affinity of the control anti-IDeg antibody (a monoclonal) used to validate the assay. However, without a high affinity control antibody that will enable appropriate validation of the anti-IDeg antibody assay, it is difficult to have confidence as to what the true levels of anti-IDeg antibody are. Therefore, the sponsor should develop a high affinity control and provide assay validation demonstrating an appropriate level of sensitivity.
Further, high degree of on-board drug interference was noted suggesting that the assay may be less sensitive than stated. the cutpoint has not been validated in the patient population and therefore it is unclear that the sensitivity of the assay is as claimed.

A related issue is the lack of a neutralizing antibody assay, which is necessary to assess the physiological significance of observed antibody levels. The sponsor should develop and validate such an assay.

Assay validation
Assay description
The sponsor's antibody assay is a RadioImmunoPrecipitation (RIA). This method has previously been validated for determination of antibodies to human insulin, and insulin analogues insulin aspart (insulin X14), NN304 and NN344. Briefly, the assay is a subtraction radioimmunoassay. The samples were incubated with ^{125}I labeled tracer ± excess insulin/insulin analogue. After incubation overnight the immunoglobulin was precipitated together with any antigen that may have bound. The precipitate was counted in a gamma counter and the amount of radioactivity was expressed in percent of the total amount of added radioactivity (%B *(bound)* /T*(total)*).

Reagents and stability

As described in previous studies in report nn960358 for the human insulin, insulin X14, and insulin NN304 antibody assays, the effects of -20 ^{0}C storage and five freeze-thaw cycles were assessed .
Reviewer comment
Similar stability and freeze-thaw studies should be performed for the reagents specific for the insulin 454 antibody assay

Assay sensitivity.
Assay sensitivity was determined as the concentration of antibody that produced a %B/T

equal to the upper 95 % limit of 150 normal serum samples.

Sensitivities were:
1800 ng/ ml for insulin 454
(similar low sensitivity was observed in a subsequent validation of method transfer)
35 ng/ml for insulin aspart
20 ng/ml for cross-reacting insulin antibodies

Reviewer comments
The sponsor notes the poor assay sensitivity for insulin 454 (1800 ng/ ml), stating that this is probably due to the low affinity of the insulin 454 specific monoclonal antibody. This level of sensitivity is over three times higher than the current recommendation (FDA 2009 draft guidance), making the assay of little or no utility for detecting anti-insulin 454 antibodies. However, the assay is of utility in detecting antibodies for insulin aspart (35 ng/ml) and insulin activities (20 ng/ ml). It is particularly important to have appropriate detection of anti-insulin antibodies, since antibodies raised to a patient's endogenous insulin (if neutralizing) could have serious safety effects.

Range of signals in normal sera
150 plasma samples from healthy donors were analyzed. The 95 % percentiles were calculated for insulin aspart insulin 454 specific (F-E, F'-E) and cross-reacting antibodies (A-C or D-F). The 95% percentile values are shown in Table 8

Table 8 95 % upper limit (%B/T)

Antibody	95 % percentile %B/T
Insulin aspart specific Ab (C-B)	4.4
Insulin 454 specific Ab (F'-E)	0.6
Cross-reacting Ab (A-C)	0.8
Insulin 454 specific Ab (F-E)	0.6
Cross-reacting Ab (D-F)	0.5

Reviewer comment
The background for anti-product signal (Insulin 454 ab) appears to be quite low. However, any signal above this background will be difficult to interpret because, as discussed in the section on assay sensitivity, the low affinity of the anti-insulin 454 control antibody makes the anti-insulin 454 assay appear to be very insensitive.

Drift during assay runs
Drifting was determined by analyzing the control samples 6 times in duplicate in the beginning and in the end of the assay. No significant difference between control samples analyzed in the beginning and in the end of the assay was seen for insulin 454 specific antibodies nor for cross reacting antibodies. There was a modest difference between results insulin aspart specific antibodies analyzed first and last in the assay, although this the sponsor did not consider this important for their analysis.

Reviewer comment
I agree with the sponsor that the insulin aspart measurements that were taken first and those that were taken last are similar, since the mean of the first series is 41.7, with a standard deviation of 1.8, while the mean of the last series is 40 with a standard deviation of 0.98. Therefore, there is a substantial overlap in these distributions, and a t test says there is p=0.016 that their means are the same, which is still above the p=0.01 level of statistical significant.

Repeatability and Intermediate variation
Repeatability and intermediate variation were investigated by analyzing in two double determinations in eight independent assays four control antibody samples designed to yield levels of insulin aspart antibodies, insulin X-14 antibodies, and cross reactive (anti-insulin) antibodies. Both the repeatability and the intermediary variation were below 10 % , which is within the acceptance limits of %CVs below 15%. The sponsor takes this to mean that antibody samples taken at various time points from the same patient do not need to be analyzed in same assay set-up.

Reviewer comments
While it may be true that inter assay variation is low and well within the 15% acceptance limits, a more general consideration is the need for system suitability specifications to ensure reproducibility between assay runs. These should be provided by the sponsor

Determination of Cut Point
Reviewer comment
Determination of a sensitivity as the concentration of antibody that produces a %B/T equal to the upper 95% limit of 150 normal serum samples is conceptually similar to setting a cutpoint equal to a 5% false positive rate for normal serum samples, as per Mire-Sluis 2004;i.e. the sponsor is classifying samples as positive that have signals equivalent to the upper 5% of normal serum samples.
Therefore the sponsor has in effect set an appropriate cutpoint for the anti-human insulin an anti-insulin aspart assays.
Sensitivity as the equivalent of cutpoint for the anti insulin 454 assay may also be acceptable, but only if appropriate sensitivity can be demonstrated.

Drug Tolerance
The interference from insulin aspart and insulin 454 in the antibody analysis was first investigated by addition of insulin aspart and insulin 454 to the four control antibody samples The control samples were divided in two and either insulin aspart or insulin 454 was added to the following final concentrations during incubation with tracer: 0, 50, 150, 450, 1350, 4050, 12150, 36450, 109350, 328050 pM. Each sample was analyzed in duplicate. Recovery of $\geq$ 80% of the no added drug signal was taking as indicating no interference.

Taking the polyclonal Guinea Pig anti-insulin antibody as a surrogate for patient antibodies, with no competitor, there was a detectable signal above background at 0.140 µg/ ml= 140 ng/ ml, well within the FDA-recommended sensitivity of 500 ng/ ml.

However, at the lowest competitor insulin 454 concentration of 200 pM, signal is lost 0.41 mg/ ml= 410 ng/ ml, with a faint signal retained at 1.2 mg/ml =1200 ng/ ml. The sponsor concluded that 200 pM insulin 454 is the highest allowable on-board product concentration. Dilution of samples did not improve the drug tolerance of the assay

The signal for monoclonal anti-Insulin 454 antibody was only weakly competed by Insulin 454, consistent with the sponsor's statement that this is a low affinity antibody.

Reviewer comments
There is concern regarding the potential for interference from both on-board insulin 454 product, as well as endogenous insulin. Following discussion with Dr. Vetheyli, I requested input from both the Pharm/Tox reviewer for this NDA (Dr. Manoj Khurana) and the Clinical Reviewer (Dr. Jean-Marc Guettier). Dr Khurana stated that from a pK study, serum concentrations can range from 45 to 2100 pmole/ l over a sampling duration of 120 hours, and in a steady state study on Type 1 diabetics, a mean Cmax of 9731 pmol/L was achieved. Furthermore, Dr. Guettier noted that most Type 2 diabetics are expected to have fasting levels of endogenous insulin at or above normal (145 pmol/ L) with fed levels increasing about 3 fold. Some patients with insulin resistance can have much higher levels.

Therefore, it is reasonable to expect serum insulin 454 product concentrations significantly above the 200 pM threshold that the sponsor has determined for on-board product interference. In addition, patients can also have substantial endogenous insulin levels, which may interfere with the assay.

I also note that the sponsor only tested the effect of 200, 2000, and 20,000 pM insulin 454, and the sponsor should explore intermediate steps between 200 and 2000 pM, since it is possible that there may be a value for adequate drug tolerance above 200 pM that would allow the sponsor to reliably detect patient antibodies in many cases.

Matrix effects
The effect of hemolysis on the antibody measurement was investigated by measuring control samples with or without addition of erythrocytes. This study was performed because in a previous validation study of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997) increases in the range 5.5%-7% were seen upon addition of dilute lysed RBCs.
Reviewer comments
There appeared to be no effect of lysed RBS at the dilutions studied, which are $\geq$ 1/200 (20 µl of packed erythrocytes in 380 µl control samples, followed by at least a 1/10 dilution). There should be a specification to avoid contaminating patient serum samples with larger amounts of RBCs.

Furthermore, in the previous validation study of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997), the sponsor also investigated the effects of bilirubin, lipid, Human Serum Albumin (HSA), and pH. Bilirubin had no effect in the rage studied, but lipid, HSA, and pH change all had

significant effects for one or more of the antibodies.

Reviewer comment
Given the effects observed on the readings for insulin or other insulin analogue antibodies, the sponsor should assess the effects of lipid, HSA, and pH on the assay for anti-insulin 454 antibodies.

Extended Discussion of NDA 203314 Immunogenicity, including tables and figures

Product Background

Insulin degludec (IDeg, generic name insulin 454) is an ultra-long acting basal insulin for once-daily (OD) subcutaneous (s.c.) administration in patients with diabetes mellitus. IDeg is modified such that the amino acid (b) (4) threonine in position B30 of human insulin has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid (palmitic acid) via a glutamic acid spacer. This structure allows IDeg to form soluble and stable multi-hexamers, resulting in a depot in the subcutaneous tissue after injection. The gradual separation of IDeg monomers from the multi-hexamers results in a slow and continuous delivery of IDeg from the s.c. injection site into the circulation, leading to the observed ultra-long pharmacokinetic and pharmacodynamic profiles. Furthermore, binding of the fatty acid moiety of IDeg to albumin contributes to some extent to the protraction mechanism. At the target tissues, IDeg monomers bind to and activate insulin receptors triggering the same cellular effects as human insulin such as promoting glucose uptake.

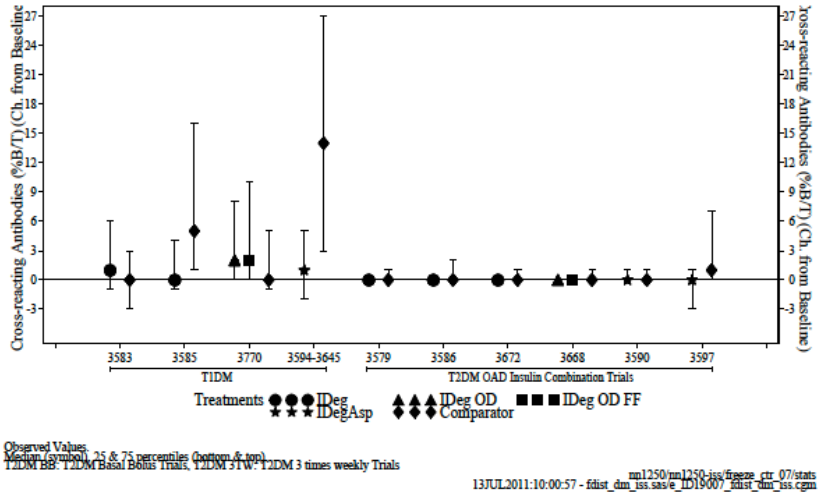
Summary of Immunogenicity Results

In the IDegLira clinical development program, one clinical pharmacology trial (Trial NN9068- 3632) was completed as of 31 January 2011. In addition, one phase 3 trial was ongoing as of 31 January 2011. Trial NN9068-3632 was a single-centre, single-dose, randomized, double-blind, double-dummy, four-period crossover trial in healthy male subjects to investigate the safety and tolerability of IDegLira compared to simultaneous, separate dose administration of liraglutide *(long-acting glucagon-like peptide-1 analog)* and IDeg, as well as single dose administration of liraglutide and single dose administration of IDeg on separate occasions. In total, 46 subjects were screened for this trial and as planned, 24 subjects were randomized and included in both the safety analysis set and the full analysis set. All 24 subjects completed the trial.

No samples were positive for liraglutide antibodies. There was no change in the level of IDeg specific antibodies or cross-reacting antibodies from baseline to the end of the trial For all subjects, the change from baseline in antibodies cross-reacting with human insulin was low and similar in all 7 trials with IDeg (Figure 3–1). As was the change from baseline in specific insulin analogue antibodies was low and similar in all 7 trials with IDeg

<u>Comparison across Trials</u>
Cross-reacting Antibodies
For all subjects, the mean change from baseline to follow-up visit in antibodies cross-reacting with human insulin was low in both the IDeg and the comparator group, and there was no difference between the treatment groups. The mean value of antibodies cross-reacting with human insulin at baseline and at the end of the trial (after 27 or 53 weeks of treatment) was similar in the IDeg and the comparator group. The majority of

subjects in both treatment groups had no or little change in antibodies cross-reacting with human insulin.

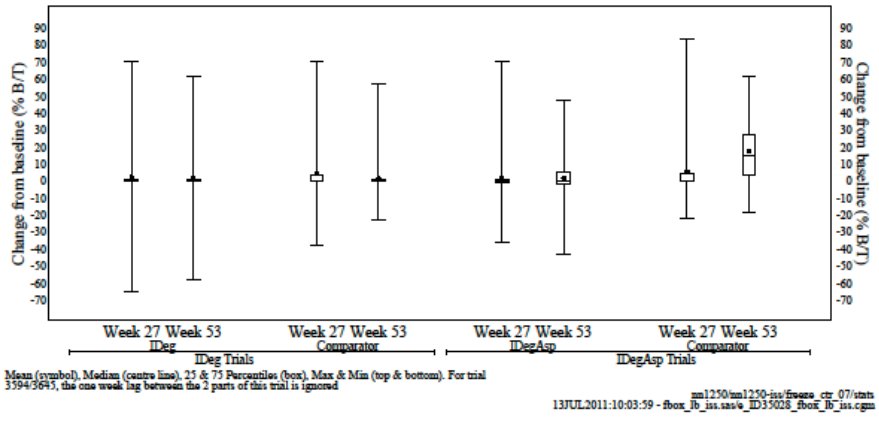


Cross-reference: Appendix 1.20, Figure 3

Figure 3–1 Cross Reacting Antibodies at Week 27/53 – Change from Baseline – All Therapeutic Confirmatory Trials – All Subjects – IDeg and IDegAsp vs. Comparator – Distribution by Trial – Safety Analysis Set

Cross-reacting Antibodies

For all subjects, the mean change from baseline to follow-up visit in antibodies cross-reacting with human insulin was low in both the IDeg and the comparator group, and there was no difference between the treatment groups (Figure 3–2). The mean value of antibodies cross-reacting with human insulin at baseline and at the end of the trial (after 27 or 53 weeks of treatment) was similar in the IDeg and the comparator group The majority of subjects in both treatment groups had no or little change in antibodies cross-reacting with human insulin



Cross-reference: Appendix 1.20, Figure 6

Figure 3–2 Cross-reacting Antibodies – Change from Baseline – All Therapeutic Confirmatory Trials – All Subjects – IDeg and IDegAsp vs. Comparator – Safety Analysis Set

Specific Insulin Analogue Antibodies
For all subjects, the mean values of specific insulin analogue antibodies showed no or very little change after 27 and 53 weeks of treatment with no difference between the IDeg and the comparator group (The majority of subjects in the IDeg group had no or little change in specific IDeg antibodies

Adverse Events and Increase in Antibodies
For all subjects, 220 (5%) subjects in the IDeg group and 145 (6%) subjects in the comparator group had an increase of 10% B/T (absolute value) or more in antibodies cross-reacting with human insulin or an increase in specific insulin analogue antibodies of 5% B/T or more

RIA Assay Validation

Overview of Method

The aim of this study was to validate a method for determination of antibodies against insulin 454 (insulin Degludec) in human serum. The method has previously been validated for determination of antibodies to human insulin, insulin aspart (insulin X14), NN304 and NN344. Briefly, the assay is a subtraction radioimmunoassay. The samples were incubated with ^{125}I labeled tracer ± excess insulin/insulin analogue. After incubation overnight the immunoglobulin was precipitated together with any antigen that may have bound. The precipitate was counted in a gamma counter and the amount of radioactivity was expressed in percent of the total amount of added radioactivity (%B *(bound)* /T*(total)*).

The complete assay setup was as follows:

Series	Assay mixture	Result represent the sum of
A	Sample + Buffer + X-14 tracer	Background, X-14 specific and cross reacting antibodies
B	Sample + Cold X-14 + X-14 tracer	Background
C	Sample + Cold 0454 + X-14 tracer	Background, X-14 specific antibodies
D	Sample + Buffer + 0454 tracer	Background, 0454 specific and cross reacting antibodies
E	Sample + Cold 0454 + 0454 tracer	Background
F	Sample + Cold insulin + 0454 tracer	Background, 0454 specific antibodies
F'	Sample + Cold X-14 + 0454 tracer	Background, 0454 specific antibodies

For each sample the following was calculated:
The amount of specific X-14 antibodies = C-B
The amount of specific 0454 antibodies = F-E, (F´-E)
The amount of cross- reacting antibodies = D-F, (D-F') (or A-C)
In practice only the necessary series will be included. This means that in clinical trials series A will often be deleted and only series F or F' will be included.

Important reagents

insulin analogue tracers

^{125}I-(Tyr A14) - X14 Batch: 57B and 63B
^{125}I- NN454 Batch: 11A, 14A, 18B and 20B

Control antibodies

The assay sensitivity was measured by dilution of the following antibodies:

polyclonal guinea pig anti-insulin antibody

3.1.2.3 Polyclonal antibodies for determination of cross-reacting antibodies

ID	Polyclonal anti-insulin
Host	Guinea pig
Antigen	Bovine and porcine insulin
Source	Novo Nordisk A/S
Lot/Batch No.	01D19E2512-1
Physical Form	Solution (PBS + 0.05% Sodium acid)
Content	7.15 mg/mL
Expiry Date	Apr-2011
Storage Conditions	5°C

monoclonal insulin 454 specific antibody

3.1.2.2 Monoclonal antibodies specific for insulin 454

ID	NN454-1 F46
Source	Novo Nordisk A/S
Lot/Batch No.	04K17J3127-4
Physical Form	Solution
Concentration	1.16 mg/mL
Expiry Date	Oct-2014
Storage Conditions	5°C

monoclonal anti-insulin aspart (insulin X14) antibody

3.1.2.1 Monoclonal antibodies specific for insulin aspart

ID	X14-6 F34
Source	Novo Nordisk A/S
Lot/Batch No.	8J13H1842-1
Physical Form	Solution
Concentration	0.26 mg/mL
Expiry Date	Oct-2008
Storage Conditions	5°C

Antibody Solutions

C2: X14-6 F34 (batch 8J13H1842-1) diluted 1:371 ~ 0.56 µg/ml
C3: GPα Insulin (batch Mix 1) diluted 1:1200 ~ 6.8 µg/ml
C8: NN454-1 F46 (batch 04K17J3127-4) diluted 1:20 ~ 58 µg/ml
C9: GPα Insulin (batch 01D19E2512-1) diluted 1:500 ~ 14.3 µg/ml

Reviewer comments

The sponsor has previously assessed stability of the reagents for measuring anti-insulin and anti-insulin aspart antibodies. Similar stability evaluation of reagents specific for the anti-insulin 454 antibody determination should be performed (^{125}I- NN454, cold NN454 solution, and anti-insulin 454)

Assay sensitivity.

The assay sensitivity was measured by dilution of the three control antibodies:
polyclonal guinea pig anti-insulin antibody
monoclonal insulin 454 specific antibody
monoclonal anti-insulin aspart antibody

Assay sensitivity was determined as the concentration of antibody that produced a %B/T equal to the upper 95 % limit of 150 normal serum samples.

Sensitivities were:
1800 ng/ ml for insulin 454
(similar low sensitivity was observed in a subsequent validation of method transfer from Novo Nordisk to (b) (4), report nn208156)
35 ng/ml for insulin aspart
20 ng/ml for cross-reacting insulin antibodies

Reviewer comments
The sponsor notes the poor assay sensitivity for insulin 454 (1800 ng/ ml), stating that this is probably due to the low affinity of the insulin 454 specific monoclonal antibody. This level of sensitivity is over three times higher than the current recommendation (FDA 2009 draft guidance), making the assay of little or no utility for detecting anti-insulin 454 antibodies. However, the assay is of utility in detecting antibodies for insulin aspart (35 ng/ml) and insulin activities (20 ng/ ml). It is particularly important to have appropriate detection of anti-insulin antibodies, since antibodies raised to a patient's endogenous insulin (if neutralizing) could have serious safety effects.

Range of signals in normal sera
150 plasma samples from healthy donors were analyzed. The 95 % percentiles were calculated for insulin aspart (X-14) specific (C-B), insulin 454 specific (F-E, F'-E) and cross-reacting antibodies (A-C or D-F). The 95% percentile values are shown in Table 8

Table 8 95 % upper limit (%B/T)

Antibody	95 % percentile %B/T
Insulin aspart specific Ab (C-B)	4.4
Insulin 454 specific Ab (F'-E)	0.6
Cross-reacting Ab (A-C)	0.8
Insulin 454 specific Ab (F-E)	0.6
Cross-reacting Ab (D-F)	0.5

Reviewer comment
The background for anti-product signal (Insulin 454 ab) appears to be quite low. However, any signal above this background will be difficult to interpret because, as discussed in the section on assay sensitivity, the low affinity of the anti-insulin 454 control antibody makes the anti-insulin 454 assay appear to be very insensitive.

Drift during assay runs

Drifting was determined by analyzing the control samples 6 times in duplicate in the beginning and in the end of the assay. The values obtained in the beginning and in the end of the assay were compared by a paired t-test using excel. The values are shown in Table 3. No significant difference between control samples analyzed in the beginning and in the end of the assay was seen for insulin 454 specific antibodies (C8) nor for cross reacting antibodies (C3). Some difference between insulin aspart specific antibodies (C2) analyzed first and last in the assay was, however, seen. The mean difference between C2 analyzed first and last in the assay was below 2 %B/T which is less than 5 % of mean %B/T of C2. The sponsor did not consider this difference to be important.

Table 3 Drifting

(Set-up ID: 25, 26 and 31-Jan-2006/BSka)

C2 % B/T Series C-B		C8 % B/T Series F-E		C3 % B/T Series A-C		C3 % B/T Series D-F	
first	last	first	last	first	last	first	last
43.1	40.2	31.6	31.7	19.7	18.6	7.4	7.7
40.7	39.2	29.5	31.6	20.1	18.8	8.3	7.9
41.3	41.0	30.8	32.4	19.3	19.6	8.0	8.0
38.8	38.4	32.4	31.9	19.2	19.8	7.8	8.1
43.0	40.6	32.1	32.8	19.6	20.0	7.6	6.1
43.3	40.4	30.8	33.8	19.1	19.3	7.8	7.6

Reviewer comment

I agree with the sponsor that the C2 measurements that were taken first and those that were taken last are similar, since the mean of C2 first series is 41.7, with a standard deviation of 1.8, while the mean of C2 last series is 40 with a standard deviation of 0.98. Therefore, there is a substantial overlap in these distributions, and a t test says there is p=0.016 that their means are the same, which is still above the p=0.01 level of statistical significant.

Repeatability and intermediate variation

The repeatability and intermediate variation was investigated by analyzing the four control antibody samples (C2, C3, C8 and C9) in two double determinations in eight independent assays. Repeatability and intermediary variation was calculated for insulin X-14 (insulin aspart) specific antibodies (C-B)(Control 2), insulin 454 specific antibodies (F-E) (Control 8) and cross-reacting antibodies (A-C or D-F) (Control 3 and 9). Since outliers were detected in assay set-up 1 it was decided to leave out assay 1 from the calculation of the variation. The results are shown in Table 1 and Table 2:

Table 1 Repeatability

Insulin Aspart antibodies C2 (C-B)			Cross-reacting antibodies C3 and C9 (A-C)			Cross-reacting antibodies C3 and C9 (D-F)			Insulin 454 specific antibodies C8 (F-E)		
Mean % B/T		%CV	Mean %B/T		%CV	Mean %B/T		%CV	Mean %B/T		%CV
C2	42.1	4.2	C3	19.3	2.8	C3	7.6	3.6	C8	32.6	6.4
-		-	C9	88.2	2.5	C9	84.3	1.2			

Table 2 Intermediary variation

Insulin Aspart antibodies C2 (C-B)			Cross-reacting antibodies C3 and C9 (A-C)			Cross-reacting antibodies C3 and C9 (D-F)			Insulin 454 specific antibodies C8 (F-E)		
Mean % B/T		%CV	Mean %B/T		%CV	Mean %B/T		%CV	Mean %B/T		%CV
C2	42.1	9.0	C3	19.3	5.3	C3	7.6	6.2	C8	32.6	6.4
-		-	C9	88.2	4.2	C9	84.3	3.4	-		-

Both the repeatability and the intermediary variation were below 10 % , which is within the acceptance limits of %CVs below 15%. The sponsor takes this to mean that antibody samples taken at various time points from the same patient do not need to be analyzed in same assay set-up.

Reviewer comments
While it may be true that inter assay variation is low and well within the 15% acceptance limits, a more general consideration is the need for specifications for system suitability to ensure reproducibility between assay runs. These should be provided by the sponsor.

Determination of Cut Point
Reviewer comment
Determination of a sensitivity as the concentration of antibody that produces a %B/T equal to the upper 95% limit of 150 normal serum samples is conceptually similar to setting a cutpoint equal to a 5% false positive rate for normal serum samples, as per Mire-Sluis 2004;i.e. the sponsor is classifying samples as positive that have signals equivalent to the upper 5% of normal serum samples.
Therefore the sponsor has in effect set an appropriate cutpoint for the anti-human insulin an anti-insulin aspart assays. The cutpoint for the anti insulin 454 assay may also be adequate if appropriate sensitivity can be demonstrated.

Drug Tolerance
The interference from insulin aspart and insulin 454 in the antibody analysis was first investigated by addition of insulin aspart and insulin 454 to the four control antibody samples
The control samples were divided in two and either insulin aspart or insulin 454 was added to the following final concentrations during incubation with tracer: 0, 50, 150, 450, 1350, 4050, 12150, 36450, 109350, 328050 pM. Each sample was analyzed in duplicate.

C3 *(Guinea Pig α Insulin ~ 6.8 µg/ml)* and C9 *(GPα Insulin ~ 14.3 µg/ml)* were measured using both insulin aspart and insulin 454 as tracers, whereas C2*(X14-6 F34*) was only measured using insulin aspart as tracer and C8 (NN454-1) only with insulin 454 as tracer. An overview of the results can be seen below in Table 4 and Table 5. Recovery of ≥ 80% of the no added drug signal was taking as indicating no interference.

Table 4 Interference from insulin aspart

Insulin aspart pM	C2 (560 ng/ml X14-6 F34) Insulin aspart specific antibodies %B/T	C3 (6.8 µg/ml guinea pig anti-insulin total IgG) Crossreacting antibodies %B/T	C9 (14.3 µg/ml guinea pig anti-insulin total IgG) Crossreacting antibodies %B/T
0	**47.1**	**18.0**	**89.3**
50	**47.8**	**16.3**	**88.6**
150	**46.6**	11.9	**85.1**
450	**44.9**	8.5	**76.3**
1350	34.3	4.3	27.3
4050	22.5	2.5	11.0
12150	9.7	0.6	5.3
36450	3.9	0.2	2.4
109350	1.1	-0.1	1.1
328050	0.1	-0.2	0.2
80% =	**37.7**	**14.4**	**71.4**

Bold = no interference

Table 5 Interference from insulin 454

Insulin 454 pM	C8 (58 µg/ml NN454-1 F46) Insulin 454 specific antibodies %B/T	C3 (6.8 µg/ml guinea pig anti-insulin total IgG) Crossreacting antibodies %B/T	C9 (14.3 µg/ml guinea pig anti-insulin total IgG Crossreacting antibodies %B/T
0	**31.0**	**7.4**	**79.1**
50	**30.4**	**6.4**	**80.9**
150	**30.6**	5.4	**75.4**
450	**30.9**	3.4	55.1
1350	**30.3**	2.2	16.3
4050	**30.6**	0.9	7.5
12150	**30.0**	0.2	3.7
36450	**28.7**	0.0	1.3
109350	23.9	-0.1	0.9
328050	12.7	-0.2	0.6
80% =	**24.8**	**5.92**	**63.28**

Bold = no interference

Reviewer comment
In Table 5, the C8 signal for monoclonal anti-Insulin 454 antibody is only weakly competed by Insulin 454, consistent with the sponsor's statement that this is a low affinity antibody.

In an attempt to enhance the drug tolerance of the assay to insulin 454, the sponsor performed experiments with several sample dilutions:

Table 6 Interference from insulin 454 and effect of sample dilution

Normal range for cross-reacting antibodies (insulin 454/human insulin) = 0.5%B/T. Numbers in italics are below normal range.

Concentration of insulin 454	Target purified GP anti-insulin µg/ml	Cross-reacting antibodies in %B/T		
		Undiluted	Diluted 1:5	Diluted 1:10
20.000 pM	100	1.5	1.6	1.4
	33	0.5	0.6	0.5
	11	*0.2*	*0.2*	*0.2*
	3.7	*0.3*	*0.1*	*0.0*
	1.2	*0.0*	*0.1*	*0.0*
	0.41	*0.0*	*0.0*	*0.1*
	0.14	*0.0*	*-0.1*	*0.2*
2000 pM	100	9.6	8.6	8.1
	33	3.4	3.2	2.9
	11	1.2	1.2	1.1
	3.7	0.6	0.6	*0.2*
	1.2	*0.3*	*0.4*	*0.2*
	0.41	*0.3*	*0.2*	*0.1*
	0.14	*0.2*	*0.0*	*0.2*
200 pM	100	89.1	78.7	61.2
	33	20.1	16.8	14.3
	11	6.5	6.3	4.7
	3.7	2.5	2.0	1.7
	1.2	0.8	0.8	0.6
	0.41	*0.2*	*0.4*	*0.2*
	0.14	*0.1*	*0.1*	*0.1*
0 pM	100	96.6	97.8	94.9
	33	96.5	94.6	93.5
	11	95.6	91.7	77.6
	3.7	90.8	59.3	27.8
	1.2	81.0	19.3	8.8
	0.41	25.6	5.6	2.7
	0.14	5.8	1.9	0.8

Taking the polyclonal Guinea Pig anti-insulin antibody as a surrogate for patient antibodies, one can see that with no competitor, there is a detectable signal above background at 0.140 µg/ ml= 140 ng/ ml, well within the FDA-recommended sensitivity of 500 ng/ ml. However, at the lowest competitor insulin 454 concentration of 200 pM, signal is lost 0.41 mg/ ml= 410 ng/ ml, with a faint signal retained at 1.2 mg/ml =1200 ng/ ml. The sponsor concludes that 200 pM insulin 454 is the highest allowable on-board product concentration. Dilution of samples did not improve the drug tolerance of the assay

Reviewer comments

There is concern regarding the potential for interference from both on-board insulin 454 product, as well as endogenous insulin. Following discussion with Dr. Vetheyli, I requested input from both the Pharm/Tox reviewer for this NDA (Dr. Manoj Khurana) and the Clinical Reviewer (Dr. Jean-Marc Guettier). Their comments are inserted below:

Subject: RE: Finalized - NDA 203314 General Consult Request (FRM-CONSULT-01)
Date: Tuesday, April 10, 2012 10:06:31 AM ET
From: Khurana, Manoj
To: Mills, Frederick, Jain, Ritesh
CC: Verthelyi, Daniela I, Calis, Karim, Hartford, Rachel, Vaidyanathan, Jayabharathi

Hi Mills,
Based on the PKPD study (NN1250-1988) a single dose of 0.4 U/kg (equivalent to 2.4 nmol/kg from 600 nmol/mL formulation) is expected to provide mean concentrations that range from 45 to 2100 pmol/L over the sampling duration from 0-120h, mean half-life was 19 hours. Dose-response study in subjects with Type 1 DM (1250-1993) showed mean Cmax value of 9731 pmol/L (range: 6260 - 13900 pmol/L) at steady-state from 0.8 U/kg (4.8 nmol/kg), the maximum dose evaluated in this study; mean terminal half life after multiple dose was 26 hours. Does that answer your questions. Also for my curiosity, can you let me know the reference for the following statement -"The sponsor has found the assay is sensitive to on-board insulin 454 product above 200 pM concentrations." in the e-mail thread below, and which assay is referred here.
Thanks
Manoj

-----Original Message-----
From: Mills, Frederick
Sent: Tuesday, April 10, 2012 9:40 AM
To: Khurana, Manoj; Jain, Ritesh
Cc: Verthelyi, Daniela I; Calis, Karim; Hartford, Rachel
Subject: FW: Finalized - NDA 203314 General Consult Request (FRM-CONSULT-01)

On 4/6/12 1:54 PM, "Guettier, Jean-Marc" <Jean-Marc.Guettier@fda.hhs.gov> wrote:

> Hello All,
>
> I am the clinical reviewer and team leader for this application. Please see my answers to your questions below. I have also cced the clinical pharmacology reviewers who may have additional comments.
>
> 1. Will the patient population be expected to produce significant levels of endogenous insulin, and if so, at what concentration range?
>
> Yes, subjects with type 2 diabetes who will be receiving this product are expected to have high endogenous insulin levels. Insulin levels will vary considerably from subject to subject depending on insulin resistance and glycemic control. For each individual subject endogenous insulin levels will also vary; due to insulin resistance and depending on whether they are fasting or fed. Most type 2 DM patient are expected to have endogenous fasting insulin levels at or above the normal range (145 pmol/L) and fed levels ~ 3 times this concentration. Again some patients

with extreme insulin resistance can have much higher levels.

2. What are the expected serum concentrations of insulin 454? The sponsor has found the assay is sensitive to on-board insulin 454 product above 200 pM concentrations.

This may best be answered by the clinical pharmacology reviewers; Dr. Khurana and Jain who have looked at PK data. What I will say is that there are really no "expected" serum concentrations since insuslin 454 will be individualized to meet the patient's need. In type 2 DM a "typical" dose would be 360-600 nmol delivered subcutaneously; I am not sure what that would translate to in terms of plasma concentration.

Best,

Jean-Marc

Therefore, it is reasonable to expect serum insulin 454 product concentrations significantly above the 200 pM threshold that the sponsor has determined for on-board product interference. In addition, patients may also have substantial endogenous levels, which may also interfere with the assay.

I also note that the sponsor only tested the effect of 200, 2000, and 20,000 pM insulin 454, and therefore should explore intermediate steps between 200 and 2000 pM, since it is possible that there may be a value for adequate drug tolerance above 200 pM that would allow the sponsor to reliably detect patient antibodies in many cases

Matrix effects

Hemolysis

The effect of hemolysis on the antibody measurement was investigated by measuring control samples with or without addition of erythrocytes. This study was performed because in a previous validation study of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997) increases in the range 5.5%-7% were seen upon addition of dilute lysed RBCs.

The following samples were prepared:
A stock lysed red blood cell (dilution E) was prepared by adding 20 µl of packed erythrocytes from a healthy donor to 380 µl control samples (C2,3,8, or 9), and then adding aliquots of these dilutions to control samples (2, 3, 8 or 9) in the following proportions:

Grade 3: 450 µl Control samples (2, 3, 8 or 9) +50 µl dilution E (C 2, 3, 8 or 9)
Grade 2: 475 µl Control samples (2, 3, 8 or 9) +25 µl dilution E (C2, 3, 8 or 9)
Grade 1: 490µl Control samples (2, 3, 8 or 9) +10 µl dilution E (C2, 3, 8 or 9)
The hemolyzed samples were compared to non-hemolyzed Control samples (2, 3, 8 or 9) For control 3 and 9 twice the amount described above were made since these controls were measured in two series. The samples were frozen at -20°C and analyzed twice in duplicate. No interference from hemolysis was seen as the values of the hemolyzed control samples were within 85-115 % of the mean value for non-hemolyzed control samples. The results are shown below:

Table 7 Effect of haemolysis on control samples

The results are shown in %B/T for the non-haemolysed control samples the mean +/- 15% is shown.

Control sample	%B/T	Control Sample	%B/T
C8 non-haemolysed F-E	**33.9 (28.8-39.0)**	**C2 non-haemolysed C-B**	**40.8 (34.7-46.7)**
C8 grade 1	33.4	C2 grade 1	40.7
C8 grade 2	31.9	C2 grade 2	42.1
C8 grade 3	32.3	C3 grade 3	43.5
C3 non-haemolysed D-F	**7.6 (6.5-8.8)**	**C9 non-haemolysed D-F**	**81.2 (69.0-93.4)**
C3 grade 1	7.7	C9 grade 1	82.3
C3 grade 2	7.6	C9 grade 2	82.2
C3 grade 3	7.6	C9 grade 3	82.1
C3 non-haemolysed A-C	**18.9 (16.1-21.7)**	**C9 non-haemolysed A-C**	**85.7 (72.8-98.6)**
C3 grade 1	18.4	C9 grade 1	88.0
C3 grade 2	18.4	C9 grade 2	89.1
C3 grade 3	17.3	C9 grade 3	86.1

Reviewer comments
There appears to be no effect of lysed RBS at the dilutions studied, which are ≥ 1/200 (1/20 x 1/10). There should be a specification to avoid contaminating patient serum samples with larger amounts of RBCs.

Other matrix effects
In the previous validation study of RIA methods for antibodies to human insulin, insulin X14, and insulin NN304 (report nn960358, from 1997), the sponsor also investigated the effects of bilirubin, lipid, Human Serum Albumin (HSA), and pH. Bilirubin had no effect in the rage studied, but lipid, HSA, and pH change all had significant effects for one or more of the antibodies.

Reviewer comment
Given the effects observed on the readings for insulin or other insulin analogue antibodies, the sponsor should assess the effects of lipid, HSA, and pH on the assay for anti-insulin 454 antibodies.

Reagent stability

This was assessed in report nn960358 for the human insulin, insulin X14, and insulin NN304 antibody assays for -20 ^{0}C storage and five freeze-thaw cycles.

Reviewer comment

Similar stability and freeze-thaw studies should be performed for the reagents specific for the insulin 454 antibody assay.

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

/s/

FREDERICK C MILLS
05/31/2012

DANIELA I VERTHELYI
05/31/2012

04/16/12

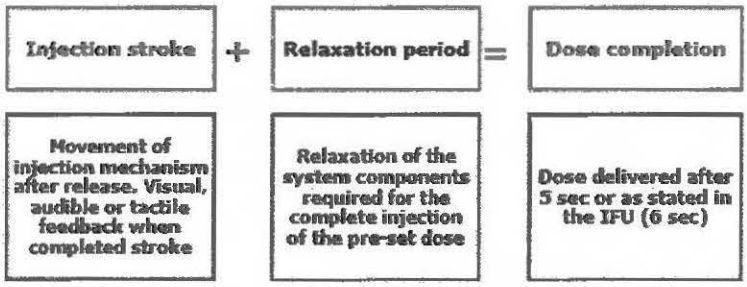
Date: April 9, 2012
From: Lana Shiu, M.D.
To: Jacqueline Ryan, M.D.
Combination Products Team Leader, W066, RM 1257
General Hospital Devices Branch, DAGID, ODE, CDRH
Subject: NDA 203314, PDS290Pen injector to deliver Tresiba®)
1. Issue

CDRH 3/6/2012 consult memo stated the following to the Sponsor:

"The dose accuracy testing submitted does not comply with ISO 111608-1, Pen-Injectors for medical use-Part 1: *Pen-injectors- Requirements and test methods.* This standard requires that the "Pen injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed." (b) (4) CDRH does not believe that this dosing accuracy failure can be or should be mitigated by labeling. You should provide a drug delivery device which is ISO 11608-1 compliant."

Novo Nordisk 3/23/2012 reply stated the following:

Figure 1: Description of a Complete Injection per ISO 11608-1



"According to the definition in ISO 11608-1, the time it takes to inject a full dose is the duration of the injection stroke plus the relaxation time. The duration of the injection stroke alone is not equivalent to the time it takes to deliver the full insulin dose. Some of the dose has been delivered during the injection stroke and the remainder during the relaxation of the system. This is the case for the PDS290 pen-injector as well as for all other marketed pre-filled insulin pen-injectors in the US, including the FlexPen, SoloStar, and KwikPen. In order to account for the relaxation of the system, which is compliant with ISO 11608-1, the Instructions For Use (IFU) state that the needle must be held under the skin for a specified amount of time."

Device Description
The PDS290 Pen injector is a prefilled disposable pen injector which, according to the sponsor is based on the FlexPen. Improvements were made for readability of the dose counter, larger inspection window, no protrusion of dose button, less dose force, more ergonomic grip, improved dose delivery and easier needle handling.

Documents Reviewed
CDRH Review Memo of Usability Test Protocol for NDAs 203314 by LT Q. Nguyen

CDRH Consult Review of NDA 203314—dated 3/6/2012 by Dr. Ryan
NDA 203314 Novo Nordisk Pen Injector Response
NDA 203314 Novo Nordisk Dose Accuracy
ISO 11608-1: 2000 - **Pen-injectors for medical use** — Part 1: **Pen-injectors — Requirements and test methods**

Review and Comments

Page 12/38 of ISO 11608-1:2000 states the following:

3.6
injection stroke
that portion of a parenteral injection involving movement of the injection mechanism following initiation by the release mechanism

NOTE It does not include the subsequent relaxation of the system components required for the complete injection of the pre-set dose.

Page 14/38 of ISO 11608-1: 2000 states the following under Section 5 – General requirements

The pen-injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed.

Page 28/38 of ISO 11608-1: 2000 states the following under Section 15.3 – Instructions for Use

h) time to wait before removing the needle from the injection site;

The sponsor, Novo Nordisk, is technically correct in their response stating that their device complies with ISO 11608-1. Their device does show a visual cue when the injection stroke volume is complete by setting the counter to zero. However, ISO 11608-1 also recognized that injection stroke is not equivalent to complete injection of the pre-set dose in that in order to complete injection, there is also subsequent relaxation of the system components following injection stroke. Thus, ISO 11608-1 under section 15.3 (Instructions for Use) also stipulated that IFU should be clear regarding the time to wait before removing the needle from the injection site in order for the patient to receive the full dose of medication.

PDS290 IFU specifies to hold the needle under the skin for 6 seconds, but the common mistake among patients is to pull out the needle as soon as the counter is re-set to zero. The larger the volume of medication to deliver, the longer time it would take for the whole dose of medication to travel through the pen-injector system to the tip of the needle and thus it is very important for those insulin-resistant patients (receiving large amounts of insulin per injection) to hold the needle under the skin for the specified period of time in order to receive the full prescribed dose of insulin.

Novo Nordisk has demonstrated that early needle removal can lead to under-dosing by as much as 20.4% in their testing and thus should prominently highlight this warning in their written labeling as well as their education of the diabetic educators so these educators can hammer this point home with their patients along with the possible hyperglycemic consequences if they disregard this warning.

Recommendation

1. **Novo Nordisk should clearly explain in their labeling that when the counter is reset to zero, the prescribed dose is not completely delivered until 6 seconds later.**
2. **Prominent warning to the patients in the labeling that if the needle is removed before counting to 6 seconds after the counter is reset to zero, then under-dosing will occur by as much as 20% and patient may have hyperglycemic consequences and require additional insulin administration.**
3. **Novo Nordisk should target the diabetic educators to highlight this under-dosing problem so that these educators can re-enforce these points with their patients regarding the clinical adverse consequences as well as the economic burden of increased medication cost (clinicians often increase the insulin dose assuming that previously prescribed insulin did not have the desired effect).**

Dr. Lana Shiu

Jacqueline Ryan
Combination Products Team Leader

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

/s/

RACHEL E HARTFORD
04/16/2012
On behalf of: Lana Shiu, M.D.
General Hospital Devices Branch, DAGID, ODE, CDRH

04/10/12

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: April 9, 2012
From: Lana Shiu, M.D.
To: Jacqueline Ryan, M.D.
Combination Products Team Leader, W066, RM 1257
General Hospital Devices Branch, DAGID, ODE, CDRH
Subject: NDA 203313, PDS290Pen injector to deliver Ryzodeg® (insulin degludec and aspart)

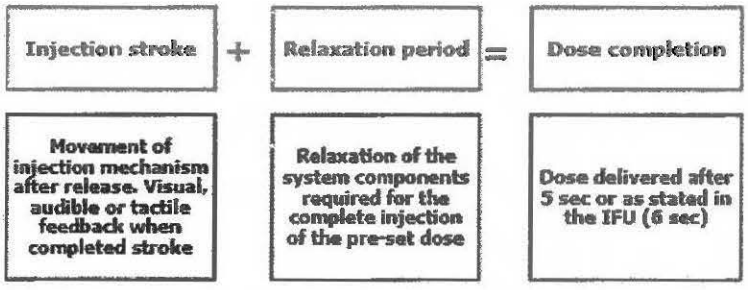
1. Issue

CDRH 3/6/2012 consult memo stated the following to the Sponsor:

"The dose accuracy testing submitted does not comply with ISO 111608-1, Pen-Injectors for medical use-Part 1: *Pen-injectors- Requirements and test methods.* This standard requires that the "Pen injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed." (b) (4) CDRH does not believe that this dosing accuracy failure can be or should be mitigated by labeling. You should provide a drug delivery device which is ISO 11608-1 compliant."

Novo Nordisk 3/23/2012 reply stated the following:

Figure 1: Description of a Complete Injection per ISO 11608-1



"According to the definition in ISO 11608-1, the time it takes to inject a full dose is the duration of the injection stroke plus the relaxation time. The duration of the injection stroke alone is not equivalent to the time it takes to deliver the full insulin dose. Some of the dose has been delivered during the injection stroke and the remainder during the relaxation of the system. This is the case

for the PDS290 pen-injector as well as for all other marketed pre-filled insulin pen-injectors in the US, including the FlexPen, SoloStar, and KwikPen. In order to account for the relaxation of the system, which is compliant with ISO 11608-1, the Instructions For Use (IFU) state that the needle must be held under the skin for a specified amount of time."

Device Description
The PDS290 Pen injector is a prefilled disposable pen injector which, according to the sponsor is based on the FlexPen. Improvements were made for readability of the dose counter, larger inspection window, no protrusion of dose button, less dose force, more ergonomic grip, improved dose delivery and easier needle handling.

Documents Reviewed
CDRH Review Memo of Usability Test Protocol for NDAs 203313 by LT Q. Nguyen
CDRH Consult Review of NDA 203313—dated 3/6/2012 by Dr. Ryan
NDA 203313 Novo Nordisk Pen Injector Response—dated 3/23/2012
NDA 203313 Novo Nordisk Dose Accuracy – dated 1/13/2012
ISO 11608-1: 2000 - **Pen-injectors for medical use** — Part 1: **Pen-injectors — Requirements and test methods**

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PDS290 IFU specifies to hold the needle under the skin for 6 seconds, but the common mistake among patients is to pull out the needle as soon as the counter is re-set to zero. The larger the volume of medication to deliver, the longer time it would take for the whole dose of medication

to travel through the pen-injector system to the tip of the needle and thus it is very important for those insulin-resistant patients (receiving large amounts of insulin per injection) to hold the needle under the skin for the specified period of time in order to receive the full prescribed dose of insulin.

Novo Nordisk has demonstrated that early needle removal can lead to under-dosing by as much as 20.4% in their testing and thus should prominently highlight this warning in their written labeling as well as their education of the diabetic educators so these educators can hammer this point home with their patients along with the possible hyperglycemic consequences if they disregard this warning.

Recommendation

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3. **Novo Nordisk should target the diabetic educators to highlight this under-dosing problem so that these educators can re-enforce these points with their patients regarding the clinical adverse consequences as well as the economic burden of increased medication cost (clinicians often increase the insulin dose assuming that previously prescribed insulin did not have the desired effect).**

Lana Shiu, M.D.

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/s/

RACHEL E HARTFORD
04/10/2012
On behalf of Lana Shiu, M.D.
General Hospital Devices Branch, DAGID, ODE, CDRH

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: March 20, 2012

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID

THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID

CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID

TO: Rachel Hartford, Senior Regulatory Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: **NDA 203313/203314**
Applicant: Novo Nordisk
Device Constituent: Ryzodeg and Tresiba PDS290 Pen Injector
Intended Treatment: Diabetes

QuynhNhu Nguyen, Combination Products Human Factors Specialist — 3/20/2012 Date

Ron Kaye, Human Factors and Device Use-Safety Team Leader — 3/20/2012 Date

Review Memo – Table of Content

CDRH Human Factors Review

Overview

The Division of Metabolism and Endocrinology requested a Human Factors consultative review of the NDAs 203313 and 203314 submitted by Novo Nordisk. This review provides CDRH's review and recommendations on the Human Factors related information contained in both of the NDAs.

The reviewer believes based on the significant proportion of the use errors and the nature of the use errors, and the additional analysis provided by Novo Nordisk, in particular those associated with the dose counter mechanism, as well as other issues, the design of the device as well as training in addition to the proposed changes to IFU, should also be considered and should be further optimized. Novo Nordisk did not provide a rationale of why they believe the IFU changes and the proposed supplemental study will be adequate in addressing use-related issues identified in the prior study.

Furthermore, the reviewer notes that the methodology of proposed study does not represent realistic use i.e. participants (b) (4) and selected participants will receive training. Furthermore, the (b) (4) does not represent realistic way users would normally behave. This methodology was also employed in the prior study. The reviewer believes that these studies are more exploratory in nature (b) (4) In the Human Factors/usability validation study, the participants should use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, Novo Nordisk should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete. In addition the extent and level of training should be identical to the training that actual users will receive. Lastly, the validation study requires that users across all users group be represented, and they (b) (4) while performing simulated use.

Please note that the device platform used in this combination product (b) (4) under NDAs 20986 and 21536, Novolog and Levemir injector. The Human Factors testing for those two NDAs illustrated major concerns regarding human factors/use-safety for which we issued an Information Request letter. For both sets of NDAs, the Human Factors testing showed use errors/failures continue to occur and therefore, findings regarding human factors/use safety concerns have not fully addressed.

Please see the recommendation section (page 16-18) for questions to be transmitted to Novo Nordisk.

Review Materials

NDA 203313
EDR Location: \\CDSESUB1\EVSPROD\NDA203313\203313.enx
eCTD Sequence Number: 0008

NDA 203314
EDR Location: \\CDSESUB1\EVSPROD\NDA203314\203314.enx
eCTD Sequence Number: 0008

The protocol is identical because both NDAs have the same device platform, which is the PDS290.

NDA 203313.pdf (6 MB)

CDRH Human Factors Review

Combination Product Device Information

Submission Number: NDAs 203313 and 203314
Applicant: Novo Nordisk
Drug Constituent: Insulin degludec
Device Constituent: PDS290 pen injectors
Intended treatment: Diabetes

CDRH Human Factors Involvement History

- 8-DEC-2012: CDRH HF provided a review of the Human Factors report contained in the NDA (See Appendix 1)
- 19-JAN-2012: CDRH HF was requested to provide a review on the Applicant's response to Human Factors request, and on a supplemental validation protocol

Review of Human Factors Related Information

This review is organized into three major sections:

- Evaluation of Novo Nordisk to deficiencies identified during the Dec 8, 2011 review
- Evaluation of proposed Supplemental Human Factors study protocol to validate IFU changes
- Preliminary Response to Novo Nordisk's letter dated January 10, 2012, Proposed Questions to FDA (page 4 of 4)

Evaluation of Novo Nordisk To Deficiencies Identified During The Dec 8, 2011 Review

Regarding FDA's question for training requirements, question # 1, for the adult subgroup, Novo Nordisk clarified that there were no untrained participants in the differentiation evaluation as a patient will never select their insulin type and device from a shelf at the pharmacy as it is a prescription product. For the HCPs (including pharmacists) subgroup, Novo Nordisk would like to clarify that there were no trained participants in the differentiation evaluation as it is likely that they will prescribe and/or give patients different insulin products and devices without having received prior introduction to the specific products. As HCPs are the first preventative measure against mix-up of insulin products, the HCP subgroup was tested in a worst case scenario; i.e., not being trained. This response was found acceptable.

Regarding FDA's question pertaining to the breakdown of participants in the studies, question # 2a, Novo Nordisk provided two tables showing a breakdown of number of participants within each user group that were trained, untrained, who reported any degree of visual impairment, experienced simulated visual impairment, who reported any degree of dexterity impairment, experienced simulated dexterity impairment, and who reported any degree of hearing impairment. Both tables showed adequate representation of the intended users population. This response was found acceptable.

Regarding FDA's question pertaining to A rationale for determining who should be receiving training, and who should not among the intended users, question # 2b, Novo Nordisk provided the following:

- UT59 (differentiation test)

The rationale for training all participants in the children, adult, elderly and caregiver groups in how to identify the PDS290 pen-injector and carton before participating in the test was based on the fact that these groups will always get some level of introduction to a product, when the insulin type and device is prescribed. Mix-up at the patient level can occur if several members in the household are using different insulin types or if individual patients use more than one type of insulin e.g. bolus and basal insulin. In case of several insulin users in a household, each user will prior to the prescription receive comprehensive training and get introduction to each of the specific insulin types prescribed and therefore these patients will know their own insulin types and device.
The rationale for not introducing HCPs (including pharmacists) to the products in UT59 is that it is likely that they will prescribe and/or give patients different insulin types and devices without having received prior introduction. As HCPs are the first preventative measure against mix-up of insulin types, the HCP group was tested in a worst case scenario; i.e., not being introduced.

- UT54 (handling test)

Participants in UT54 comprised both trained and untrained users. The rationale for training all participants in the children group was based on a general experience that children will not be self-injecting without prior comprehensive training in correct handling of their pen-injector. The rationale for having both trained and untrained participants in the adult, elderly, caregiver and HCP groups was to reflect that the level of training will vary in real life and by having both trained and untrained participants from these groups, the possible realistic scenarios would be tested.

Regarding FDA's question pertaining to a rationale for [redacted] (b) (4) question # 2c, is an approach that represents realistic use. Novo Nordisk reported that [redacted] (b) (4) As training and the IFU are important elements in the overall assessment of the test results, Novo Nordisk decided to use this relatively comprehensive approach. The reviewer notes that this approach does not reflect realistic use of the IFU.

Regarding FDA's question pertaining to adequate representation of diabetic patients having medical conditions such as retinopathy and neuropathy, question # 3, Novo Nordisk stated that:

- In UT59, four participants (2 elderly, 2 adult) recruited had self reported visual impairments, including cataracts (1 elderly, 1 adult), retinopathy (1 adult), colour blindness (1 adult), and loss of sight in one eye (1 elderly). The number of participants with visual impairment including participants using glasses or lenses was 34 out of the 57 participants, and in the elderly and adult segment, 75% used glasses or lenses. In addition, to ensure diversity pertaining to visual impairment, 20 participants (10 adults and 10 elderly) performed some differentiation tasks while visually impaired "artificially" using glasses to simulate diabetic retinopathy. In addition, one elderly participant had tendonitis and arthritis in her hands, limiting her hand dexterity.
- In UT54, no visual impairments were reported. However, 32 of the 61 participants with diabetes used glasses or lenses, and in the elderly segment 17 out of 21 used glasses or lenses. The elderly group included participants with up to 30 years of insulin use. In addition, to ensure diversity pertaining to visual impairment, 16 participants (8 adults and 8 elderly) performed some handling tasks while visually impaired "artificially" using glasses to simulate diabetic retinopathy. In addition, five participants recruited had at least one form of self-reported dexterity impairment including arthritis in fingers, poor rotational ability in right hand, missing finger, and mild diabetic neuropathy. In addition, to ensure diversity pertaining to dexterity impairment, 8 participants (3 adults and 5 elderly) performed some handling tasks while dexterity was impaired "artificially" using sensation and movement limiting gloves to simulate diabetic neuropathy.

Additional provided by Novo Nordisk showed that adequate representation of the intended users population including those with medical conditions such as retinopathy and neuropathy. This response was found acceptable.

Regarding FDA's question on the User Differential Study, UT59, question # 4, Novo Nordisk clarified that during the carton retrieval task, three participants committed use errors, two participants each committed a use error and one did not fulfil the task. Further investigation reveals that:

- During the exit interview the participant, A13, was made aware that he had retrieved the wrong carton and pen-injector throughout the tasks, since he retrieved (b) (4) and not (b) (4) as stated on the task card. A13 explained that he believed that (b) (4) was the name of the company producing the product and not of the insulin type itself. The participant stressed that he had misinterpreted the task as it would have been no problem for him to retrieve the carton with (b) (4). He explained that he saw the blue colour of the (b) (4) carton in the refrigerator every time he moved it in order to get to the (b) (4) carton. He also said that all cartons were easily identifiable. As a result, Novo Nordisk concluded that the main root cause behind the error was due to the test subject misunderstanding the task.
- Another participant's, A15, subjective feedback indicated that they saw NovoLog® and selected that carton because it is the product that they are currently using, which was a mistake. The participant opened the refrigerator again and retrieved the correct carton with (b) (4) and completed the remaining five tasks successfully. Novo Nordisk concluded that the error in the first task was due to a misunderstanding of the task and that he was able to clearly identify the correct carton and peninjector.

- Another participant's, E3, subjective feedback showed that they did not select a carton because they was not able to differentiate the different cartons. Novo Nordisk concluded that the participant made the correct choice by not selecting a carton in situation where dim light minimize his ability to differentiate.

Based on the above clarification, the response was found acceptable. It appears that the use errors were caused by testing artifacts.

Regarding FDA's question on the User Handling Study, UT54, question # 5, Novo Nordisk reported that current pen-users performed two baseline injection tasks with a pen injector matching the same type of pen injector they currently use (b) (4) (b) (4). For the actual test, only the PDS290 pen-injector, representing the intended commercial product, was used while performing the tasks. In conclusion, all handling tasks in UT54 were performed using PDS290 pen-injectors represented by the commercial product (b) (4) This clarification was found acceptable.

Regarding FDA's question on the Validation of Deivce use (UT59 and UT54 NN Report, Dated June 29, 2011), question # 6, which reported 94 of 105 participants committed 226 errors across tasks associated with delivering an injection and some of the errors resulted in needlestick injuries, question # 6, Novo Nordisk provided the following additional information:

- 11 participants did not set the dose correctly for their injection:

Of these participants, 9 participants experienced issues associated with device feedback with the dose counter. For example, the participant might have dialed the dose correctly i.e. 36 units but when attempting to inject the dose not realizing that there is a blocked needle, the dose counter did not show "0" but showed "28". Novo Nordisk reported that with the blocked needle condition, the dose counter may decrease up to a maximum 7 units due to internal compression inherent with pen injectors and cartridges. These were not aware of the block needle and how the dose counter behaves. The reviewer is concerned that the dose counter, which serves as a visual feedback to the users, can decrease up to a maximum of 7 units when the needle is blocked. In this case, the users were not aware and therefore misinterpreted that some insulin has been delivered because the number on the dose counter is less than what they originally set. However, in fact, no insulin was delivered. As a result, when users then tried to deliver what they think was the remaining amount, 28 units, which in fact it should have been 36, this could result underdosing, which could be clinically significant. While Novo Nordisk believes that the dose counter works properly i.e. it shows only set dose, and it is designed to return to "0" when a full dose has been delivered, the reviewer believes that these test findings demonstrated that the design of the dose counter as designed can be misleading and confusion. If no insulin is delivered, the dose counter display should show the originally set amount of insulin units. However, there appears to be some mechanical related issue that impacts the dose counter display that activates the dose counter to lead it to display a lower amount of insulin. The reviewer believes that since the dose counter serves as a useful feedback the users, the dose counter should be designed so that it provides the correct number of units of insulin pre- and post-deliver taken into account block needle or other problems.

Of these participants, 1 participant did not know how to change the dose from 41 to 27 units because they did not know that it was possible to reverse dose. This would have resulted in

an overdosing. This test finding demonstrated that training and/or instructions for use did not provide adequate mitigations to prevent these types of use errors.
Of these participants, 1 participant was confused by the instructions and delivered 2 units more than prescribed. The participant indicted that they read the instructions for priming the device and interpreted to mean that they should inject 2 units. This testing finding demonstrated that the instructions for use might have been confusing for this particular user, which resulted in an overdosing.
Of these participants, 1 participant inserted the needle with out setting a dose. It was unclear if this user received training and/or did review the IFU before use.
Of these participants, 1 participant delivered 48 units less than prescribed because there was the current pen was nearly empty. They did not know how to resolve this type of situation i.e. use a new pen to deliver a full dose, or use both pens to deliver a full dose (2 units from one pen and 48 units from another pen). This issue is discussed further in the immediate section below.
Overall, these test findings demonstrate that the device design, instructions for use, and training have not been optimized for the use of the product. The reviewer notes that Novo Nordisk proposed to make revisions to IFU. However, the reviewer believes that both the IFU and device design as well as training should be further optimized to address these issues, and that any additional mitigation will require validation.

- 9 participants miscalculated the second dose when using two pens

Of these participants, 1 child user did not know how to carry out the split dose task between two pens. Novo Nordisk reported that this participant was in-experienced and they were forced to perform a task which they had not performed before, where they would have received assistance. As a result the test administrator provided assistance, and a correct dose was delivered. Novo Nordisk argued that the test set up reflect actual use where when assistance was provided to a child user, the child was able to perform self-injection. The reviewer disagrees with this assessment. First, the test conditions and set up did not reflect actual use i.e. pairing of a child user and a parent/caregiver. Second, if child users are not expected to self-inject, they should not be asked to self-inject. The test set-up let the child user to first self-inject, and then noted that they had issues, where moderator's assistance was then provided to correct the issues. If children are not expected to self-inject, they should not self-inject, and this information should be made clear in both the device labeling/instructions for use as well as in communications to prescribing physicians.
Of these participants, 9 participants did not calculate correctly the proper dose for each of the two pens resulting in mis-dosing. Of these 9 participants, the majority did not realize that they mis-calculated and delivered incorrect dose.
Overall, these test findings demonstrate that many users can not perform the split dose calculations between two pens. The reviewer notes that Novo Nordisk proposed to make revisions to IFU.The reviewer believes that both the IFU and device design as well as training should be further optimized to address these issues, and that any additional mitigation will require validation.

- 2 participants did not hold the dose button down until it scales back to the 0 position

Novo Nordisk argued that there are existing mitigations such as visual (dose counter), audible (clicking sound), tactile (tapping sensation), and instructions for use, to minimize the

occurrence of use errors. However, one participant misunderstood the dosing task three times, and did not hold the dose button down until the scale was back to "0". The reviewer notes that Novo Nordisk proposed to make revisions to IFU. However, the reviewer believes that both the IFU and device design as well as training should be further optimized to address these issues, and that any additional mitigation will require validation.

- 47 participants did not hold the needle in the skin for an appropriate amount of time (6 seconds)

In addition to waiting for the dose counter to scale back to "0", Novo Nordisk recommended that the needle should be held in the skin for 6 seconds to ensure that a full dose has been delivered. Novo Nordisk indicated that the 6 seconds hold time can be regarded as a safety precaution. Novo Nordisk also provided summarized data from dose accuracy testing, which did not clearly provide the necessary information in that it should show the amount of insulin delivered between 0-1 seconds, 1-2 seconds, 2-3 seconds, 3-4 seconds, 5-6 seconds, and >6 seconds. The reviewer believes that Novo Nordisk needs to decide whether the 6 second hold time is clinically relevant, and whether the high proportion of use errors reported should be of concerned. The reviewer notes that Novo Nordisk proposed to make revisions to IFU. However, if these user errors are clinically significant, Novo Nordisk will need to further optimize the design and/or IFU and training to address these issues, and that any additional mitigation will require validation.

- 8 participants experienced needlestick injuries

Novo Nordisk reported that in order to alert the user and make the user handle the pen-injector and needle in the most safe way possible to avoid needle sticks, statements and instructions are made in the IFU to mitigate this use error. However, participants continue to commit use errors that resulted in needlestick injuries. These test findings demonstrate that the either the Instructions for Use or the design of the device could be further optimized. he reviewer notes that Novo Nordisk proposed to make revisions to IFU only.

- 7 participants either did not remove the needle or reused the needle

Novo Nordisk reported that to mitigate these use errors, the IFU states to always use a new needle, and to always remove the used needle. If the user omits to change the needle and omits performing the required priming step, the user may be alerted that the needle is blocked, when attempting to inject the insulin dose, as the dose counter will not return to "0". Consequently, a series of mitigation steps have to be disregarded in order to not detect a blocked needle. However, participants continue to commit use errors. At this time the reviewer believes that in addition to Novo Nordisk's proposal to improve the IFU, the training program can be further optimized to educate users on the consequences of not removing the needle or reusing needles.

- 4 participants did not put the cap back on after use

Novo Nordisk reported that based on the results of forced degradation study, short term light exposure has no clinical relevant impact on the insulin. This response was found acceptable.

- 3 participants did not detect a blocked needle

Novo Nordisk reported that a blocked needle will be very unlikely to occur for a user, who uses a new needle for each injection and carefully attaches the needle as recommended in the training material. However, as previously discussed in relation to the dose setting task, the dose counter is not designed to account for the decrease up to a maximum of 7 units when the needle is blocked. The reviewer notes that Novo Nordisk proposed to make revisions to IFU. However, Novo Nordisk will need to further optimize the design and/or IFU and training to address these issues, and that any additional mitigation will require validation

- Close calls/Deviations

Regarding the close calls on participants did not hold dose button until scale was back to "0", and the close calls on blocked needle Novo Nordisk stated that the dose counter stops if the dosing is interrupted. This may aid the user in seeing the amount of missing units. It should be noted that the amount of unit displayed can be less than the set dose but that does not mean that the difference is the amount of the units have been delivered. It was noted that there was no subjective data provided from the perspective of the participants on how they perceived the close calls, and were able to correct themselves. The discussion focused on Novo Nordisk's assessment of those close calls.

Regarding FDA's question on its expectation and review of a validation report, question # 7, Novo Nordisk indicated that they will be making changes to the IFU to address the use errors. However, the reviewer believes based on the significant proportion of the use errors and the nature of the use errors, and the additional analysis provided by Novo Nordisk, in particular those associated with the dose counter mechanism, as well as other issues, the design of the device as well as training in addition to the proposed changes to IFU, would also need to be further optimized.

Evaluation of proposed Supplemental Human Factors study protocol to validate IFU changes

This section of the memo provides a review of Novo Nordisk's proposed supplemental Human Factors study protocol to validate IFU changes. In this study, Novo Nordisk seeks evidence that mitigations that have been implemented to the Degludec PDS290 pen-injector's instructions for use (IFU) reduce use errors and demonstrate that the PDS290 pen-injector is reasonably safe and effective for the intended users, uses, and use conditions. Such evidence, if found, is intended to address concerns stated in the FDA's December 23, 2011 response regarding use errors that occurred during a preceding usability test (PDS290-UT54-2011). Based on the FDA feedback, a human factors/usability evaluation was performed for the PDS290 pen-injector, IFU, carton label, and container label. It was determined that the PDS290 IFU should be updated within specific areas in order to mitigate specific use errors with the PDS290 peninjector. In addition, Novo Nordisk will generate an (b) (4).

Test Population

In the preceding usability test PDS290-UT54-2011, 5 distinct user groups were tested, namely health care professionals (HCPs), caregivers and three patient groups: children, adults and elderly. The overall success rate for caregivers was similar to the adult patient population, whereas the HCP group success rate was higher. Consequently the proposed summative usability test for handling of the PDS290 pen-injector (UT86) includes 3 distinct user groups: Children with diabetes mellitus type 1 or type 2, 10-17 years of age, adults with diabetes mellitus type 1 or

type 2, 18 to 64 years of age, and elderly with diabetes mellitus type 1 or type 2, _ 65 years of age.

Study Methodology
The supplemental summative usability test will include two parts.

- Part A will include up to 36 participants (18 children, 9 adults, and 9 elderly) who receive formal training on how to use the PDS290 pen-injector from a diabetes educator. As described in *Section 7: Participant Training*, the training will include (b) (4) reviewing the IFU in detail. Part A participants will have the option to read the IFU (b) (4) before and while performing the hands-on tasks during the usability test session.
- Part B will include up to 18 untrained participants (9 adults and 9 elderly) who are required to read the IFU before starting the hands-on tasks (i.e., at the start of the test session). These participants will also be required (and reminded, as needed) to refer to the IFU before performing each hands-on task. (b) (4) but the test administrator will not explicitly direct them to do so.

A delay between training and actual test will be built in the study. The test sessions will take place 2-32 hours after the end of the training session. Prior to administering the hands-on tasks, the test administrator will direct Part B (untrained) participants to review the IFU. The test administrator will provide Part A (trained) participants with the option to review the IFU. The hands-on portion of the test will require participants to perform four or five simulated injection tasks

After the participant completes (or attempts to complete) each task, (b) (4) will ask him/ her to rate the ease of performing the task on a 1-7 scale (1 = poor, 7 = excellent). (b) (4) will ask follow-up questions as needed to gain a full understanding of the root cause associated with any reported use errors, close calls, operational difficulties, and deviations. (b) (4) will also seek to collect information regarding what the participant might have done differently (if anything) if performing the task at home.

The test administrator (b) (4) as they perform tasks. Novo Nordisk recognizes (b) (4) can distort task performance by leading participants to concentrate more on their work and be more observant and reflective. Novo Nordisk will to perform a follow-up analysis of every use error, close call, and operational difficulty described in the usability test report. This analysis will determine if any of the interactive difficulties pose an unacceptable risk to device users. The analysis will also serve to determine whether any task failures occurred during testing.

Review Comments
The reviewer believes based on the significant proportion of the use errors and the nature of the use errors, and the additional analysis provided by Novo Nordisk, in particular those associated with the dose counter mechanism, as well as other issues, the design of the device as well as training in addition to the proposed changes to IFU, should also be considered and should be further optimized. Novo Nordisk did not provide a rationale of why they believe the IFU

changes and the proposed supplemental study will be adequate in addressing use-related issues identified in the prior study.

Furthermore, the reviewer notes that the methodology of proposed study does not represent realistic use i.e. participants will be forced read the IFU, and selected participants will receive training. Furthermore, the think aloud approach does not represent realistic way users would normally behave. This methodology was also employed in the prior study. The reviewer believes that these studies are more exploratory in nature where forced and unrealistic conditions are applied. In the Human Factors/usability validation study, the participants should use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, Novo Nordisk should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete. In addition the extent and level of training should be identical to the training that actual users will receive. Furthermore, the validation study requires that users across all users group be represented, and they (b) (4) while performing simulated use.

Preliminary Response to Novo Nordisk's letter dated January 10, 2012, Proposed Questions to FDA (page 4 of 4)

Question 1: Does the Agency agree that the Usability Test Synopsis sufficiently addresses the FDA concerns and requests for validation of further optimization and would be adequate pending satisfactory outcome of the test to support approval of the PDS290 pen-injector?

Proposed Response: No, we do not agree. We believe that that the significant proportion of use errors, and the nature of the use errors, and the additional analysis that you provided, in particular those associated with the dose counter mechanism, as well as other issues, the design of the device as well as training in addition to the proposed changes to IFU, should also be considered and should be further optimized. You did not provide a rationale of why you believe the IFU changes and the proposed supplemental study will be adequate in addressing use-related issues identified in the prior study.

In addition, we have the following remaining concerns regarding your analysis of use errors, response to question # 6, FDA Information Request letter dated 23-DEC-2011.

- 11 participants did not set the dose correctly for their injection:

You reported that 9 participants experienced issues associated with device feedback with the dose counter. For example, the participant might have dialed the dose correctly i.e. 36 units but when attempting to inject the dose not realizing that there is a blocked needle, the dose counter did not show "0" but showed "28". You reported that with the blocked needle condition, the dose counter may decrease up to a maximum 7 units due to internal compression inherent with pen injectors and cartridges. However, the users were not aware of the block needle and how the dose counter functions. The Agency is concerned that the dose counter, which serves as a visual feedback to the users, can decrease up to a maximum of 7 units when the needle is blocked. In this case, the users were not aware and therefore misinterpreted that some insulin has been delivered because the number on the dose counter is less than what they originally set. However, in fact, no insulin was delivered. As a result,

when users then tried to deliver what they think was the remaining amount, 28 units, which in fact it should have been 36, this could result underdosing, which could be clinically significant. While the dose counter works properly, the Agency believes that these test findings demonstrated that the design of the dose counter as designed can be misleading and confusion.

Of these participants, 1 participant did not know how to change the dose from 41 to 27 units because they did not know that it was possible to reverse dose. This would have resulted in an overdosing. This test finding demonstrated that training and/or instructions for use did not provide adequate mitigations to prevent these types of use errors.

Of these participants, 1 participant was confused by the instructions and delivered 2 units more than prescribed. The participant indicted that they read the instructions for priming the device and interpreted to mean that they should inject 2 units. This testing finding demonstrated that the instructions for use might have been confusing for this particular user, which resulted in an overdosing.

Of these participants, 1 participant inserted the needle with out setting a dose. It was unclear if this user received training and/or did review the IFU before use.

Of these participants, 1 participant delivered 48 units less than prescribed because there was the current pen was nearly empty. They did not know how to resolve this type of situation i.e. use a new pen to deliver a full dose, or use both pens to deliver a full dose (2 units from one pen and 48 units from another pen). This issue is discussed further in the immediate section below.

Overall, these test findings demonstrate that the device design, instructions for use, and training have not been optimized for the use of the product. The Agency notes that you proposed to make revisions to IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

- 9 participants miscalculated the second dose when using two pens

Your reported that of these participants, 1 child user did not know how to carry out the split dose task between two pens. This participant was described to in-experienced and they were forced to perform a task which they had not performed before, where they would have received assistance. As a result the test administrator provided assistance, and a correct dose was delivered. You stated that the test set up reflect actual use where when assistance was provided to a child user, the child was able to perform self-injection. Please note that the Agency has a different perspective. First, the test conditions and set up did not reflect actual use i.e. pairing of a child user and a parent/caregiver. Second, if child users are not expected to self-inject, they should not be asked to self-inject. The test set-up let the child user to first self-inject, and then noted that they had issues, where moderator's assistance was then provided to correct the issues. If children are not expected to self-inject, they should not self-inject, and this information should be made clear in both the device labeling/instructions for use as well as in communications to prescribing physicians.

Of these participants, 9 participants did not calculate correctly the proper dose for each of the two pens resulting in mis-dosing. Of these 9 participants, the majority did not realize that they mis-calculated and delivered incorrect dose.

Overall, these test findings demonstrate that many users can not perform the split dose calculations between two pens. The Agency notes that you proposed to make revisions to

IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

- 2 participants did not hold the dose button down until it scales back to the 0 position

You reported that there are existing mitigations such as visual (dose counter), audible (clicking sound), tactile (tapping sensation), and instructions for use, to minimize the occurrence of use errors. However, one participant misunderstood the dosing task three times, and did not hold the dose button down until the scale was back to "0". The Agency notes that you proposed to make revisions to IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

- 47 participants did not hold the needle in the skin for an appropriate amount of time (6 seconds)

In addition to waiting for the dose counter to scale back to "0", you recommended that the needle should be held in the skin for 6 seconds to ensure that a full dose has been delivered. You indicated that the 6 seconds hold time can be regarded as a safety precaution. In the same response, you also provided summarized data from dose accuracy testing, which did not clearly show the amount of insulin delivered between 0-1 seconds, 1-2 seconds, 2-3 seconds, 3-4 seconds, 5-6 seconds, and >6 seconds. Please decide whether the 6 second hold time is clinically relevant, and whether the high proportion of use errors reported should be of concerned. The Agency notes that you proposed to make revisions to IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

- 8 participants experienced needlestick injuries

You reported that in order to alert the user and make the user handle the pen-injector and needle in the most safe way possible to avoid needle sticks, statements and instructions are made in the IFU to mitigate this use error. However, participants continue to commit use errors that resulted in needlestick injuries. The Agency notes that you proposed to make revisions to IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

- 7 participants either did not remove the needle or reused the needle

You reported that to mitigate these use errors, the IFU states to always use a new needle, and to always remove the used needle. If the user omits to change the needle and omits performing the required priming step, the user may be alerted that the needle is blocked, when attempting to inject the insulin dose, as the dose counter will not return to "0". Consequently, a series of mitigation steps have to be disregarded in order to not detect a blocked needle. However, participants continue to commit use errors. The Agency notes that you proposed to make revisions to IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

- 3 participants did not detect a blocked needle

You reported that a blocked needle will be very unlikely to occur for a user, who uses a new needle for each injection and carefully attaches the needle as recommended in the training

material. However, as previously discussed in relation to the dose setting task, the dose counter is not designed to account for the decrease up to a maximum of 7 units when the needle is blocked. The Agency notes that you proposed to make revisions to IFU. However, the Agency believes that additional mitigations are necessary, and that any additional mitigation will require validation.

CDRH Human Factors Review Recommendations

Please transmit the following comments to Novo Nordisk:

Question 1: Does the Agency agree that the Usability Test Synopsis sufficiently addresses the FDA concerns and requests for validation of further optimization and would be adequate pending satisfactory outcome of the test to support approval of the PDS290 pen-injector?

CDRH Human Factors Proposed Response: No, we do not agree based on our review of your response to our IR letter and the proposed test protocols for both NDAs, 203313 and 203314. The significant proportion of use errors, and the nature of the use errors that were previously identified, and the additional analysis that you provided, in particular those associated with the dose counter mechanism, as well as other reported issues, indicate that specific modifications are necessary that may not be limited to IFU. Furthermore, you did not provide a rationale or evidence that the IFU changes will adequately address the use-related issues in your prior study.

The proposed study is not acceptable as described since it involves (b) (4) . This approach does not represent realistic use. Furthermore, (b) (4) does not represent realistic way users would normally behave in actual. We noted that this type of approach was also employed in you prior study. These studies are more exploratory in nature (b) (4) . In the Human Factors/usability validation study, we expect that the participants to use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, you should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete. In addition the extent and level of training should be identical to the training that actual users will receive. Furthermore, the validation study requires that users across all users group be represented, and they (b) (4) while performing simulated use.

We continue to remain concerned based on your analysis of use errors specifically with the response that you provided to question # 6 to FDA Information Request letter dated 23-DEC-2011. Some of our concerns are highlighted below:

- 11 participants did not set the dose correctly for their injection:

  You reported that 9 participants experienced issues associated with device feedback with the dose counter. For example, the participant might have dialed the dose correctly i.e. 36 units but when attempting to inject the dose not realizing that there is a blocked needle, the dose counter did not show "0" but showed "28". You reported that with the blocked needle condition, the dose counter may decrease up to a maximum 7 units due to internal compression inherent with pen injectors and cartridges. However, the users were not aware of the block needle and how the dose counter functions. The Agency is concerned that the dose counter, which serves as a visual feedback to the users, can decrease up to a maximum of 7 units when the needle is blocked. In this case, the users were not aware and therefore misinterpreted that some insulin has been delivered because the number on the dose counter is less than what they originally set. However, in fact, no insulin was delivered. As a result, when users then tried to deliver what they think was the remaining amount, 28 units, which

in fact it should have been 36, this could result underdosing, which could be clinically significant. The Agency believes that these test findings demonstrated that the design of the dose counter as designed can be misleading and confusion. In addition, patients would either over-compensate or under-compensate for the amount of insulin that they require for subsequent injections.

- 9 participants miscalculated the second dose when using two pens

Your reported that of these participants, 1 child user did not know how to carry out the split dose task between two pens. This participant was described to in-experienced and they were forced to perform a task which they had not performed before, where they would have received assistance. As a result the test administrator provided assistance, and a correct dose was delivered. You stated that the test set up reflect actual use where when assistance was provided to a child user, the child was able to perform self-injection. The test set-up let the child user to first self-inject, and then noted that they had issues, where moderator's assistance was then provided to correct the issues. If children are not expected to self-inject, they should not self-inject, and this information should be made clear in both the device labeling/instructions for use as well as in communications to prescribing physicians. In addition, of these participants, 9 participants did not calculate correctly the proper dose for each of the two pens resulting in mis-dosing. Of these 9 participants, the majority did not realize that they mis-calculated and delivered incorrect dose. Overall, these test findings demonstrate that many users can not perform the split dose calculations between two pens despite mitigations that are currently in placed.

- 47 participants did not hold the needle in the skin for an appropriate amount of time (6 seconds)

In addition to waiting for the dose counter to scale back to "0", you recommended that the needle should be held in the skin for 6 seconds to ensure that a full dose has been delivered. You indicated that the 6 seconds hold time can be regarded as a safety precaution. In the same response, you also provided summarized data from dose accuracy testing, which did not clearly show the amount of insulin delivered between 0-1 seconds, 1-2 seconds, 2-3 seconds, 3-4 seconds, 5-6 seconds, and >6 seconds. Please decide whether the 6 second hold time is clinically relevant, and a rationale for why the high proportion of use errors reported should be of concerned.

- 8 participants experienced needlestick injuries

You reported that in order to alert the user and make the user handle the pen-injector and needle in the most safe way possible to avoid needle sticks, statements and instructions are made in the IFU to mitigate this use error. However, participants continue to commit use errors that resulted in needlestick injuries indicating that current mitigations are not effective.

- 7 participants either did not remove the needle or reused the needle

You reported that to mitigate these use errors, the IFU states to always use a new needle, and to always remove the used needle. If the user omits to change the needle and omits performing the required priming step, the user may be alerted that the needle is blocked, when attempting to inject the insulin dose, as the dose counter will not return to "0". Consequently, a series of mitigation steps have to be disregarded in order to not detect a

blocked needle. However, participants continue to commit use errors indicating that current mitigations are not effective.

- 3 participants did not detect a blocked needle

You reported that a blocked needle will be very unlikely to occur for a user, who uses a new needle for each injection and carefully attaches the needle as recommended in the training material. However, as previously discussed in relation to the dose setting task, the dose counter is not designed to account for the decrease up to a maximum of 7 units when the needle is blocked.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management,* available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.

Appendix A: Review of Applicant's Evaluation of Prior Human Factors Report (Dated June 29, 2011)

Review Materials

Links to submissions:
\\CDSESUB5\EVSPROD\NDA203314\203314.enx
\\CDSESUB5\EVSPROD\NDA203313\203313.enx
Sequence 0000 (original submission, part 1, quality, 3.2.P drug product, 3.2.P.7. Container Closure System)

CDRH Human Factors Review

Device Description

Insulin degludec is an ultra-long-acting basal insulin. Insulin degludec is intended for treatment of diabetes mellitus. Insulin degludec is administered once-daily at any time of the day, independent of meals, and is injected subcutaneously (s.c.) in the thigh, the upper arm or the abdominal wall.

For patients with type 2 diabetes mellitus, the recommended daily starting dose of insulin degludec is 10 units, followed by individual dosage adjustments. For patients with type 1 diabetes mellitus, insulin degludec is to be used once-daily with meal-time insulin and requires subsequent individual dosage adjustments. Insulin degludec has been developed in two strengths as insulin degludec 100 U/ml and insulin degludec 200 U/ml.

- Insulin degludec 100 U/ml is intended to be marketed (b) (4) (b) (4) as a pre-filled disposable PDS290 pen-injector with a dose range of 1-80 U/injection, which can be dialled in 1 U increments.
- Insulin degludec 200 U/ml is intended for the market in a pre-filled disposable PDS290 pen-injector with a dose range of 2-160 U/injection, which can be dialled in 2 U increments.

Volume and Strength

Formulation	Total volume in cartridge	Strength	Total units available in presentation	Max dose per injection	Dose increment
Insulin Degludec U100	3 mL	100 U/mL	300 U	80 U	1 U
Insulin Degludec U200	3 mL	200 U/mL	600 U	160 U	2 U
Insulin Degludec/Insulin Aspart	3 mL	100 U/mL	300 U	80 U	1 U

(b) (4)

Figure 1: Insulin Degludec (100 U/mL) pen-injector (left), Insulin Degludec(200 U/mL) peninjector (centre) and Insulin Degludec/Insulin Aspart (100 U/mL) pen-injector (right). Pens are shown without caps.

PDS290 is a pen-shaped, prefilled device containing (b) (4). Therefore the drug is not in contact with the device. The device is intended to function with a (b) (4) needle

(b) (4). The PDS290-pen injector is currently approved by FDA for use with growth hormone (Norditropin FlePro).

PDS290 physical characteristics:

(b) (4)

PDS290 was developed to fulfil the international standard for drug injectors, ISO 11608-1 (Peninjectors for medical use - Part1: Requirements and test methods).
The design of the pen-injector enables the users to always have a display of the chosen amount of insulin units selected for injection, independent of drug concentration.

The PDS290 is different than the FlexPen regarding the following features:

(b) (4)

(b) (4)

Compared to FlexPen®, some of the new features of the PDS290 pen-injector are:

(b) (4)

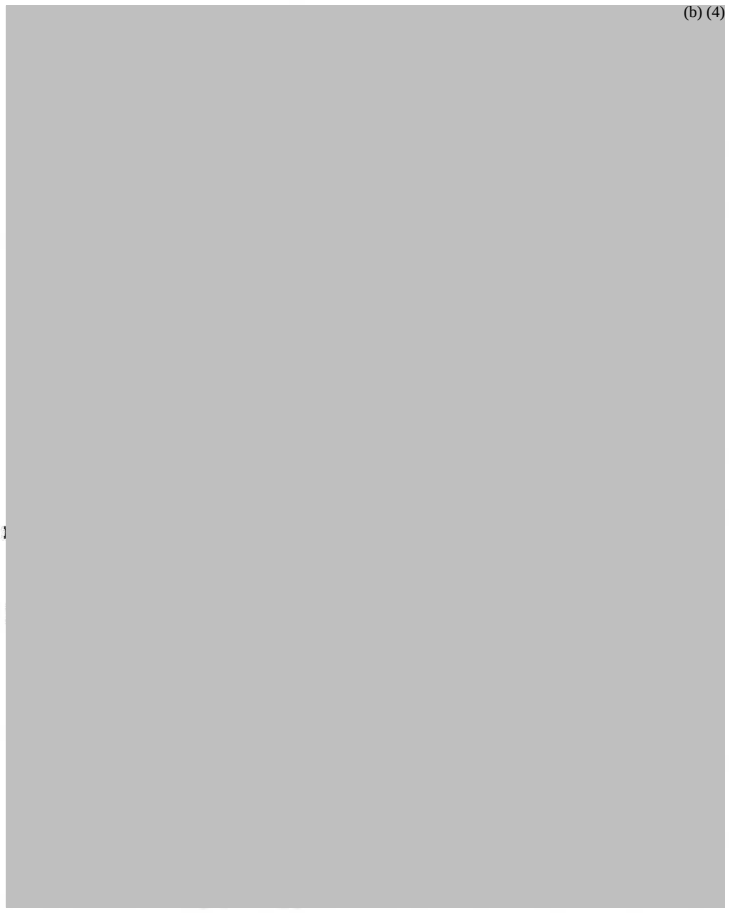

Figure 4: Exploded View of Internal Device Components

Summary of Human Factors Information

The sponsor submitted two main documents for Human Factors review:

- Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011)
- Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011)

The device will be used in the home environment and hospital setting. Training is required for use with the product including identifying insulin variant(s). Once prescribed, the users can inject themselves or are injected by a caregiver.

To prepare the pen-injector, a new needle is mounted by the user and the pen-injector is primed, thereafter the intended dose is set by rotating the dose selector clockwise (when looking directly at the PDS290 pen-injectors' dose button) until the required dose is visible in the display. The dose button does not protrude from the PDS290 pen-injector when dialling the dose selector. Dose delivery is accomplished by inserting the needle subcutaneously and pressing the dose button. During dose delivery, the PDS290 pen-injector (b) (4) . A distinct end-of-dose-click indicates when the display has returned to "0" (The clicks are only a supportive feedback). The full dose is delivered when the needle has been kept inserted into the skin at least 6 seconds after the display has returned to "0". The "6

second" duration is a conservative approach, and that exact duration is not safety critical, from a medical perspective provided that the timing is kept below 6 seconds, as the PDS290 pen-injector is within the dosage requirements, in accordance with ISO 11608-1 before the "6 second" duration.

When performing an injection with the PDS290 pen-injector, the following user steps/primary operation functions must be carried out.
Step 1: Pick the correct PDS290 carton/pen-injector with the intended insulin product
Step 2: Cap removal
Step 3: Verification via label and cartridge holder that it is the correct pen
Step 4: Check that the insulin in the pen-injector is clear and colourless
Step 5: Needle mounting
Step 6: Checking the insulin flow (priming)
Step 7: Setting intended dose (reversing the dose setting, if necessary)
Step 8: Understand the End-of-content indication (feature ensuring that no larger dose can be dialled than is left in the cartridge)
    o This step only applies if the user is going to inject a dose larger than the remaining left in cartridge
Step 9: Subcutaneous needle insert
Step 10: Injecting the dose, including checking that scale drum returns to "0", and 6 seconds waiting time with needle in the skin, that is, full dose has been delivered
Step 11: Needle removal and disposal of used needle
Step 12: Cap mounting

The intended users of the pen-injector include patients, caregivers and healthcare professionals. There are five distinct user groups:

- Children (age 10 to 17) who self inject without a parent's involvement. 15 participants were included in the study.
- Adults (age 18 to 64) who self-inject. 25 participants were included in the study.
- Elderly (age 65 and older) who self-inject. 21 participants were included in the study.
- Caregivers (age 18 to 64) who perform injections on others, such as young children, spouses and elderly. 22 participants were included in the study.
- Healthcare professionals who provide injection pen prescriptions and teach others how to perform injections. 22 participants were included in the study.

The sponsor noted the following potential User Impairment:

- The PDS290 pen-injector should not be used by people, who are blind or have severe visual problems, but should be assisted by a person who has functional eyesight and is trained to use the PDS290 pen-injector
- Dexterity and freedom to move arm/hand (left or right) to be capable of holding/dialling/dosing the PDS290 pen-injector is required

The testing included use scenarios which can result in potential hazards:
Scenario 1 – The user does not receive the correct insulin due to a mix-up

This scenario includes the hazards where the user does not receive or select his prescribed insulin due to a mix-up, which potentially can lead to medication errors. The hazard can take place when the product is dispensed e.g. at the pharmacy or at product selection in the home environment.
Scenario 2 – The user does not use the pen-injector as described in IFU
This scenario includes the hazards taking place in the normal use environment.

The following table/flowchart shows the methodology for training and testing different user groups.

DEGLUDEC overview of introduction/training and tests

	Children (age 10 to 17) who self inject without a parent's involvement. We are treating children as a distinct user population because their intellectual development and motor skills may be substantially different from adults in ways that could influence how they interact with a pen-injector.		**Adults (age 18 to 64)** who self inject. **Elderly (age 65 and older)** who self inject. Establishing this distinct user group recognises that there might be a substantial difference in the ability of elderly individuals, some of whom might have impairments, to interact effectively with a pen-injector as compared to people who are younger. **Caregivers (age 18 to 64)** who perform injections on others, such as young children, spouses and elderly.				**Healthcare professionals** who provide injection pen prescriptions and teach others how to perform injections. We have placed all of these individuals into a single group because they have clinical training (suggesting good aptitude when it comes to interacting with medication delivery pen injectors) and interact with pen injectors in a professional capacity.				
	Introduced/Trained		**Introduced/Trained**				**Untrained**			**Introduced/ Trained**		**Untrained**		
	Pen naive (non pen users)	**Current pen users**	**Pen naive (non pen users)**		**Current pen users**		**Pen naive (non pen users)**		**Current pen users**	**HCP except pharmacists**		**HCP except pharmacists**		**Pharmacists**
Differentiation														
Introduction to differentiation	X	X	X	X	X	X	No	No	No	No	No	No	No	No
Differentiation test, Pen-injector	X	X	X	X	X	X	No	No	No	No	No	No	X	No
Differentiation test, Carton	X	X	X	X	X	X	No	No	No	No	No	No	X	X
Handling														
Basal... handling	No	X	No	No	X	X	No	X	X	X	X	X	X	No
Forced reading of IFU	No	No	No	X	No	X	X	No	X	No	X	X	No	No
Training, handling	X	X	X	X	X	X	No	No	No	X	X	No	No	No
Handling test	X	X	X	X	X	X	X	X	X	X	X	X	X	No

Review Comments
I have reviewed both documents and have several concerns.

Two separate studies were conducted: user differentiation and user handling. Each study consisted of the same group of 105 participants. Based on the above table, it is not clear why under the adults subgroup, the untrained participants did not undergo the differentiation evaluation. In addition, under the HCP subgroup, the trained HCP did not undergo the differentiation evaluation.

Also, the following items could not be located for review:

- A breakdown of the number of participants for the different user groups, trained and untrained. Include in this breakdown, the number of participants with visual, dexterity, and hearing impairment.
- A rationale for determining who should be receiving training, and who should not among the intended users
- A rationale for (b) (4) is an approach that represents realistic use

The Agency understands that diabetic patients have medical symptoms such as retinopathy and neuropathy, and these symptoms are progressively worsening over time. Therefore, each medical symptom represents unique user profiles that can impact safe and effective use of the product. As a result, the study participants should consist of at least 15 diabetic patients with retinopathy and 15 diabetic patients with neuropathy.

In addition, in reviewing the UT54 final report, version 2, it appears that none of the devices used for the testing was the modified device (b) (4) Flextouch). A discrepancy was also noted between the number of reported errors in the UT54 final report, and summary report (Validation of Device Use).

Regarding the study results for both studies, I have the following specific concerns:

User Differentiation Study:
The study reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions. Two participants had negative transfer from their use experience with other similar products, and one participant could not identify the green color carton.
The study also reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions, and this same participant committed three errors with the previous task of selecting the correct carton.

The Instructions for Use (IFU) does include a statement to have users check the (b) (4) label. Based on the risk analysis if undetected when a patient injects a different type of insulin other than intended, the clinical outcome can be hypoglycemia or hyperglycemia. There are different use scenarios for which this hazard exists. Either the pharmacists/HCP chooses the wrong carton and dispenses to the patients, and the patient does not recognize the wrong insulin carton; or the patient has more than one type of insulin available, and the patient chooses the wrong carton. The results are not clear in terms of which user group (children/adult/cargiver/HCP) the three participants were part of.

It is concerning to the reviewer that not all users are able successfully complete these two tasks and that serious clinical impact can occur. The reviewer is concerned that participants were not able to identify the carton and pen-injector with the correct insulin despite the use of colors and instructions provided in the IFU, and therefore the risks associated with these aspects of use are not successfully mitigated. The reviewer believes that further design optimization can be done the pen label to clearly identify the insulin type, and the dose.

User Handling Study

A discrepancy was noted between the Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) report and test report PDS290-UT54-2011. The test report PDS290-UT54-2011 provided in several tables a listing of different types of injectors (FlexPen, KwikPen, SoloStar), and various baseline tasks. It was not clear if the product used for the final validation study represented the commercial product of the (b) (4) product.

The Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) reported 94 of 105 participants committed 226 errors across tasks associated with delivering an injection and some of the errors resulted in needle-prick injuries. The reviewer is most concerned with the following findings. Of the 105, participants,

- 11 participants did not set the dose correctly for their injection resulting in 12 use errors.
- 9 participants miscalculated second dose when using two pens resulting in 9 use errors.
- 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors
- 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors
- 7 participants either did not remove the needle or reuse the needle resulting in 10 use errors
- 8 participants experienced needle prick injuries resulting in 10 use errors
- 4 participants did not put the cab back on after use resulting in 4 use errors
- 3 participants did not detect blocked needle resulting in 3 use errors

Most of the use errors can result in underdosing, or when users not able to set the correct dose, can result in overdosing. Other use errors can result in needle-prick injuries, contamination, and infection. The sponsor provided some root cause analysis along with the position that the current mitigations are effective and that the residual risks are minimal. However, to fully assess the extent of the use errors, additional clarification is necessary for the following items:

- For the use errors associated with 11 participants did not set the dose correctly for their injection resulting in 12 use errors, the narrative provided in the root cause analysis section was not clear on how the use error occurred among the sequence of use interaction steps, and what "visual feedback" the users received or did not receive from the device. The report indicated that 7 of the use errors occurred after other use errors that previously occurred i.e. users neglected the priming step, or attempted to inject with a blocked needle. It was also not clear if any of the users recognize that a full dose has not been delivered, and what aspect of the device designed allowed them to do so. The sponsor should be asked to provide a side by side comparison of the correct injection sequence versus the sequence for which all of the use errors occurred, and to clearly describe how the user errors occurred along with screen shots of the device status at each of the steps, subjective feedback from users on the root cause of the use errors, and to indicate which of these participants ultimately delivered/did not deliver a correct dose. The sponsor will need to provide a clarification on the "visual feedback" and clarification on the clinical significance of the one participant who injected both a priming dose and a prescribed dose. It appeared that one participant committed the error twice but the report did not provide details on this participant. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence

demonstrating that the device can be used safely and effective. The sponsor should provide a table that clearly describe for each of the use errors, the sponsor should indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement the to device design will not fully mitigate those use related risks.

- For the use errors associated with 9 participants miscalculated second dose when using two pens resulting in 9 use errors, the report indicated that one use error was associated with one 10-year old participant found the instructions to be confusion, failed the split dose task and was assisted by the moderator. A discrepancy was noted in the sponsor's assessment of this use error. The sponsor stated in the report that in real-life situation, a 10 year-old child may perform the injection but never have the full responsibility for insulin administration. However, in the Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011), the sponsor stated that Children (age 10 to 17) are considered as part of the 5 distinct user groups, who self inject without a parent's involvement. Since the report showed that a representative test user in the children subgroup could not successfully perform an injection, and since they represent a group where special considerations should be incorporated in the design of the product, the reviewer recommends that this use-related risk be fully mitigated. In addition, the remaining 8 use errors did not the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. The report remained unclear in terms of which of these participants ultimately delivered/did not deliver a correct dose. The sponsor should be asked to provide information that address the above concerns.
- For the use errors associated with 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors, the reviewer notes that this is a critical task in ensuring that the patients receive a full dose of intended insulin. One participant repeatedly misunderstood the dosing task three times, and believed that by simply activating the dose button but did not hold the dose button down until the dose counter returned to 0. Another participant did not hold the dose button down. While there were only two participants who committed this use error, the clinical impact is significant in that the patients would not receive a full dose. It is also not clear if these two participants held the needle in the skin for the 6 seconds task. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.
- For the use errors associated with 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors, the sponsor indicated that dose accuracy testing showed that a full dose is delivered 1 second after the dose counter returns to "0" with the needle remains in the skin. However, 123 of the 171 use errors, the needle was removed 1 second or more, and 48 of the 171 use errors occurred when the needle was removed less than 1 second, which resulted in underdosing. It is unclear to reviewer why the sponsor specified that the needle should be held in the skin for 6 seconds, but stated that dose accuracy testing demonstrated that a full dose can be delivered 1 second after the dose counter returns to "0." The report did not include the necessary subjective data that are focused on identifying the root cause of the failures and

potential design improvements recommendations from the perspective of representative users. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

- For the use errors associated with 8 participants experienced needle prick injuries resulting in 10 use errors, the reviewer believes that needle prick injuries can result in patient harm during use with the product and requests that the sponsor optimize the IFU and training to minimize the rate of occurrence of needle prick injuries.
- For the use errors associated with 7 participants either did not remove the needle from the device or reuse the needle resulting in 10 use errors, the sponsor stated that these tasks are incorporated in the use of the product to prevent blocked needles, contamination, infection, and inaccurate dosing. Four participants committed 4 use errors in not removing the needle from the device, and 3 participants committed 3 use errors in reusing previously inserted needle. Again, please note that stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. Since these use errors can result in negative impact to the patients, the sponsor should provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.
- For the use errors associated with 4 participants did not put the cab back on after use resulting in 4 use errors, the sponsor stated these errors can result in underdosing. It is not clear how degradation caused by exposure to sunlight due to cap not mounted after use can result in underdosing. Furthermore, it is not clear what is the clinical impact of patients injecting insulin that has been degraded, and how would the patient detect that the insulin has been degraded. The reviewer believes the device user interface can be further optimized to improve use performance.
- For the use errors associated with 3 participants did not detect blocked needle resulting in 3 use errors , the sponsor stated that the resulting harm is that patient may miss a dose. It is not clear if the pen-injector provides any feedback to user in this situation, and whether or not the users recognize that they did not receive any insulin. The sponsor also clarified that the block needle task is an experimental artifact because in real life, the blocked needle only occurs if a patient reuses a needle or uses a defective needle. The testing showed that indeed 3 participants opt to reuse the needles, and therefore it is not an experimental artifact. The sponsor should indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement the to device design will not fully mitigate those use related risks.

The sponsor also reported deviations (page 95 of 102), and close calls (page 96 of 102). While these are "deviations" and "close-calls" that did no result in medical consequences, the sponsor did not discuss how users were able to recognize the potential failures and what steps they took correct themselves. The sponsor should include in their discussion how the design of the device and its labeling influenced the patient's behavior for self-correction.

CDRH Human Factors Recommendations

Two separate studies were conducted: user differentiation and user handling. Each study consisted of the same group of 105 participants. Please address the following for both NDA submissions (NDA 203313 and 203314):

1. Based on the table provided on page 40 of the Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011), it is not clear to the Agency why under the adults subgroup, the untrained participants did not undergo the differentiation evaluation. In addition, under the HCP subgroup, the trained HCP did not undergo the differentiation evaluation.

2. Also, the following items could not be located for review, and should be submitted for review:
   - A breakdown of the number of participants for the different user groups, trained and untrained. Include in this breakdown, the number of participants with visual, dexterity, and hearing impairment.
   - A rationale for determining who should be receiving training, and who should not among the intended users
   - A rationale for why (b) (4) is an approach that represents realistic use

3. The Agency understands that diabetic patients have medical symptoms such as retinopathy and neuropathy, and these symptoms are progressively worsening over time. Provide a justification for why test participants included in the study adequate representation of the intended user group.

Regarding the study results for both studies, please address the following specific concerns:

User Differentiation Study:

4. The study reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions. Two participants had negative transfer from their use experience with other similar products, and one participant could not identify the green color carton. The study also reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions, and this same participant committed three errors with the previous task of selecting the correct carton.

   The Instructions for Use (IFU) does include a statement to have users check the (b) (4) (b) (4) Based on the risk analysis if undetected when a patient injects a different type of insulin other than intended, the clinical outcome can be hypoglycemia or hyperglycemia. There are different use scenarios for which this hazard exists. Either the pharmacists/HCP chooses the wrong carton and dispenses to the patients, and the patient

does not recognize the wrong insulin carton; or the patient has more than one type of insulin available, and the patient chooses the wrong carton. The results are not clear in terms of which user group (children/adult/cargiver/HCP) the three participants were part of.

It is concerning to the Agency that not all users are able successfully complete these two tasks and that serious clinical impact can occur. The Agency is concerned that participants were not able to identify the carton and pen-injector with the correct insulin despite the use of colors and instructions provided in the IFU, and therefore the risks associated with these aspects of use are not successfully mitigated. The Agency believes that further design optimization can be done the pen label to clearly identify the insulin type, and the dose.

User Handling Study

5. A discrepancy was noted between the Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) report and test report PDS290-UT54-2011. The test report PDS290-UT54-2011 provided in several tables a listing of different types of injectors (FlexPen, KwikPen, SoloStar), and various baseline tasks. It was not clear if the product used for the final validation study represented the commercial product of the (b) (4) product.

6. The Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) reported 94 of 105 participants committed 226 errors across tasks associated with delivering an injection and some of the errors resulted in needle-prick injuries. The Agency is most concerned with the following findings. Of the 105, participants,
   - 11 participants did not set the dose correctly for their injection resulting in 12 use errors.
   - 9 participants miscalculated second dose when using two pens resulting in 9 use errors.
   - 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors
   - 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors
   - 7 participants either did not remove the needle or reuse the needle resulting in 10 use errors
   - 8 participants experienced needle prick injuries resulting in 10 use errors
   - 4 participants did not put the cab back on after use resulting in 4 use errors
   - 3 participants did not detect blocked needle resulting in 3 use errors

   Most of the use errors can result in underdosing, or when users not able to set the correct dose, can result in overdosing. Other use errors can result in needle-prick injuries, contamination, and infection. You provided some root cause analysis along with the position that the current mitigations are effective and that the residual risks are minimal. However, to fully assess the extent of the use errors, additional clarification is necessary for the following items:
   a. For the use errors associated with 11 participants did not set the dose correctly for their injection resulting in 12 use errors, the narrative provided in the root cause

analysis section was not clear on how the use error occurred among the sequence of use interaction steps, and what "visual feedback" the users received or did not receive from the device. The report indicated that 7 of the use errors occurred after other use errors that previously occurred i.e. users neglected the priming step, or attempted to inject with a blocked needle. It was also not clear if any of the users recognize that a full dose has not been delivered, and what aspect of the device designed allowed them to do so. Please address the above concerns and provide a side by side comparison of the correct injection sequence versus the sequence for which all of the use errors occurred, and to clearly describe how the user errors occurred along with screen shots of the device status at each of the steps, subjective feedback from users on the root cause of the use errors, and to indicate which of these participants ultimately delivered/did not deliver a correct dose. Please also provide a clarification on the "visual feedback" and clarification on the clinical significance of the one participant who injected both a priming dose and a prescribed dose. It appeared that one participant committed the error twice but the report did not provide details on this participant. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective.

b. For the use errors associated with 9 participants miscalculated second dose when using two pens resulting in 9 use errors, the report indicated that one use error was associated with one 10-year old participant found the instructions to be confusion, failed the split dose task and was assisted by the moderator. A discrepancy was noted in your assessment of this use error. You stated in the report that in real-life situation, a 10 year-old child may perform the injection but never have the full responsibility for insulin administration. However, in the Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011), you stated that Children (age 10 to 17) are considered as part of the 5 distinct user groups, who self inject without a parent's involvement. Since the report showed that a representative test user in the children subgroup could not successfully perform an injection, and since they represent a group where special considerations should be incorporated in the design of the product, the reviewer recommends that this use-related risk be fully mitigated. In addition, the remaining 8 use errors did not the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. The report remained unclear in terms of which of these participants ultimately delivered/did not deliver a correct dose. Please provide additional information that addresses the above concerns.

c. For the use errors associated with 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors, the Agency notes that this is a critical task in ensuring that the patients receive a full dose of intended insulin. One participant repeatedly misunderstood the dosing task three times, and believed that by simply activating the dose button but did not hold the dose button down until the dose counter returned to 0. Another participant did not hold

the dose button down. While there were only two participants who committed this use error, the clinical impact is significant in that the patients would not receive a full dose. It is also not clear if these two participants held the needle in the skin for the 6 seconds task. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

d. For the use errors associated with 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors, you indicated that dose accuracy testing showed that a full dose is delivered 1 second after the dose counter returns to "0" with the needle remains in the skin. However, 123 of the 171 use errors, the needle was removed 1 second or more, and 48 of the 171 use errors occurred when the needle was removed less than 1 second, which resulted in underdosing. It is unclear to reviewer why the sponsor specified that the needle should be held in the skin for 6 seconds, but stated that dose accuracy testing demonstrated that a full dose can be delivered 1 second after the dose counter returns to "0." The report did not include the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.
e. For the use errors associated with 8 participants experienced needle prick injuries resulting in 10 use errors, the Agency is concerned with needle prick injuries associated with the use of this product and requests that you optimize the design and/or IFU and training to minimize the rate of occurrence of needle prick injuries.
f. For the use errors associated with 7 participants either did not remove the needle from the device or reuse the needle resulting in 10 use errors, you stated that these tasks are incorporated in the use of the product to prevent blocked needles, contamination, infection, and inaccurate dosing. Four participants committed 4 use errors in not removing the needle from the device, and 3 participants committed 3 use errors in reusing previously inserted needle. Again, please note that stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. Since these use errors can result in negative impact to the patients, please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

g. For the use errors associated with 4 participants did not put the cab back on after use resulting in 4 use errors, the sponsor stated these errors can result in underdosing. It is not clear how degradation caused by exposure to sunlight due to cap not mounted after use can result in underdosing. Furthermore, it is not clear what is the clinical impact of patients injecting insulin that has been degraded, and how would the patient detect that the insulin has been degraded. The Agency believes the device user interface can be further optimized to improve use performance.

h. For the use errors associated with 3 participants did not detect blocked needle resulting in 3 use errors , you stated that the resulting harm is that patient may miss a dose. It is not clear if the pen-injector provides any feedback to user in this situation, and whether or not the users recognize that they did not receive any insulin. You also provided a clarification that the block needle task is an experimental artifact because in real life, the blocked needle only occurs if a patient reuses a needle or uses a defective needle. The testing showed that indeed 3 participants opt to reuse the needles, and therefore it is not an experimental artifact. Please indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement the to device design will not fully mitigate those use related risks.

i. You also reported deviations (page 95 of 102), and close calls (page 96 of 102). While these are "deviations" and "close-calls" that did no result in medical consequences, you did not provide a discussion of how users were able to recognize the potential failures and what steps they took correct themselves. Please provide in your discussion how the design of the device and its labeling influenced the patient's behavior for self-correction.

7. Please note that the Agency expects to review a report of the human factors/usability evaluation and validation testing with any pattern of use errors, and a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions can be determined based on the test results. At this time, the Agency is concerned with that your testing did not provide the level of evidence to conclude that the device can be used safely and effectively. The Agency recommends that you take the results of these evaluations and use them to further optimize the training, IFU and/or device user interface so that use errors are effectively minimized. Please note that improvements should be demonstrated through focused HF/usability validation.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management,* available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm.

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.

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/s/

RACHEL E HARTFORD
03/30/2012
on behalf of QuynhNhu Nguyen
Biomedical Engineer/Human Factors Reviewer
CDRH/ODE/DAGID

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Human Factors (Usability Study) Protocol Review

Date:	March 30, 2012
Reviewer:	Richard A Abate, RPh, MS, Safety Evaluator Division of Medication Error Prevention and Analysis
Deputy Director:	Kellie Taylor, PharmD, MPH Division of Medication Error Prevention and Analysis
Drug Name(s):	Ryzodeg (70% Insulin Degludec and 30% Insulin Aspart [rDNA origin]), 100 units/mL (U-100) FlexTouch Pen and Tresiba (Insulin Degludec [rDNA origin]) Injection, 100 units/mL (U-100) and 200 units/mL (U-200) FlexTouch Pen
Application Type/Number:	NDA 203313 (Ryzodeg) NDA 203314 (Tresiba)
Applicant:	NovoNordisk, Inc.
OSE RCM#:	2012-701

1 INTRODUCTION

This memo summarizes the Division of Medication Error Prevention and Analysis' (DMEPA's) evaluation of the protocol for a summative Usability Study for the PDS290 (FlexTouch Pen) to be used for the administration of Insulin Degludec containing products as proposed in NDAs 203313 (Ryzodeg) and 203314 (Tresiba). The protocol was submitted as an amendment to both NDAs on February 16, 2012. Novo Nordisk submitted the protocol for this user handling usabilty study in response to comments provided by the Office of Device Evaluation (ODE) in Center for Device and Radiological Health (CDRH) in a letter December 23, 2011. The intended objective of the usability study described in the protocol is to validate that the PDS290 pen injector can be used safely and effectively by the intended users, uses, and use conditions.

1.1 REGULATORY HISTORY

The pen injector (PDS290) was included as the FlexTouch Pen presentation for Ryzodeg (70% Insulin Degludec and 30% Insulin Aspart [rDNA origin]), 100 units/mL (U-100) in NDA 203313 and Tresiba (Insulin Degludec [rDNA origin]) Injection, 100 units/mL (U-100) and 200 units/mL (U-200) in NDA 203314. NovoNordisk submitted data from two summative usability studies in support of these applications with their NDAs submissions on September 29, 2011. Usability Study PDS290-UT54-2011 (UT54) is a user handling study, and Usability Study PDS290-UT59-2011 is a user differentiation study. CDRH\ODE\DGAID Human Factors Team provided comments for both studies noting needed improvements. Additionally, CDRH completed their review of the PDS290 pen injector and found it to be not in compliance with ISO standard 111608-1. The Applicant was notified of these findings March 20, 2012.

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the protocol for PDS290-UT86-2012 (UT86) submitted on February 16, 2012. In addition, we considered CDRH's comments forwarded to the Applicant on December 23, 2011 (See Appendix A) as well as the comments and response that CDRH provided to this protocol on March 20, 2012.

3 RESULTS AND DISCUSSION

We provide our findings for the protocol and a discussion for these findings in the following sections.

3.1 INTENDED USERS OF PDS290 AND TEST PARTICIPANTS

The protocol for UT86 includes only patient user groups and omits inpatient nurses as a defined user for this disposable pen-injector (PDS290). We note the protocol describes the intended users of the PDS290 with Ryzodeg and Tresiba are patients who self-administer insulins, caregivers who administer the insulin to a family member in the home, or a healthcare provider who interact with this device by teaching patients to perform injections similar to the participants in UT54. Additionally, the Risk Management Analysis noted the inpatient setting as a secondary setting and thus omitted the inpatient nurse as an intended user. However, hospitals use pen-injectors to

administer insulin to patients in current practice making inpatient nurses an end user for the PDS290. In addition, Ryzodeg and Tresiba both lack a vial presentation for nurses to utilize when administering these medications. Therefore, inpatient nurses will have no alternative but to use the PDS290 to administer these medications when prescribed to hospitalized patients.

In addition, the submitted protocol notes that there was no appreciable difference in the type and frequency of use errors between patients versus caregivers and healthcare professionals during completed user handling study UT54 as a rationale for only including the patient user groups of Children, Adults, and Elderly in this study. However, DMEPA disagrees with limiting the user groups to those proposed. The types and frequency of errors observed does not mean the results of one user group are necessarily representative of another user group. An inpatient nurse user group should be included in future user handling studies for this device when used with insulin products.

Finally, the inpatient nurse user group must include participants that are untrained and trained on the use of the PDS290 prior to complete any use tasks. Although hospitals often require competency with new device prior to use, the similarity of this pen injector to the marketed FlexPen and other disposable insulin pen injectors may cause nurses to mistakenly believe it is not any difference in the delivery of insulin and not require additional training prior to use. Thus, inpatient nurses encounter the PDS290 in practice with or without receiving training. This concern was not noted by CDRH.

3.2 TRAINING OF PARTICIPANTS

(b) (4)

. This is problematic because patients will not always read IFUs before using pen devices in actual use of your product. This concern was also noted by CDRH.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that revisions to the protocol are needed with respect to the user groups included and the training of participants. Specifically, DMEPA concludes that a key user group, inpatient nurses, has been omitted as a defined user for the PDS290 pen injector in the Risk Management Analysis and the user handling study. This concern was not identified by CDRH. This user group should be included in usability studies moving forward until it is demonstrated this user group can safely and effectively use the PDS290 for the administration of insulin products. Additionally, DMEPA concludes that

(b) (4)

. This concern was also shared by CDRH. DMEPA provides the following comments for the Applicant:

A. Human Factors Study Protocol (PDS290-UT86-2012)

1. Your participant groups do not include any inpatient nursing staff. Please include a user group at least 15 inpatient nurses (not CDE or DE) in any future studies, Nurses are a user group for the PDS290 device because hospitals use pen injectors to administer insulin to patients in current

practice. Additionally, evaluate these HCP participants both trained and untrained.

2. With the exception of the Children user group, include an equal number of trained and untrained participants (who are not required to read the IFU) in each user group. (b) (4)

APPENDICES

Appendix A: CDRH comments regarding the user handling study UT-54 and user differentiation study (UT-59)

Regarding the study results for both studies, please address the following specific concerns:

User Differentiation Study:

1. The study reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions. Two participants had negative transfer from their use experience with other similar products, and one participant could not identify the green color carton. The study also reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions, and this same participant committed three errors with the previous task of selecting the correct carton.

   The Instructions for Use (IFU) does include a statement to have users (b) (4) . Based on the risk analysis if undetected when a patient injects a different type of insulin other than intended, the clinical outcome can be hypoglycemia or hyperglycemia. There are different use scenarios for which this hazard exists. Either the pharmacists/HCP chooses the wrong carton and dispenses to the patients, and the patient does not recognize the wrong insulin carton; or the patient has more than one type of insulin available, and the patient chooses the wrong carton. The results are not clear in terms of which user group (children/adult/caregiver/HCP) the three participants were part of.

   It is concerning to the Agency that not all users are able successfully complete these two tasks and that serious clinical impact can occur. The Agency is concerned that participants were not able to identify the carton and pen-injector with the correct insulin despite the use of colors and instructions provided in the IFU, and therefore the risks associated with these aspects of use are not successfully mitigated. The Agency believes that further design optimization can be done the pen label to clearly identify the insulin type, and the dose.

User Handling Study

2. A discrepancy was noted between the Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) report and test report PDS290-UT54-2011. The test report PDS290-UT54-2011 provided in several tables a listing of different types of injectors (FlexPen, KwikPen, SoloStar), and various baseline tasks. It was not clear if the product used for the final validation study represented the commercial product of the (b) (4) product.
3. The Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) reported 94 of 105 participants committed 226 errors across tasks associated with delivering an injection and some of the errors resulted in needle-prick injuries.

The Agency is most concerned with the following findings. Of the 105, participants,

- 11 participants did not set the dose correctly for their injection resulting in 12 use errors.
- 9 participants miscalculated second dose when using two pens resulting in 9 use errors.
- 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors
- 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors
- 7 participants either did not remove the needle or reuse the needle resulting in 10 use errors
- 8 participants experienced needle prick injuries resulting in 10 use errors
- 4 participants did not put the cab back on after use resulting in 4 use errors
- 3 participants did not detect blocked needle resulting in 3 use errors

Most of the use errors can result in underdosing, or when users not able to set the correct dose, can result in overdosing. Other use errors can result in needle-prick injuries, contamination, and infection. You provided some root cause analysis along with the position that the current mitigations are effective and that the residual risks are minimal. However, to fully assess the extent of the use errors, additional clarification is necessary for the following items:

a. For the use errors associated with 11 participants did not set the dose correctly for their injection resulting in 12 use errors, the narrative provided in the root cause analysis section was not clear on how the use error occurred among the sequence of use interaction steps, and what "visual feedback" the users received or did not receive from the device. The report indicated that 7 of the use errors occurred after other use errors that previously occurred i.e. users neglected the priming step, or attempted to inject with a blocked needle. It was also not clear if any of the users recognize that a full dose has not been delivered, and what aspect of the device designed allowed them to do so. Please address the above concerns and provide a side by side comparison of the correct injection sequence versus the sequence for which all of the use errors occurred, and to clearly describe how the user errors occurred along with screen shots of the device status at each of the steps, subjective feedback from users on the root cause of the use errors, and to indicate which of these participants ultimately delivered/did not deliver a correct dose. Please also provide a clarification on the "visual feedback" and clarification on the clinical significance of the one participant who injected both a priming dose and a prescribed dose. It appeared that one participant committed the error twice but the report did not provide details on this participant. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective.

b. For the use errors associated with 9 participants miscalculated second dose when using two pens resulting in 9 use errors, the report indicated that one use error was associated with one 10-year old participant found the instructions to be confusion, failed the split dose task and was assisted by the moderator. A discrepancy was noted in your assessment of this use error. You stated in the report that in real-life situation, a 10 year-old child may perform the injection but never have the full responsibility for insulin administration. However, in the Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011), you stated that Children (age 10 to 17) are considered as part of the 5 distinct user groups, who self inject without a parent's involvement. Since the report showed that a representative test user in the children subgroup could not successfully perform an injection, and since they represent a group where special considerations should be incorporated in the design of the product, the reviewer recommends that this use-related risk be fully mitigated. In addition, the remaining 8 use errors did not the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. The report remained unclear in terms of which of these participants ultimately delivered/did not deliver a correct dose. Please provide additional information that addresses the above concerns.

c. For the use errors associated with 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors, the Agency notes that this is a critical task in ensuring that the patients receive a full dose of intended insulin. One participant repeatedly misunderstood the dosing task three times, and believed that by simply activating the dose button but did not hold the dose button down until the dose counter returned to 0. Another participant did not hold the dose button down. While there were only two participants who committed this use error, the clinical impact is significant in that the patients would not receive a full dose. It is also not clear if these two participants held the needle in the skin for the 6 seconds task. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

d. For the use errors associated with 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors, you indicated that dose accuracy testing showed that a full dose is delivered 1 second after the dose counter returns to "0" with the needle remains in the skin. However, 123 of the 171 use errors, the needle was removed 1 second or more, and 48 of the 171 use errors occurred when the needle was removed less than 1 second, which resulted in underdosing. It is unclear to reviewer why the sponsor specified that the needle should be held in the skin for 6 seconds, but stated that dose accuracy testing demonstrated that a full dose can be delivered 1 second after the dose

counter returns to "0." The report did not include the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

e. For the use errors associated with 8 participants experienced needle prick injuries resulting in 10 use errors, the Agency is concerned with needle prick injuries associated with the use of this product and requests that you optimize the design and/or IFU and training to minimize the rate of occurrence of needle prick injuries.
f. For the use errors associated with 7 participants either did not remove the needle from the device or reuse the needle resulting in 10 use errors, you stated that these tasks are incorporated in the use of the product to prevent blocked needles, contamination, infection, and inaccurate dosing. Four participants committed 4 use errors in not removing the needle from the device, and 3 participants committed 3 use errors in reusing previously inserted needle. Again, please note that stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. Since these use errors can result in negative impact to the patients, please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.
g. For the use errors associated with 4 participants did not put the cab back on after use resulting in 4 use errors, the sponsor stated these errors can result in underdosing. It is not clear how degradation caused by exposure to sunlight due to cap not mounted after use can result in underdosing. Furthermore, it is not clear what is the clinical impact of patients injecting insulin that has been degraded, and how would the patient detect that the insulin has been degraded. The Agency believes the device user interface can be further optimized to improve use performance.
h. For the use errors associated with 3 participants did not detect blocked needle resulting in 3 use errors , you stated that the resulting harm is that patient may miss a dose. It is not clear if the pen-injector provides any feedback to user in this situation, and whether or not the users recognize that they did not receive any insulin. You also provided a clarification that the block needle task is an experimental artifact because in real life, the blocked needle only occurs if a patient reuses a needle or uses a defective

needle. The testing showed that indeed 3 participants opt to reuse the needles, and therefore it is not an experimental artifact. Please indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement the to device design will not fully mitigate those use related risks.

i. You also reported deviations (page 95 of 102), and close calls (page 96 of 102). While these are "deviations" and "close-calls" that did no result in medical consequences, you did not provide a discussion of how users were able to recognize the potential failures and what steps they took correct themselves. Please provide in your discussion how the design of the device and its labeling influenced the patient's behavior for self-correction.

Please note that the Agency expects to review a report of the human factors/usability evaluation and validation testing with any pattern of use errors, and a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions can be determined based on the test results. At this time, the Agency is concerned with that your testing did not provide the level of evidence to conclude that the device can be used safely and effectively. The Agency recommends that you take the results of these evaluations and use them to further optimize the training, IFU and/or device user interface so that use errors are effectively minimized. Please note that improvements should be demonstrated through focused HF/usability validation.

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/s/

RICHARD A ABATE
03/30/2012

KELLIE A TAYLOR
03/30/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: March 6, 2012
From: Jacqueline Ryan, Combination Products Team Leader, WO66, RM 1257
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Rachel Hartford, Regulatory Project Manager, CDER/ DMEP
Subject: CDRH Consult, NDA 203313, PDS290Pen injector to deliver Ryzodeg® (insulin degludec and aspart)

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 203313. The device constituent of this combination product consists of the PDS290 Pen injector to deliver Ryzodeg® (insulin degludec and aspart)

2. Device Description

The PDS290 Pen injector is a prefilled disposable pen injector which, according to the sponsor is based on the FlexPen®. Improvements were made for readability of the dose counter, larger inspection window, no protrusion of dose button, less dose force, more ergonomic grip, improved dose delivery and easier needle handling.

3. Documents Reviewed

NDA 203313

4. CDRH Review and Comments

Sponsor's comments:
Four dose accuracy tests, measuring the dose delivered as a function of time, have been carried out as described in ISO 11608-1. For all tests, the actual delivered dose was recorded at the time 0, 1, 2, 3, 4, 5 and 6 seconds after the scale on the dose counter had returned to "0".
The PDS290 pen-injectors were tested at three temperatures 5°C, 20°C, and 40°C to account for temperature induced changes in viscosity. The test shows that from the time "one second" to "six seconds" after the scale drum has returned to "0", all results comply with ISO 11608-1:2000.
At the time 0 seconds after the scale drum has returned to "0", corresponding to the user withdrawing the needle immediately as the drum returns to "0", the results with the biggest deviation from the intended dose are as follows:

Worst case scenario test results which may lead to an underdose:
Intended dose 40 units, delivered at 40°C:
31.9 units delivered at the time 0 -missing 20.4% of set dose
Intended dose 80 units, delivered at 40°C:

64.9 units delivered at the time 0- missing 18.9 % of set dose

Reviewer's comment:
The dose accuracy testing submitted does not comply with ISO 111608-1, Pen-Injectors for medical use-Part 1: Pen-injectors- Requirements and test methods. This standard requires that the "Pen injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed." (b) (4)

5. CDRH Recommendation

The following deficiency should be relayed to the sponsor:

The dose accuracy testing submitted does not comply with ISO 111608-1, Pen-Injectors for medical use-Part 1: *Pen-injectors- Requirements and test methods.* This standard requires that the "Pen injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed." (b) (4) CDRH does not believe that this dosing accuracy failure can be or should be mitigated by labeling. You should provide a drug delivery device which is ISO 11608-1 compliant.

If you have any questions, please contact Jacqueline Ryan at 301-796-9599.

Sincerely,

Jacqueline Ryan
Combination Products Team Leader, GHDB

Concurred By:

Richard Chapman
Branch Chief, GHDB

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/s/

RACHEL E HARTFORD
03/06/2012
On behalf of Jackie Ryan, CDRH

03/06/12

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: March 6, 2012
From: Jacqueline Ryan, Combination Products Team Leader, WO66, RM 1257
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Rachel Hartford, Regulatory Project Manager, CDER/ DMEP
Subject: CDRH Consult, NDA 203314, PDS290Pen injector to deliver Tresiba® (insulin degludec)

1. **Issue**

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 203314. The device constituent of this combination product consists of the PDS290 Pen injector to deliver Tresiba® (insulin degludec.)

2. **Device Description**

The PDS290 Pen injector is a prefilled disposable pen injector which, according to the sponsor is based on the FlexPen®. Improvements were made for readability of the dose counter, larger inspection window, no protrusion of dose button, less dose force, more ergonomic grip, improved dose delivery and easier needle handling.

3. **Documents Reviewed**
NDA 203314

4. **CDRH Review and Comments**
Sponsor's comments:
Four dose accuracy tests, measuring the dose delivered as a function of time, have been carried out as described in ISO 11608-1. For all tests, the actual delivered dose was recorded at the time 0, 1, 2, 3, 4, 5 and 6 seconds after the scale on the dose counter had returned to "0".
The PDS290 pen-injectors were tested at three temperatures 5°C, 20°C, and 40°C to account for temperature induced changes in viscosity. The test shows that from the time "one second" to "six seconds" after the scale drum has returned to "0", all results comply with ISO 11608-1:2000.
At the time 0 seconds after the scale drum has returned to "0", corresponding to the user withdrawing the needle immediately as the drum returns to "0", the results with the biggest deviation from the intended dose are as follows:

Worst case scenario test results which may lead to an underdose:
Intended dose 40 units, delivered at 40°C:
31.9 units delivered at the time 0 -missing 20.4% of set dose
Intended dose 80 units, delivered at 40°C:

64.9 units delivered at the time 0- missing 18.9 % of set dose

Reviewer's comment:
The dose accuracy testing submitted does not comply with ISO 111608-1, Pen-Injectors for medical use-Part 1: Pen-injectors- Requirements and test methods. This standard requires that the "Pen injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed." (b) (4)

5. **CDRH Recommendation**
The following deficiency should be relayed to the sponsor:

The dose accuracy testing submitted does not comply with ISO 111608-1, Pen-Injectors for medical use-Part 1: *Pen-injectors- Requirements and test methods.* This standard requires that the "Pen injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed." (b) (4)

CDRH does not believe that this dosing accuracy failure can be or should be mitigated by labeling. You should provide a drug delivery device which is ISO 11608-1 compliant.

If you have any questions, please contact Jacqueline Ryan at 301-796-9599.

Sincerely,

Jacqueline Ryan
Combination Products Team Leader, GHDB

Concurred By:

Richard Chapman
Branch Chief, GHDB

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/s/

RACHEL E HARTFORD
03/06/2012
On behalf of Jackie Ryan, CDRH

01/03/12

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE:	**December 8, 2011**
FROM:	QuynhNhu Nguyen, BS, Biomedical Engineer/Human Factors Reviewer, DAGID
THROUGH:	Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, DAGID
	Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID
TO:	Jackie Ryan, Combination Products Team Leader, CDRH/ODE/DAGID/GHDB
SUBJECT:	NDAs 203313 and 203314, **Ryzodeg (Insulin) Pen Injector, Novo Nordisk**
	Project Manager: Rachel Hartford
CTS Consult:	GEN1101027/CON1118169 - Human Factors/Usability Review

Per your request, I have reviewed the Human Factors information contained in this submission. I have identified 7 requests for additional information. See page 12 under Recommendation.

Review Memo - Table of Content

Review of Applicant's Evaluation of Human Factors Report (Dated June 29, 2011)

Review Materials

Links to submissions:
\\CDSESUB5\EVSPROD\NDA203314\203314.enx
\\CDSESUB5\EVSPROD\NDA203313\203313.enx
Sequence 0000 (original submission, part 1, quality, 3.2.P drug product, 3.2.P.7. Container Closure System)

Review

Device Description

Insulin degludec is an ultra-long-acting basal insulin. Insulin degludec is intended for treatment of diabetes mellitus. Insulin degludec is administered once-daily at any time of the day, independent of meals, and is injected subcutaneously (s.c.) in the thigh, the upper arm or the abdominal wall.

For patients with type 2 diabetes mellitus, the recommended daily starting dose of insulin degludec is 10 units, followed by individual dosage adjustments. For patients with type 1 diabetes mellitus, insulin degludec is to be used once-daily with meal-time insulin and requires subsequent individual dosage adjustments. Insulin degludec has been developed in two strengths as insulin degludec 100 U/ml and insulin degludec 200 U/ml.

- Insulin degludec 100 U/ml is intended to be marketed (b) (4), (b) (4) as a pre-filled disposable PDS290 pen-injector with a dose range of 1-80 U/injection, which can be dialled in 1 U increments.
- Insulin degludec 200 U/ml is intended for the market in a pre-filled disposable PDS290 pen-injector with a dose range of 2-160 U/injection, which can be dialled in 2 U increments.

Volume and Strength

Formulation	Total volume in cartridge	Strength	Total units available in presentation	Max dose per injection	Dose increment
Insulin Degludec U100	3 mL	100 U/mL	300 U	80 U	1 U
Insulin Degludec U200	3 mL	200 U/mL	600 U	160 U	2 U
Insulin Degludec/Insulin Aspart	3 mL	100 U/mL	300 U	80 U	1 U

(b) (4)

Figure 1: Insulin Degludec (100 U/mL) pen-injector (left), Insulin Degludec(200 U/mL) peninjector (centre) and Insulin Degludec/Insulin Aspart (100 U/mL) pen-injector (right). Pens are shown without caps.

PDS290 is a pen-shaped, prefilled device containing a 3 ml cartridge with insulin. Therefore the drug is not in contact with the device. The device is intended to function with a (b) (4) needle (b) (4) The PDS290-pen injector is currently approved by FDA for use with growth hormone (Norditropin FlePro).

PDS290 physical characteristics:

(b) (4)

PDS290 was developed to fulfil the international standard for drug injectors, ISO 11608-1 (Peninjectors for medical use - Part1: Requirements and test methods).
The design of the pen-injector enables the users to always have a display of the chosen amount of insulin units selected for injection, independent of drug concentration.

The PDS290 is different than the FlexPen regarding the following features:

(b) (4)
(b) (4)

Figure 2: PDS290 Pen Injector

Figure 3: Currently marketed FlexPen

Compared to FlexPen®, some of the new features of the PDS290 pen-injector are:

(b) (4)

- Improved ergonomic pen design – shorter and wider pen
- Different click sound when dialling back (compared to dialling forward)

(b) (4)

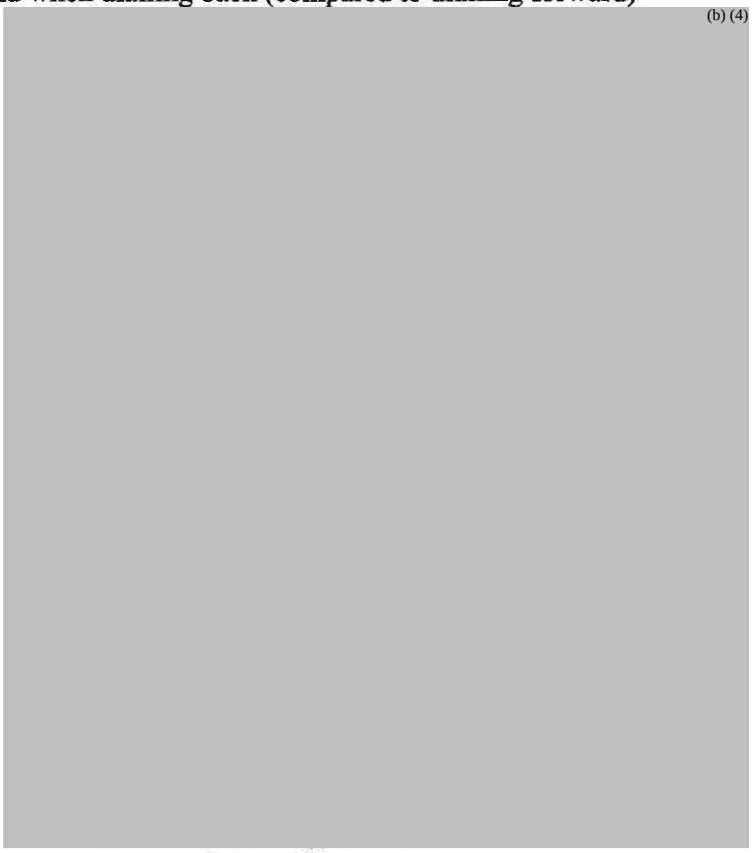

Figure 4: Exploded View of Internal Device Components

Summary of Human Factors Information

The sponsor submitted two main documents for Human Factors review:

- Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011)
- Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011)

The device will be used in the home environment and hospital setting. Training is required for use with the product including identifying insulin variant(s). Once prescribed, the users can inject themselves or are injected by a caregiver.

To prepare the pen-injector, a new needle is mounted by the user and the pen-injector is primed, thereafter the intended dose is set by rotating the dose selector clockwise (when looking directly at the PDS290 pen-injectors' dose button) until the required dose is visible in the display. The dose button does not protrude from the PDS290 pen-injector when dialling the dose selector. Dose delivery is accomplished by inserting the needle subcutaneously and pressing the dose button. During dose delivery, the PDS290 pen-injector (b) (4) A distinct end-of-dose-click indicates when the display has returned to

"0" (The clicks are only a supportive feedback). The full dose is delivered when the needle has been kept inserted into the skin at least 6 seconds after the display has returned to "0". The "6 second" duration is a conservative approach, and that exact duration is not safety critical, from a medical perspective provided that the timing is kept below 6 seconds, as the PDS290 pen-injector is within the dosage requirements, in accordance with ISO 11608-1 before the "6 second" duration.

When performing an injection with the PDS290 pen-injector, the following user steps/primary operation functions must be carried out.

- Step 1: Pick the correct PDS290 carton/pen-injector with the intended insulin product
- Step 2: Cap removal
- Step 3: Verification via label and cartridge holder that it is the correct pen
- Step 4: Check that the insulin in the pen-injector is clear and colourless
- Step 5: Needle mounting
- Step 6: Checking the insulin flow (priming)
- Step 7: Setting intended dose (reversing the dose setting, if necessary)
- Step 8: Understand the End-of-content indication (feature ensuring that no larger dose can be dialled than is left in the cartridge)
    - This step only applies if the user is going to inject a dose larger than the remaining left in cartridge
- Step 9: Subcutaneous needle insert
- Step 10: Injecting the dose, including checking that scale drum returns to "0", and 6 seconds waiting time with needle in the skin, that is, full dose has been delivered
- Step 11: Needle removal and disposal of used needle
- Step 12: Cap mounting

The intended users of the pen-injector include patients, caregivers and healthcare professionals. There are five distinct user groups:

- Children (age 10 to 17) who self inject without a parent's involvement. 15 participants were included in the study.
- Adults (age 18 to 64) who self-inject. 25 participants were included in the study.
- Elderly (age 65 and older) who self-inject. 21 participants were included in the study.
- Caregivers (age 18 to 64) who perform injections on others, such as young children, spouses and elderly. 22 participants were included in the study.
- Healthcare professionals who provide injection pen prescriptions and teach others how to perform injections. 22 participants were included in the study.

The sponsor noted the following potential User Impairment:

- The PDS290 pen-injector should not be used by people, who are blind or have severe visual problems, but should be assisted by a person who has functional eyesight and is trained to use the PDS290 pen-injector
- Dexterity and freedom to move arm/hand (left or right) to be capable of holding/dialling/dosing the PDS290 pen-injector is required

The testing included use scenarios which can result in potential hazards:
Scenario 1 – The user does not receive the correct insulin due to a mix-up
This scenario includes the hazards where the user does not receive or select his prescribed insulin due to a mix-up, which potentially can lead to medication errors. The hazard can take place when the product is dispensed e.g. at the pharmacy or at product selection in the home environment.
Scenario 2 – The user does not use the pen-injector as described in IFU
This scenario includes the hazards taking place in the normal use environment.

The following table/flowchart shows the methodology for training and testing different user groups.

DEGLUDEC overview of introduction/training and tests

	Children (age 10 to 17) who self inject without a parent's involvement. We are treating children as a distinct user population because their intellectual development and motor skills may be substantially different from adults in ways that could influence how they interact with a pen-injector.		**Adults (age 18 to 64)** who self inject. **Elderly (age 65 and older)** who self inject. Establishing this distinct user group recognises that there might be a substantial difference in the ability of elderly individuals, some of whom might have impairments, to interact effectively with a pen-injector as compared to people who are younger. **Caregivers (age 18 to 64)** who perform injections on others, such as young children, spouses and elderly.							**Healthcare professionals** who provide injection pen prescriptions and teach others how to perform injections. We have placed all of these individuals into a single group because they have clinical training (suggesting good aptitude when it comes to interacting with medication delivery pen injectors) and interact with pen injectors in a professional capacity.				
	Introduced/Trained		**Introduced/Trained**				**Untrained**			**Introduced/ Trained**		**Untrained**		
	Pen naive (non pen users)	**Current pen users**	**Pen naive (non pen users)**		**Current pen users**		**Pen naive (non pen users)**	**Current pen users**		**HCP except pharmacists**		**HCP except pharmacists**		**Pharmacists**
Differentiation														
Introduction to differentiation	X	X	X	X	X	X	No	No	No	No	No	No	No	No
Differentiation test, Pen-injector	X	X	X	X	X	X	No	No	No	No	No	No	X	No
Differentiation test, Carton	X	X	X	X	X	X	No	No	No	No	No	No	X	X
Handling														
Baseline, handling	No	X	No	No	X	X	No	X	X	X	X	X	X	No
Forced reading of IFU	No	No	No	X	No	X	X	No	X	No	X	X	No	No
Training, handling	X	X	X	X	X	X	No	No	No	X	X	No	No	No
Handling test	X	X	X	X	X	X	X	X	X	X	X	X	X	No

Review Comments
I have reviewed both documents and have several concerns.

Two separate studies were conducted: user differentiation and user handling. Each study consisted of the same group of 105 participants. Based on the above table, it is not clear why under the adults subgroup, the untrained participants did not undergo the differentiation evaluation. In addition, under the HCP subgroup, the trained HCP did not undergo the differentiation evaluation.

Also, the following items could not be located for review:

- A breakdown of the number of participants for the different user groups, trained and untrained. Include in this breakdown, the number of participants with visual, dexterity, and hearing impairment.
- A rationale for determining who should be receiving training, and who should not among the intended users
- A rationale for (b) (4) is an approach that represents realistic use

The Agency understands that diabetic patients have medical symptoms such as retinopathy and neuropathy, and these symptoms are progressively worsening over time. Therefore, each medical symptom represents unique user profiles that can impact safe and effective use of the product. As a result, the study participants should consist of at least 15 diabetic patients with retinopathy and 15 diabetic patients with neuropathy.

In addition, in reviewing the UT54 final report, version 2, it appears that none of the devices used for the testing was the modified device (b) (4) Flextouch). A discrepancy was also noted between the number of reported errors in the UT54 final report, and summary report (Validation of Device Use).

Regarding the study results for both studies, I have the following specific concerns:

User Differentiation Study:
The study reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions. Two participants had negative transfer from their use experience with other similar products, and one participant could not identify the green color carton.
The study also reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions, and this same participant committed three errors with the previous task of selecting the correct carton.

The Instructions for Use (IFU) does include a statement to have users check the (b) (4) label. Based on the risk analysis if undetected when a patient injects a different type of insulin other than intended, the clinical outcome can be hypoglycemia or hyperglycemia. There are different use scenarios for which this hazard exists. Either the pharmacists/HCP chooses the wrong carton and dispenses to the patients, and the patient does not recognize the wrong insulin carton; or the patient has more than one type of insulin available, and the patient chooses the wrong carton. The results are not clear in terms of which user group (children/adult/cargiver/HCP) the three participants were part of.

It is concerning to the reviewer that not all users are able successfully complete these two tasks and that serious clinical impact can occur. The reviewer is concerned that participants were not able to identify the carton and pen-injector with the correct insulin despite the use of colors and instructions provided in the IFU, and therefore the risks associated with these aspects of use are

not successfully mitigated. The reviewer believes that further design optimization can be done the pen label to clearly identify the insulin type, and the dose.

User Handling Study
A discrepancy was noted between the Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) report and test report PDS290-UT54-2011. The test report PDS290-UT54-2011 provided in several tables a listing of different types of injectors (FlexPen, KwikPen, SoloStar), and various baseline tasks. It was not clear if the product used for the final validation study represented the commercial product of the (b) (4) product.

The Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) reported 94 of 105 participants committed 226 errors across tasks associated with delivering an injection and some of the errors resulted in needle-prick injuries. The reviewer is most concerned with the following findings. Of the 105, participants,

- 11 participants did not set the dose correctly for their injection resulting in 12 use errors.
- 9 participants miscalculated second dose when using two pens resulting in 9 use errors.
- 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors
- 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors
- 7 participants either did not remove the needle or reuse the needle resulting in 10 use errors
- 8 participants experienced needle prick injuries resulting in 10 use errors
- 4 participants did not put the cab back on after use resulting in 4 use errors
- 3 participants did not detect blocked needle resulting in 3 use errors

Most of the use errors can result in underdosing, or when users not able to set the correct dose, can result in overdosing. Other use errors can result in needle-prick injuries, contamination, and infection. The sponsor provided some root cause analysis along with the position that the current mitigations are effective and that the residual risks are minimal. However, to fully assess the extent of the use errors, additional clarification is necessary for the following items:

- For the use errors associated with 11 participants did not set the dose correctly for their injection resulting in 12 use errors, the narrative provided in the root cause analysis section was not clear on how the use error occurred among the sequence of use interaction steps, and what "visual feedback" the users received or did not receive from the device. The report indicated that 7 of the use errors occurred after other use errors that previously occurred i.e. users neglected the priming step, or attempted to inject with a blocked needle. It was also not clear if any of the users recognize that a full dose has not been delivered, and what aspect of the device designed allowed them to do so. The sponsor should be asked to provide a side by side comparison of the correct injection sequence versus the sequence for which all of the use errors occurred, and to clearly describe how the user errors occurred along with screen shots of the device status at each of the steps, subjective feedback from users on the root cause of the use errors, and to indicate which of these participants ultimately delivered/did not deliver a correct dose. The sponsor will need to provide a clarification on the "visual feedback" and clarification on the clinical significance of the one participant who injected both a priming dose and a prescribed dose. It appeared that one participant committed the error twice but the report

did not provide details on this participant. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. The sponsor should provide a table that clearly describe for each of the use errors, the sponsor should indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement the to device design will not fully mitigate those use related risks.

- For the use errors associated with 9 participants miscalculated second dose when using two pens resulting in 9 use errors, the report indicated that one use error was associated with one 10-year old participant found the instructions to be confusion, failed the split dose task and was assisted by the moderator. A discrepancy was noted in the sponsor's assessment of this use error. The sponsor stated in the report that in real-life situation, a 10 year-old child may perform the injection but never have the full responsibility for insulin administration. However, in the Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011), the sponsor stated that Children (age 10 to 17) are considered as part of the 5 distinct user groups, who self inject without a parent's involvement. Since the report showed that a representative test user in the children subgroup could not successfully perform an injection, and since they represent a group where special considerations should be incorporated in the design of the product, the reviewer recommends that this use-related risk be fully mitigated. In addition, the remaining 8 use errors did not the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. The report remained unclear in terms of which of these participants ultimately delivered/did not deliver a correct dose. The sponsor should be asked to provide information that address the above concerns.
- For the use errors associated with 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors, the reviewer notes that this is a critical task in ensuring that the patients receive a full dose of intended insulin. One participant repeatedly misunderstood the dosing task three times, and believed that by simply activating the dose button but did not hold the dose button down until the dose counter returned to 0. Another participant did not hold the dose button down. While there were only two participants who committed this use error, the clinical impact is significant in that the patients would not receive a full dose. It is also not clear if these two participants held the needle in the skin for the 6 seconds task. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.
- For the use errors associated with 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors, the sponsor indicated that dose accuracy testing showed that a full dose is delivered 1 second after the dose counter returns to "0" with the needle remains in the skin. However, 123 of the 171 use errors, the needle was removed 1 second or more, and 48 of the 171 use errors occurred when the needle was removed less than 1 second, which resulted in underdosing. It is unclear to reviewer why the sponsor specified that the needle should be held in the skin for 6

seconds, but stated that dose accuracy testing demonstrated that a full dose can be delivered 1 second after the dose counter returns to "0." The report did not include the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

- For the use errors associated with 8 participants experienced needle prick injuries resulting in 10 use errors, the reviewer believes that needle prick injuries can result in patient harm during use with the product and requests that the sponsor optimize the IFU and training to minimize the rate of occurrence of needle prick injuries.
- For the use errors associated with 7 participants either did not remove the needle from the device or reuse the needle resulting in 10 use errors, the sponsor stated that these tasks are incorporated in the use of the product to prevent blocked needles, contamination, infection, and inaccurate dosing. Four participants committed 4 use errors in not removing the needle from the device, and 3 participants committed 3 use errors in reusing previously inserted needle. Again, please note that stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. Since these use errors can result in negative impact to the patients, the sponsor should provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.
- For the use errors associated with 4 participants did not put the cab back on after use resulting in 4 use errors, the sponsor stated these errors can result in underdosing. It is not clear how degradation caused by exposure to sunlight due to cap not mounted after use can result in underdosing. Furthermore, it is not clear what is the clinical impact of patients injecting insulin that has been degraded, and how would the patient detect that the insulin has been degraded. The reviewer believes the device user interface can be further optimized to improve use performance.
- For the use errors associated with 3 participants did not detect blocked needle resulting in 3 use errors , the sponsor stated that the resulting harm is that patient may miss a dose. It is not clear if the pen-injector provides any feedback to user in this situation, and whether or not the users recognize that they did not receive any insulin. The sponsor also clarified that the block needle task is an experimental artifact because in real life, the blocked needle only occurs if a patient reuses a needle or uses a defective needle. The testing showed that indeed 3 participants opt to reuse the needles, and therefore it is not an experimental artifact. The sponsor should indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement the to device design will not fully mitigate those use related risks.

The sponsor also reported deviations (page 95 of 102), and close calls (page 96 of 102). While these are "deviations" and "close-calls" that did no result in medical consequences, the

sponsor did not discuss how users were able to recognize the potential failures and what steps they took correct themselves. The sponsor should include in their discussion how the design of the device and its labeling influenced the patient's behavior for self-correction.

Human Factors Recommendations

Two separate studies were conducted: user differentiation and user handling. Each study consisted of the same group of 105 participants. Please address the following for both NDA submissions (NDA 203313 and 203314):

1. Based on the table provided on page 40 of the Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011), it is not clear to the Agency why under the adults subgroup, the untrained participants did not undergo the differentiation evaluation. In addition, under the HCP subgroup, the trained HCP did not undergo the differentiation evaluation.

2. Also, the following items could not be located for review, and should be submitted for review:
   - A breakdown of the number of participants for the different user groups, trained and untrained. Include in this breakdown, the number of participants with visual, dexterity, and hearing impairment.
   - A rationale for determining who should be receiving training, and who should not among the intended users
   - A rationale for [redacted] (b) (4) is an approach that represents realistic use

3. The Agency understands that diabetic patients have medical symptoms such as retinopathy and neuropathy, and these symptoms are progressively worsening over time. Provide a justification for why test participants included in the study adequate representation of the intended user group.

Regarding the study results for both studies, please address the following specific concerns:

User Differentiation Study:

4. The study reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions. Two participants had negative transfer from their use experience with other similar products, and one participant could not identify the green color carton. The study also reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committed the same error on three occasions, and this same participant committed three errors with the previous task of selecting the correct carton.

   The Instructions for Use (IFU) does include a statement to have users check the [redacted] (b) (4) label. Based on the risk analysis if undetected when a patient injects a different type of insulin other than intended, the clinical outcome can be hypoglycemia or hyperglycemia. There are different use scenarios for which this hazard exists. Either the pharmacists/HCP chooses the wrong carton and dispenses to the patients, and the patient does not recognize the wrong insulin carton; or the patient has more than one type of

insulin available, and the patient chooses the wrong carton. The results are not clear in terms of which user group (children/adult/cargiver/HCP) the three participants were part of.

It is concerning to the Agency that not all users are able successfully complete these two tasks and that serious clinical impact can occur. The Agency is concerned that participants were not able to identify the carton and pen-injector with the correct insulin despite the use of colors and instructions provided in the IFU, and therefore the risks associated with these aspects of use are not successfully mitigated. The Agency believes that further design optimization can be done the pen label to clearly identify the insulin type, and the dose.

User Handling Study

5. A discrepancy was noted between the Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) report and test report PDS290-UT54-2011. The test report PDS290-UT54-2011 provided in several tables a listing of different types of injectors (FlexPen, KwikPen, SoloStar), and various baseline tasks. It was not clear if the product used for the final validation study represented the commercial product of the (b) (4) product.

6. The Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) reported 94 of 105 participants committed 226 errors across tasks associated with delivering an injection and some of the errors resulted in needle-prick injuries. The Agency is most concerned with the following findings. Of the 105, participants,
   - 11 participants did not set the dose correctly for their injection resulting in 12 use errors.
   - 9 participants miscalculated second dose when using two pens resulting in 9 use errors.
   - 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors
   - 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors
   - 7 participants either did not remove the needle or reuse the needle resulting in 10 use errors
   - 8 participants experienced needle prick injuries resulting in 10 use errors
   - 4 participants did not put the cab back on after use resulting in 4 use errors
   - 3 participants did not detect blocked needle resulting in 3 use errors

   Most of the use errors can result in underdosing, or when users not able to set the correct dose, can result in overdosing. Other use errors can result in needle-prick injuries, contamination, and infection. You provided some root cause analysis along with the position that the current mitigations are effective and that the residual risks are minimal. However, to fully assess the extent of the use errors, additional clarification is necessary for the following items:
   a. For the use errors associated with 11 participants did not set the dose correctly for their injection resulting in 12 use errors, the narrative provided in the root cause analysis section was not clear on how the use error occurred among the sequence

of use interaction steps, and what "visual feedback" the users received or did not receive from the device. The report indicated that 7 of the use errors occurred after other use errors that previously occurred i.e. users neglected the priming step, or attempted to inject with a blocked needle. It was also not clear if any of the users recognize that a full dose has not been delivered, and what aspect of the device designed allowed them to do so. Please address the above concerns and provide a side by side comparison of the correct injection sequence versus the sequence for which all of the use errors occurred, and to clearly describe how the user errors occurred along with screen shots of the device status at each of the steps, subjective feedback from users on the root cause of the use errors, and to indicate which of these participants ultimately delivered/did not deliver a correct dose. Please also provide a clarification on the "visual feedback" and clarification on the clinical significance of the one participant who injected both a priming dose and a prescribed dose. It appeared that one participant committed the error twice but the report did not provide details on this participant. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective.

b. For the use errors associated with 9 participants miscalculated second dose when using two pens resulting in 9 use errors, the report indicated that one use error was associated with one 10-year old participant found the instructions to be confusion, failed the split dose task and was assisted by the moderator. A discrepancy was noted in your assessment of this use error. You stated in the report that in real-life situation, a 10 year-old child may perform the injection but never have the full responsibility for insulin administration. However, in the Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011), you stated that Children (age 10 to 17) are considered as part of the 5 distinct user groups, who self inject without a parent's involvement. Since the report showed that a representative test user in the children subgroup could not successfully perform an injection, and since they represent a group where special considerations should be incorporated in the design of the product, the reviewer recommends that this use-related risk be fully mitigated. In addition, the remaining 8 use errors did not the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. The report remained unclear in terms of which of these participants ultimately delivered/did not deliver a correct dose. Please provide additional information that addresses the above concerns.

c. For the use errors associated with 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors, the Agency notes that this is a critical task in ensuring that the patients receive a full dose of intended insulin. One participant repeatedly misunderstood the dosing task three times, and believed that by simply activating the dose button but did not hold the dose button down until the dose counter returned to 0. Another participant did not hold the dose button down. While there were only two participants who committed

this use error, the clinical impact is significant in that the patients would not receive a full dose. It is also not clear if these two participants held the needle in the skin for the 6 seconds task. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

d. For the use errors associated with 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors, you indicated that dose accuracy testing showed that a full dose is delivered 1 second after the dose counter returns to "0" with the needle remains in the skin. However, 123 of the 171 use errors, the needle was removed 1 second or more, and 48 of the 171 use errors occurred when the needle was removed less than 1 second, which resulted in underdosing. It is unclear to reviewer why the sponsor specified that the needle should be held in the skin for 6 seconds, but stated that dose accuracy testing demonstrated that a full dose can be delivered 1 second after the dose counter returns to "0." The report did not include the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.
e. For the use errors associated with 8 participants experienced needle prick injuries resulting in 10 use errors, the Agency is concerned with needle prick injuries associated with the use of this product and requests that you optimize the design and/or IFU and training to minimize the rate of occurrence of needle prick injuries.
f. For the use errors associated with 7 participants either did not remove the needle from the device or reuse the needle resulting in 10 use errors, you stated that these tasks are incorporated in the use of the product to prevent blocked needles, contamination, infection, and inaccurate dosing. Four participants committed 4 use errors in not removing the needle from the device, and 3 participants committed 3 use errors in reusing previously inserted needle. Again, please note that stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. Since these use errors can result in negative impact to the patients, please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.
g. For the use errors associated with 4 participants did not put the cab back on after use resulting in 4 use errors, the sponsor stated these errors can result in

underdosing. It is not clear how degradation caused by exposure to sunlight due to cap not mounted after use can result in underdosing. Furthermore, it is not clear what is the clinical impact of patients injecting insulin that has been degraded, and how would the patient detect that the insulin has been degraded. The Agency believes the device user interface can be further optimized to improve use performance.

h. For the use errors associated with 3 participants did not detect blocked needle resulting in 3 use errors , you stated that the resulting harm is that patient may miss a dose. It is not clear if the pen-injector provides any feedback to user in this situation, and whether or not the users recognize that they did not receive any insulin. You also provided a clarification that the block needle task is an experimental artifact because in real life, the blocked needle only occurs if a patient reuses a needle or uses a defective needle. The testing showed that indeed 3 participants opt to reuse the needles, and therefore it is not an experimental artifact. Please indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement the to device design will not fully mitigate those use related risks.

i. You also reported deviations (page 95 of 102), and close calls (page 96 of 102). While these are "deviations" and "close-calls" that did no result in medical consequences, you did not provide a discussion of how users were able to recognize the potential failures and what steps they took correct themselves. Please provide in your discussion how the design of the device and its labeling influenced the patient's behavior for self-correction.

7. Please note that the Agency expects to review a report of the human factors/usability evaluation and validation testing with any pattern of use errors, and a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions can be determined based on the test results. At this time, the Agency is concerned with that your testing did not provide the level of evidence to conclude that the device can be used safely and effectively. The Agency recommends that you take the results of these evaluations and use them to further optimize the training, IFU and/or device user interface so that use errors are effectively minimized. Please note that improvements should be demonstrated through focused HF/usability validation.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management,* available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm.

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.

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/s/

RACHEL E HARTFORD
01/03/2012
On behalf of QuynhNhu Nguyen