CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208751Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: September 20, 2017

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

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for FIASP® (insulin aspart injection) for subcutaneous or intravenous use

NDA: 208751

In response to DMEP's consult request dated March 29, 2017, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the NDA resubmission for FIASP® (insulin aspart injection) for subcutaneous or intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMEP (Callie Cappel-Lynch) on September 11, 2017, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 8, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at (301) 796-4530 or Ankur.Kalola@fda.hhs.gov.

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/s/

ANKUR S KALOLA
09/20/2017

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 19, 2017
To:	Jean-Marc Guettier, MD Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon Williams, MSN, BSN, RN Acting Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, PharmD Consumer Safety Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFUs)
Drug Name (established name):	FIASP (insulin aspart injection)
Dosage Form and Route:	injection for subcutaneous or intravenous use
Application Type/Number:	NDA 208751
Applicant:	Novo Nordisk

1 INTRODUCTION

On March 29, 2017, Novo Nordisk resubmitted for the Agency's review a New Drug Application for FIASP (insulin aspart injection). The Application was orginially submitted on December 8, 2015 however, it received a complete response on October 7, 2016 due to clinical pharmacology and immunogenicity deficiencies.

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 3, 2017 and March 29, 2017 respectively for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFUs) for FIASP (insulin aspart injection) for subcutaneous or intravenous use.

2 MATERIAL REVIEWED

- Draft FIASP (insulin aspart injection) PPI and IFUs received on March 29, 2017, and received by DMPP and OPDP on September 11, 2017.
- Draft FIASP (insulin aspart injection) Prescribing Information (PI) received on March 29, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 11, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFUs the target reading level is at or below an 8th grade level.

Additionally, 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 reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI and IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFUs are consistent with the Prescribing Information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the PPI and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI 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 PPI and IFUs are 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 PPI and IFUs.

Please let us know if you have any questions.

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/s/

AMANPREET K SARAI
09/19/2017

SHARON W WILLIAMS
09/19/2017

ANKUR S KALOLA
09/20/2017

LASHAWN M GRIFFITHS
09/20/2017

U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products
Division of Biotechnology Review and Research II

IMMUNOGENICITY CONSULT REVIEW MEMORANDUM

DATE:	August 16, 2017
NDA:	208751/0028(29)
PRIMARY REVIEW:	Bruce Huang, PhD; Product Quality Reviewer
THROUGH:	William Hallett, PhD; Biologist (Team Leader)
PRODUCT:	Fiasp® - Insulin aspart for injection (faster aspart)
RPM:	Callie Cappel-Lynch
CLINICAL DIVISION:	DMEP/ODEII/CDER
INDICATION:	Glycemic control for patients with diabetes mellitus
SPONSOR:	Novo Nordisk
SUBMISSION DATE:	March 29, 2017
PDUFA GOAL DATE:	September 29, 2017

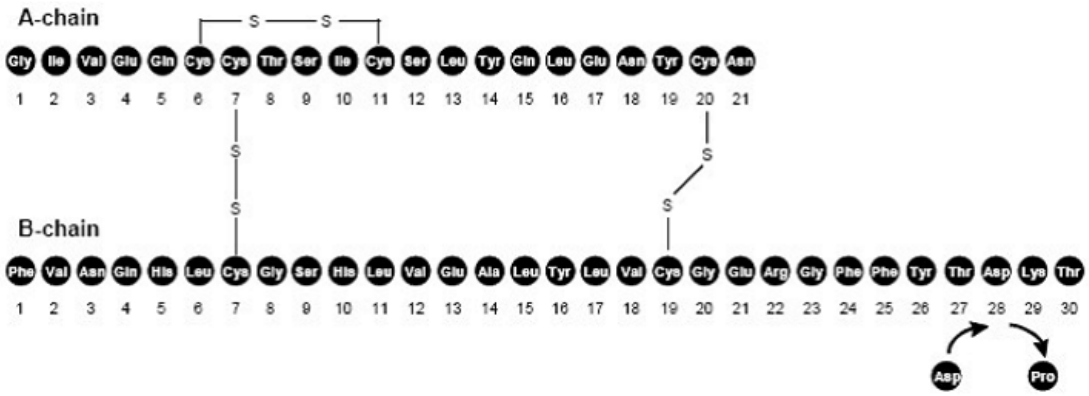
EXECUTIVE SUMMARY:

The sponsor has adequately responded to the immunogenicity CR comments. NDA 208751 is approvable from an immunogenicity perspective.

REVIEW

Summary of drug and use in proposed indication:

Fiasp (faster insulin aspart) is a meal-time insulin administered for improvement of glycemic control in adult diabetes mellitus patients. The molecular sequence and structure of insulin aspart is identical to endogenous human insulin with the sole difference of the substitution of a proline amino acid, replaced by an aspartic acid (see diagram below), which aids in inhibition of self-association, and improves availability of the active form:



Immunogenicity analysis of faster insulin aspart compared with NovoLog®

The molecular structure for Fiasp is identical to NovoLog® (aka NovoRapid®, approved June 2000), however the formulation of Fiasp differs from NovoLog® in the addition of nicotinamide and L-arginine hydrochloride (both USP-grade) as excipients, which are expected to provide

enhancement of stability and absorption rate. However, it is also possible that the difference in formulation could lead to a potential alteration in immunogenicity.

The Sponsor conducted evaluations of anti-drug antibody (ADA) and overall antibodies incidence in patients treated with Fiasp or NovoLog®, using serum samples collected in their clinical trial NN1218-3852, and submitted two validation reports in support of their immunogenicity data analysis. Agency review of these reports drew attention to major deficiencies found therein (see REV-QUALITY-21 by Steven Bowen, loaded to DARRTS 09/29/16), contributing to the Complete Response decision mailed on 10/07/16. Subsequently, a resubmission was received from Novo Nordisk on 03/29/17, containing responses to the items relating to Immunogenicity (issues #10-#19, and "CRL additional comment: Immunogenicity", of Complete Response Letter); the CRL responses from the Sponsor (Section 1.6.3 NNI Response to CRL re. Immunogenicity) are reviewed in this memorandum.

- **1.1 - CRL Issue 10:** *Validation Report 215373 describes the QC3 suitability control as a guinea pig polyclonal anti-human insulin (GP anti-Insulin). Table 1-6 of Section 2.7.1 of the NDA (Summary of biopharmaceutic studies and associated analytical methods) describes QC3 as a polyclonal anti-insulin aspart antibody. Explain the discrepancy between the two descriptions of QC3 and indicate what immunogen was used to raise the QC3 antibodies used during the testing of clinical samples.*

The Sponsor Response to issue 10 indicates that "QC3" is an anti-insulin antibody raised in guinea pigs, using insulin as the immunogen, which recognizes the structure of insulin aspart that is similar to human insulin. Furthermore, QC3 was used as a control for detection of cross-reaction by insulin aspart-antibodies against human insulin. Specific detection of insulin aspart (without cross-reaction to human insulin) is achieved using the monoclonal antibody X14-6F34 (QC2), which was raised against insulin aspart. The descriptions located in Section 2.7.1, Part 1.3.2.3, and Section 5.3.1.4, 215373, have been corrected to indicate that X14-6F34 (QC2) is an anti-insulin aspart-specific monoclonal antibody, while QC3 (GP anti-insulin) is a polyclonal guinea pig anti-insulin antibody.

Reviewer comment*: The corrections made to Validation Report 215373 and Section 2.7.1, Part 1.3.2.3 have clarified the issue of the QC3 discrepancy, and are acceptable. The response to CRL Issue 10 is acceptable.*

- **1.2 - CRL Issue 11:** *It is not clear whether the patient samples were diluted prior to testing. If patient samples were diluted prior to testing, provide data demonstrating the suitability of the minimum required dilution.*

The Sponsor Response to issue 11 indicates that although an explicit MRD was not applied to patient serum samples prior to testing, radiolabeled tracer and competing drug/buffer were added to all the serum samples in clinical testing, in a proportion of 1:1:1, therefore the effective MRD could be considered as being 1:3. The Sponsor performed assays to investigate potential matrix effects on assay operation, and found that MRD ranging from 1:3 to 1:12 all had acceptable signal-to-noise ratio when tested with both the insulin aspart-specific mouse monoclonal antibody (X14-6F34) and the mouse monoclonal antibody recognizing an insulin aspart/insulin common epitope (HUI-001). Furthermore, the most sensitive assay arrangement was achieved by

use of samples without pre-dilution, therefore the 1:3 MRD (50 µl serum sample, 50 µl radiolabeled drug tracer, 50 µl cold-competitor drug / buffer) was chosen.

Reviewer comment: *The Sponsor has clarified the MRD that was used for their analytical immunogenicity RIA assays, and adequately justified their use of a 1:3 MRD. The response to CRL Issue 11 is acceptable.*

- **1.3 - CRL Issue 12:** *Serum samples were tested in three parallel conditions: D, E, and F. Conditions E and F involved competition with unlabeled insulin aspart and human insulin, respectively. However, the concentrations of unlabeled insulin aspart and insulin used in the assay are not provided. Indicate the concentrations of unlabeled insulin aspart and human insulin used in the assay as well as the rationale for the selected concentrations.*

It is indicated in the Sponsor Response that the insulin aspart and human insulin cold competitor solutions were used at concentrations of 240 µg/ml (40 µM) - this detail is specifically documented in the footnote to the "3.2.3.2 Cold solutions" chart, in Section 5.3.1.4, Study 216352. These concentrations of cold competitor were chosen to represent a vast molar excess in comparison to the insulin aspart tracer (600 pM) in the reactions, to make certain that even the highest assay signals resulting from elevated concentrations of ADA could be inhibited, which is crucial in the case of the described RIA assays, in which levels of background signals are subtracted.

Reviewer comment*: The Sponsor has satisfactorily provided the requested concentrations of unlabeled insulin aspart and insulin used in the RIA assay, as well as a rationale for these concentrations. Therefore, the response to CRL Issue 12 is acceptable.*

- **1.4 - CRL Issue 13:** *You did not provide data demonstrating the tolerance of the assay to on-board insulin aspart. The tolerance of the assay to human insulin was determined during assay development but supporting data was not provided. Provide data demonstrating the assay tolerance of insulin aspart and human insulin to ensure that on-board levels of these proteins will not interfere with assay performance.*

The Sponsors Response made reference to Study Number 216352 (included in Section 5.3.1.4 of the re-submission), entitled "Additional validation of an anti-insulin aspart antibody RIA in human serum for documentation of drug tolerance and stability of positive control antibodies". Experiments related to tolerance were conducted using healthy-patient serum with a fixed concentration of positive control antibody, mixed with various concentrations of unlabeled insulin aspart, insulin detemir, insulin degludec, or human insulin (any of which might conceivably be found in serum from a diabetes patient). The positive control antibodies were X14-6F34, HUI-001, and GP anti-Insulin (previously described above) at 100 ng/ml concentrations. The maximum tolerable concentrations of the human insulin or insulin analogue drugs were defined as being the highest possible concentrations which still yielded assay signals above the cut point (see Tables 5-7 below, from the Study 216352 Report; cut point calculations for the subtractive assay series were previously described in Study 215373, and were found acceptable by agency review - see Table 3 below).

Table 3 Cut point values for anti-insulin aspart antibodies

Series	Description	Upper limit (%B/T) – cut point
D-E	Total anti-insulin aspart antibodies	1.9
F-E	Specific anti-insulin aspart antibodies	1.9
D-F	Anti-insulin aspart antibodies cross-reacting to human insulin	0.7

The test series D through F are defined in the table below:

Series	Assay Mixture	Results represent the sum of:
D	Sample+buffer+insulin aspart tracer	Background, insulin aspart-specific, and x-rxn Ab
E	Sample+unlabeled insulin aspart+ insulin aspart tracer	Background
F	Sample+unlabeled huInsulin+ insulin aspart tracer	Background, insulin aspart-specific Ab

Table 5 Drug tolerance of X14-6F34

Antibody group	Cut point for each series (%B/T)	Drug concentration (nM)	Results (%B/T)			
			Insulin aspart	Insulin detemir	Human insulin	Insulin degludec
Total insulin antibodies (D-E)	1.9	16	N/A	N/A	N/A	15.1
		12	N/A	N/A	N/A	16.8
		8	6.9	12.0	14.3	17.0
		4	9.1	10.4	13.3	15.2
		2	11.6	12.5	13.0	14.7
		1	12.4	13.0	14.4	19.5
		0.5	12.8	12.5	14.2	N/A
		0.25	12.0	14.5	14.2	N/A
		0	11.5	14.1	13.7	15.5
Insulin aspart specific antibodies (F-E)	1.9	16	N/A	N/A	N/A	13.0
		12	N/A	N/A	N/A	13.5
		8	6.0	12.1	11.4	12.9
		4	9.1	12.0	10.9	12.8
		2	10.3	10.5	11.5	14.0
		1	11.5	11.0	11.4	14.3
		0.5	12.0	10.8	12.3	N/A
		0.25	11.8	11.5	11.2	N/A
		0	13.3	12.6	10.9	14.4

Shaded cells correspond to values above or equal to cut point. The cut point for each series was determined in validation study 215373 (3): 1.9 %B/T for both (D-E) and for (F-E), and 0.7 %B/T for (D-F).

N/A: Not applicable, as this drug concentration was not tested.

- Shown in Table 5 (above), the subtractive immunogenicity assays representing the total insulin antibodies (D-E), and antibodies specific for insulin aspart (F-E) using 100 ng/ml of the X14-6F34 insulin aspart-specific monoclonal antibody, were found to result in assay readouts exceeding the cut point (defining tolerance) for concentrations of all tested drugs, and human insulin, of at least 8 nM.

***Reviewer comment**: The greatest anticipated on-board concentrations of human insulin, or insulin drugs, is not expected to exceed 8 nM in human subjects, thus the demonstrated tolerance for RIA assays using the X14-6F34 antibody is acceptable.*

Table 6 Drug tolerance of HUI-001

Antibody group	Cut point for each series (%B/T)	Drug concentration (nM)	Results (%B/T)			
			Insulin aspart	Insulin detemir	Human insulin	Insulin degludec
Total insulin antibodies (D-E)	1.9	16	N/A	N/A	N/A	13.4
		12	N/A	N/A	N/A	15.7
		8	3.2	10.3	1.4	19.2
		4	6.7	19.7	3.1	30.9
		2	15.5	32.0	7.2	43.5
		1	30.2	42.4	21.0	50.1
		0.5	44.1	48.2	34.6	N/A
		0.25	51.0	50.1	44.5	N/A
		0	54.8	53.4	51.8	55.1
Cross-reacting antibodies (D-F)	0.7	16	N/A	N/A	N/A	11.9
		12	N/A	N/A	N/A	14.2
		8	2.8	9.6	0.8	18.4
		4	6.2	19.0	2.6	29.1
		2	15.1	31.5	7.2	41.8
		1	29.6	41.6	20.7	48.1
		0.5	43.3	47.7	34.0	N/A
		0.25	50.4	49.3	44.0	N/A
		0	53.9	52.5	51.1	53.2

Shaded cells correspond to values above or equal to cut point. The cut point for each series was determined in validation study 215373 (3): 1.9 %B/T for both (D-E) and for (F-E), and 0.7 %B/T for (D-F).

N/A: Not applicable, as this drug concentration was not tested.

- Shown in Table 6 (above), are the subtractive immunogenicity assays data representing the total insulin antibodies (D-E), and antibodies cross-reacting between insulin aspart and human insulin (D-F), using 100 ng/ml of the HUI-001 monoclonal antibody that is specific for a part of the insulin aspart molecule that is identical to human insulin. The results demonstrate that the HUI-001 cross-reactive antibody could be assessed successfully (resulting in readings above the cut point) in the presence of at least 8 nM insulin aspart, insulin detemir, and 16 nM insulin degludec. The maximum tolerable concentration of human insulin for the HUI-001 monoclonal antibody was found to be only 4 nM, however the comparatively lower concentration should not be problematic, as the target patients will likely have very low endogenous insulin.

***Reviewer comment**: The demonstrated tolerance for on-board concentrations of human insulin, or insulin drugs, in the RIA assays using the HUI-001 antibody is acceptable.*

Table 7 Drug tolerance of GP anti-Insulin

Antibody group	Cut point for each series (%B/T)	Drug concentration (nM)	Results (%B/T)			
			Insulin aspart	Insulin detemir	Human insulin	Insulin degludec
Total insulin antibodies (D-E)	1.9	16	N/A	N/A	N/A	7.3
		12	N/A	N/A	N/A	8.0
		8	2.4	3.7	2.2	10.4
		4	3.4	5.3	3.5	12.9
		2	5.6	8.2	5.0	18.0
		1	7.7	11.9	8.2	21.7
		0.5	11.2	14.1	10.8	N/A
		0.25	14.9	20.5	14.4	N/A
		0	26.1	26.8	26.9	37.8
Cross-reacting antibodies (D-F)	0.7	16	N/A	N/A	N/A	6.0
		12	N/A	N/A	N/A	6.7
		8	2.2	3.8	2.0	9.2
		4	2.7	5.2	3.3	11.3
		2	5.3	7.8	4.6	16.5
		1	7.2	11.6	7.9	20.1
		0.5	10.9	14.4	10.4	N/A
		0.25	14.6	20.0	14.6	N/A
		0	25.4	25.8	26.3	35.2

Shaded cells correspond to values above or equal to cut point. The cut point for each series was determined in validation study 215373 (3): 1.9 %B/T for both (D-E) and for (F-E), and 0.7 %B/T for (D-F).

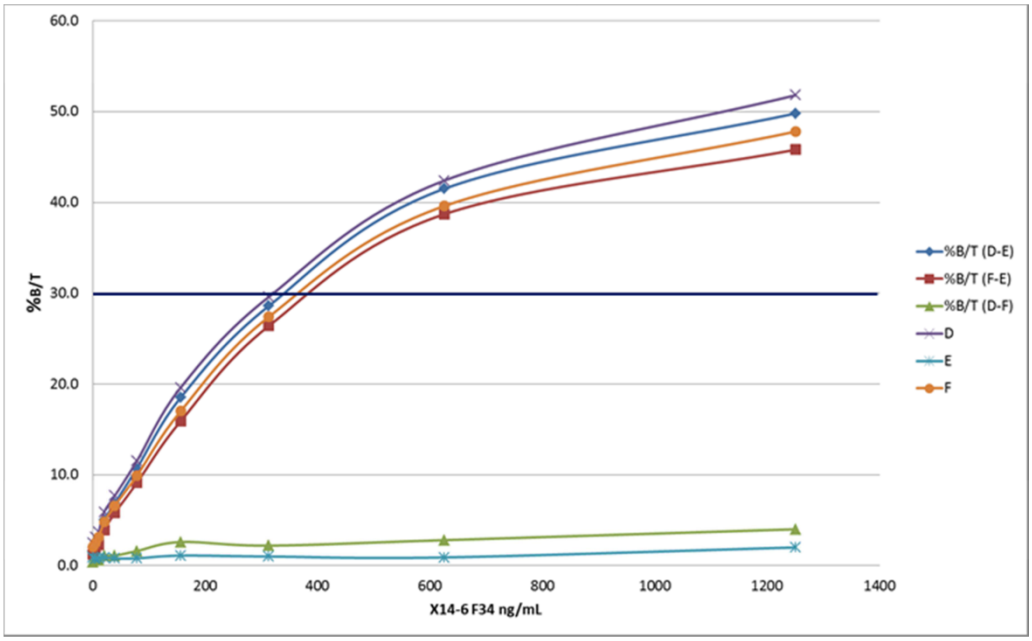
N/A: Not applicable, as this drug concentration was not tested.

- Shown in Table 7 (above), are the subtractive immunogenicity assays data representing the total insulin antibodies (D-E), and antibodies cross-reacting between insulin aspart and human insulin (D-F), using 100 ng/ml of the polyclonal guinea pig anti-insulin antibody (GP anti-insulin), which cross-reacts with human insulin, and the insulin drugs. All tested concentrations of human insulin, or insulin drugs (at least up to 8 nM), were shown to be tolerable by the assay for detection of the GP anti-insulin antibody (results were found to exceed the cut point).

Reviewer comment*: The demonstrated tolerance for on-board concentrations of human insulin, or insulin drugs, in the RIA assays using the GP anti-insulin antibody is acceptable. The results of the RIA assays shown above in Tables 5-7 support the assertion that the assay performance can tolerate levels of insulins at clinically-relevant concentrations without interfering in the successful performance of the immunogenicity assay. The response to CRL Issue 13 is acceptable.*

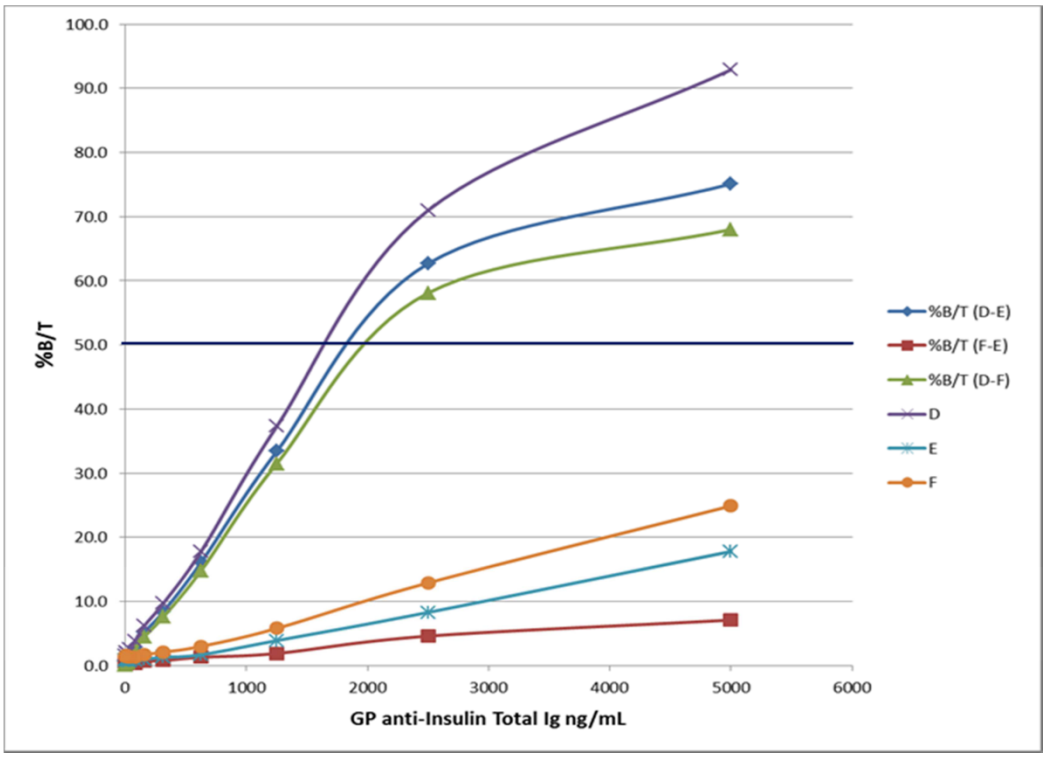
- **1.5 - CRL Issue 14 and FDA EOR meeting comment to Q11:** *The levels of total ADA, insulin aspart-specific antibodies, and antibodies cross-reactive with human insulin are quantitated using the percentage of total radiolabeled tracer (insulin aspart) that are co-precipitated with Ig (%B/T). However, there is insufficient data in the Validation Reports to demonstrate that the assay is quantitative. One approach to address this deficiency and support the use of the %B/T value as a quantitative measure of antibodies in patient samples would be to demonstrate that there is a linear relationship between the positive control antibody concentration and the %B/T signal. Include a graphical and tabular analysis for each series (D, E, F) and the subtracted (D-E, D-F, F-E) values.*

The Sponsors Response argued that in this case, ADA detection immunoassays could only be quasi-quantitative at best, due to the unavailability of suitable calibrator reference antibodies. Reference was made to Study Number 215373 (included in Section 5.3.1.4 of the re-submission), entitled "Validation to document assay sensitivity and normal ranges in an anti-insulin aspart antibody RIA method". The study report shows the results of RIA sensitivity progressive dilutional set-up assays using the two control antibodies mAb X14-6F34 (insulin aspart-specific mAb) and GP anti-insulin (guinea pig insulin-specific pAb). The assays were performed four times, though result data from only one run per antibody analysis are shown in the Response to CRL packet. The most current iteration of the Validation Report 215373 (included with the current submission) contains the data and graphs from all four set-up repetitions of the experimental assays, using both X14-6F34 and GP anti-insulin antibodies. The Sponsor continues with the assertion that the graphs depicting the results of the X14-6F34 insulin aspart-specific mAb assays demonstrate linearity in %B/T signals up to ~30% for X14-6F34 and ~50% for GP anti-insulin (see Figure 1 and 2 from CRL Response document, below, depicting one repetition of each assay):



The line marks the linear range (≤30 %B/T)

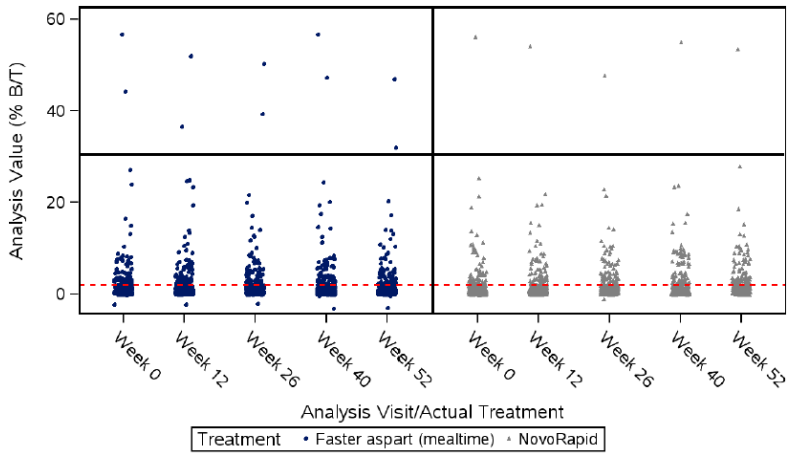
Figure 1. Concentration of anti-insulin aspart specific antibody (X14-6 F34) (ng/ml) in series D, E, F, D-E, F-E and D-F versus %B/T



The line marks the linear range (≤ 50 %B/T)

Figure 2. Concentration of GP anti-insulin (total Ig in ng/ml) in series D, E, F, D-E, F-E and D-F versus %B/T

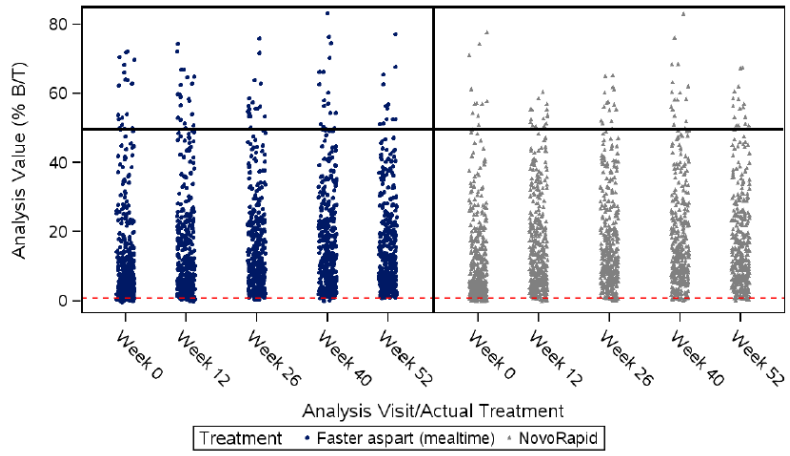
Furthermore, the Sponsor provides data demonstrating analysis of clinical data which found that at each visit, ~99% of patients had anti-insulin aspart-specific antibody readings below 30% B/T (meaning within the linear range of the assay), and ~94% of patients had antibodies cross-reacting between insulin aspart and human insulin at readings below 50% B/T (within the linear range), see Figures 3 and 4, below:



Observed data. Jitter values are randomly distributed around each visit to clarify the plot. NovoRapid is known as NovoLog in the U.S.
The red line at 1.9 % B/T represents the cut-point for determination of antibody positivity.

The line marks the linear range (≤30 %B/T). N range: 335-386. NovoRapid is known as NovoLog in the US.

Figure 3 Anti-insulin aspart specific antibodies (%B/T) in subjects by analysis visit week for faster aspart (mealtime) and NovoLog® in trial 3852 (52 weeks)



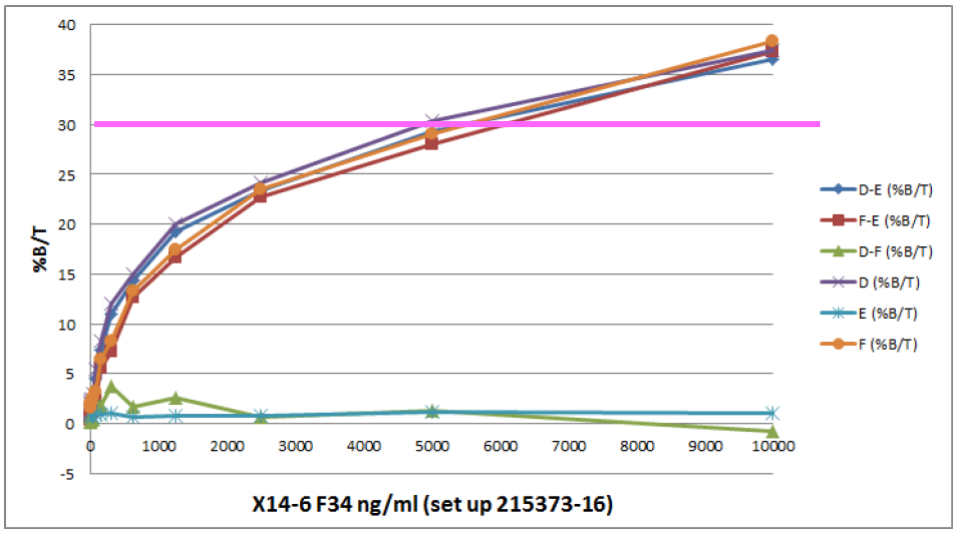
Observed data. Jitter values are randomly distributed around each visit to clarify the plot. NovoRapid is known as NovoLog in the U.S.
The red line at 0.7 % B/T represents the cut-point for determination of antibody positivity.

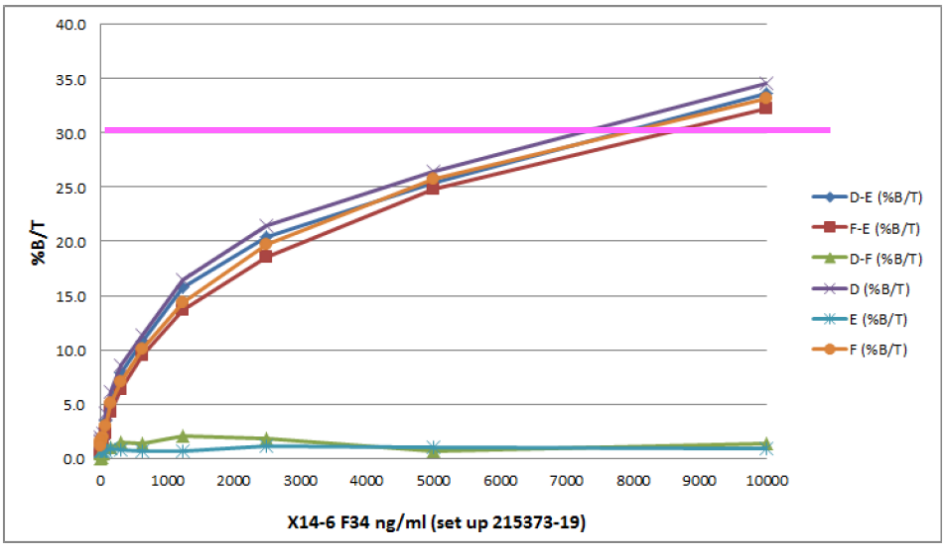
The line marks the linear range (≤ 50 %B/T). N range: 336-386. NovoRapid is known as NovoLog in the U.S

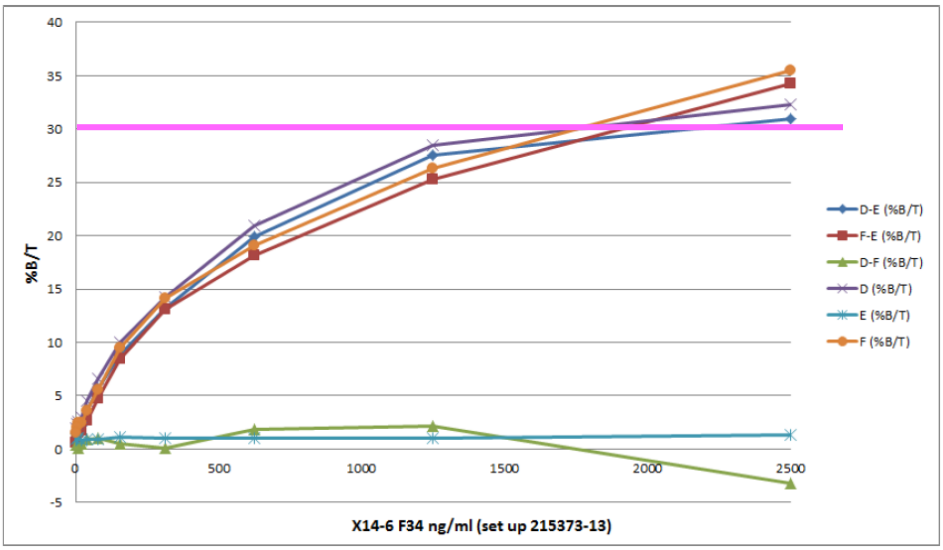
Figure 4 Anti-insulin aspart antibodies cross-reacting to human insulin (%B/T) in subjects by analysis visit week for faster aspart (mealtime) and NovoLog® in trial 3852 (52 week)

Reviewer comment: *The data shown in the "Response to CRL" packet (Figures 1-4, above) do appear to support the Sponsor's assertion of linearity in the assays using the X14-6F34 and GP anti-insulin antibodies, for %B/T signals of up to ~30% and ~50%, respectively. The patient data shown in Figures 3 and 4 support the significance of the ~30% and ~50%linear ranges stated by the Sponsor's analysis. However, detailed examination of the four set-up repetitions of the validation assays, using the X14-6F34 antibody, revealed that the linear range value given as*

"up to ~30% B/T" did not appear to be consistent over all four runs (see graphs, below, depicting results of the three further repetitions of the assay, runs 16, 19, and 13, in addition to the assay shown in Figure 1, above, which was revealed to be run 22). Data from all assays was found in Section 5.3.1.4, Study Number 215373 Report:







The data supporting linearity (defined as a "straight-line relationship") of the assays using the X14-6F34 positive control antibody (see Figure 1, and graphs for set up 215373-16, -19, and -13, above) are varied. While the curves of run 215373-22 seen in Figure 1 do support the stated linear range of %B/T signals of up to ~30% in X14-6F34 antibody assays, the other assay runs shown in the Study Number 215373 Report depict somewhat different results. The linear ranges of the X14-6F34 antibody assay setups 215373-16, -19, and -13 do not seem to extend to %B/T signals of up to ~30% (indicated by the reviewer with ***heavy magenta*** *lines on the graphs). The assay results indicate that the linear portion of the curve is associated with X14-6F34 antibody concentrations of up to approximately 400-500 ng/ml, which is most likely sufficient for detection of ADA in patient samples (Agency recommendations call for sensitivity to 500 ng/ml). In any case, linearity at the low end of the curve is usually more important in relevance to evaluation of actual clinical samples, than linearity at the high end. Therefore, although we do not completely agree with the Sponsor's interpretation of the data, the response to CRL Issue 14 is acceptable.*

- **1.6 - CRL Issue 15 and FDA EOR meeting comment to Q12:** *Section 2.7.1 Table 1-6 indicates that the two positive suitability controls used for analysis of clinical samples were QC2 (monoclonal anti-insulin aspart, 560 ng/ml) and QC3(guinea pig polyclonal anti-human insulin antibody, 23-230 ng/ml). The sensitivity analysis described in Validation Report 215373 indicates that both QC2 and QC3 are toward the upper limit of quantitation of the assay. This raises concerns that your suitability controls are inadequate to ensure the detection of low levels of ADA. Low positive controls should be set to have a 1% failure rate based on the assay cutpoint. Indicate how the detection of low levels of ADA was demonstrated during clinical testing.*

In clinical testing with patient samples (Trial NN1218-3852: Efficacy and Safety of Fiasp Compared to Insulin Aspart – Both in Combination with Insulin Detemir in Adults with Type 1 Diabetes), the Fiasp-specific mAb QC2 and GP anti-insulin QC3 suitability controls gave mean values of 49.17% and 32.43% B/T, respectively (see Study Report CA10238, Tables 4 and 7, not reproduced here). The observed failure rate was 1.1% (3/282) for the QC2, and 1.4% (4/278) for the QC3. The QC3 (low QC) concentration was chosen to comply with the 2009 FDA Draft Guidance recommendation for 250-500 ng/ml, however as shown in the Figure 2 graph (see CRL

Issue 14, above), titration of the antibody by several dilutions still resulted in %B/T values above the assay cut point. Thus the QC3 control is compliant with the latest 2016 FDA Immunogenicity Draft Guidance recommendations of ≥100 ng/ml quantitation for sensitivity. Additionally, as shown below in Table 7, ≥98% of the trial subjects tested positive for ADA cross-reacting with insulin by week 52 (red box), thus the risk of false negative results is very low.

Table 7 Incidence of anti-insulin aspart antibody positive subjects by visit (trial 3852, 52 weeks)

		Anti-insulin aspart antibody positive											
	Number of subjects	Week 0			Week 12			Week 26			Week 40			Week 52		
		N	P	(%)	N	P	(%)	N	P	(%)	N	P	(%)	N	P	(%)
Cross-reacting antibodies																
Faster aspart (mealtime)	386	386	348	(90.2)	379	360	(95.0)	366	359	(98.1)	344	340	(98.8)	336	335	(99.7)
NovoRapid	380	376	353	(93.9)	374	365	(97.6)	372	363	(97.6)	349	340	(97.4)	342	335	(98.0)
Specific antibodies																
Faster aspart (mealtime)	386	386	67	(17.4)	379	77	(20.3)	366	80	(21.9)	340	77	(22.6)	335	69	(20.6)
NovoRapid	380	378	70	(18.5)	374	77	(20.6)	372	80	(21.5)	349	79	(22.6)	340	75	(22.1)

N: Number of subjects, P: Number of subjects with positive measurements, %: Percentage of subjects with positive measurements
Limits: Cross-reacting antibodies > 0.7 % B/T, Specific antibodies > 1.9 % B/T
NovoRapid is known as NovoLog in the U.S.

Cross-reference: Appendix 1, Table 2

Additionally, new low QC antibody controls have been described (Validation Report VCA21755-01, Ref. #300047, 03/29/2017) containing:
- QC1Low: X14-6 F34 mAb – 9 ng/ml (to assay total, and Fiasp-specific ADA)
- QC2Low: HUI-001 mAb – 3 ng/ml (to assay total, and cross-reacting ADA)

The new low QC antibody controls are being used for immunogenicity analysis in the on-going clinical trials NN1218-4131 and NN1218-4101, and subsequent future immunogenicity analysis for trials involving Fiasp.

Reviewer comment*: The assays have demonstrated sensitivity to the low QC antibody controls at various dilutions below 100 ng/ml, as recommended by the 2016 FDA Guidance. The response to CRL Issue 15 is acceptable.*

- **1.7 - CRL Issue 16 and FDA EOR meeting comment to Q10:** *Some of the assay parameters, such as intra-assay precision, inter-assay precision, and robustness, were validated by analyzing only the D-E series. However, the clinical samples were evaluated using the D-F and F-E series. Therefore, assay parameters validated using only the D-E conditions need to be validated using the D-F and F-E series.*

The Sponsor responded to CRL Issue 16 by submitting the tables with information on inter- and intra-assay precision recorded for the D-F and F-E subtractive immunoassay series. Precision was determined at low, medium, and high levels for each analytical series. Data related to Inter-assay precision is addressed in Table 2, below:

Table 2 Overview of inter-assay precision data (validation study 300047[1])

Inter Assay precision	QC Level[2]	D-E series Total insulin aspart antibodies	D-F series Cross reactive antibodies	F-E series Antibodies specific for insulin aspart
Results obtained for mAb X14-6F34 (Insulin aspart specific mAb)	QC1low (9 ng/ml)	*Mean: 3.3 %B/T* %CV: 6.9	N/A[3]	*Mean: 2.7 B/T* %CV: 6.4
	QC1med (100 ng/ml)	*Mean: 23.2 %B/T* %CV: 3.7	N/A[3]	*Mean: 19.7 %B/T* %CV: 4.1
	QC1high (400 ng/ml)	*Mean: 50.9 %B/T* %CV: 3.2	N/A[3]	*Mean: 46.3 %B/T* %CV: 3.3
Results obtained for mAb HUI-001 (mAb for cross reactive antibodies)	QC2low (3 ng/ml)	*Mean: 3.1 %B/T* %CV: 7.6	*Mean: 2.6 %B/T* %CV: 8.1	N/A[4]
	QC2med (30 ng/ml)	*Mean: 23.4 %B/T* %CV: 3.1	*Mean: 22.7 %B/T* %CV: 3.1	N/A[4]
	QC2high (80 ng/ml)	*Mean: 51.2 %B/T* %CV: 4.0	*Mean: 50.5 %B/T* %CV: 3.8	N/A[4]

[1]: Data from Table 31, 32, 33, 34, 35 and 36 in study 300047.

[2]: These QC's are only used in study 300047 and are not equal to QC2, QC2low and QC3 applied in other validations and during clinical analysis.

[3]: N/A because mAb X14-6F34 targets an epitope specific for insulin aspart and can therefore not be used for measuring antibodies cross reactive between insulin aspart and human insulin.

[4]: N/A because.mAb HUI-001 targets an epitope in common for insulin aspart and human insulin and can therefore not be used for measuring insulin aspart specific antibodies.

Reviewer comment: The low %CV values shown above in Table 2 (none greater than 8.1%) are indicative of acceptable inter-assay precision.

To further evaluate inter-assay precision, and also appraise intra-assay precision and robustness, the QC samples were analyzed over an 18 month period, utilizing 10 different lots of tracer. The aggregate results of the assays are shown in Table 3, below:

Table 3 Overview of in-study intra- and inter-assay assay precision for QC samples analysed in Trial 3852[1]

Assay precision	QC level[2]	D-F series Cross reactive antibodies	F-E series Antibodies specific for insulin aspart
Intra- assay precision	QC2	N/A[3]	*Mean: 49.17 B/T* %CV: 2
	QC3	*Mean: 32.35 %B/T* %CV: 2	N/A[4]
Inter-assay precision	QC2	N/A[3]	*Mean: 49.17 B/T* %CV: 5
	QC3	*Mean: 32.35 %B/T* %CV: 7	N/A[4]

[1]:These precision data are based on QC data from analysis of clinical samples in trial 3852, M 5.3.1.4. Study CA10238, Appendix A, Table 4 and Appendix B, Table 7.

[2]: Each QC (QC2: batch Sep-2010/BSka, QC3: batch Aug-2010/BSka) was included three times in each assay set-up and the precision data are based on 101 assay set-ups during analysis of clinical samples in NN1218-3852.

[3]: N/A because QC2 (monoclonal anti-insulin aspart X14-6F34, 560 ng/ml) targets an epitope specific for insulin aspart and can therefore not be used for measuring antibodies cross reactive between insulin aspart and human insulin.

[4]: N/A because QC3 (polyclonal guinea pig polyclonal anti-human insulin antibody, 23-230 ng/ml) targets epitopes in common for insulin aspart and human insulin and can therefore not be used for measuring insulin aspart specific antibodies.

Reviewer comment: The low %CV values shown above in Table 3 indicate that precision and robustness are acceptable in the D-F and F-E subtractive immunoassay series. The response to CRL Issue 16 is acceptable.

- **1.8 - CRL Issue 17:** *You did not provide data demonstrating the stability of the positive control antibodies used during the testing of clinical samples. In order to demonstrate that the X14-6F34 and GPa Insulin antibodies remain stable under normal testing conditions*

assess the performance of the antibodies under long-term storage, freeze thaw, and benchtop conditions.

The Sponsor responded to CRL Issue 17 with data showing that experiments performed with the positive control antibodies X14-6F34 (QC2, mu mAb specific for Fiasp) and GP anti-Insulin (gp pAb specific for insulin) are stable for up to 18 months, and relatively resistant to benchtop temperatures and freeze thaw cycles that might be expected during normal testing conditions.

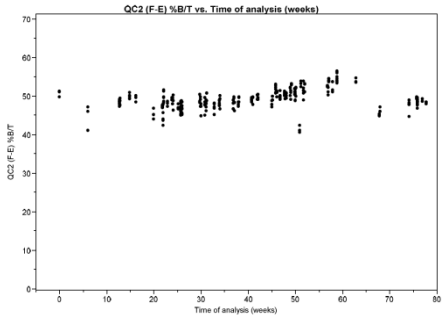


Figure 5 QC2 values (%B/T) over time (weeks) series F-E (trial 3852)

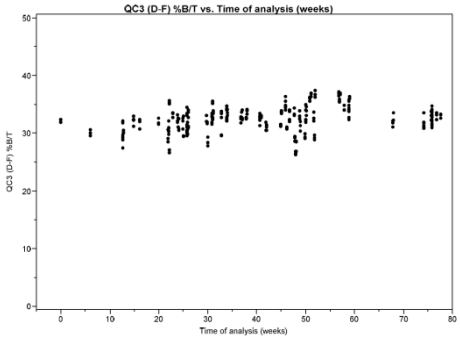


Figure 6 QC3 values (%B/T) over time (weeks) for series D-F (trial 3852)

***Reviewer comment**: The results of D-F subtractive assay series using batches of the X14-6F34 and GP anti-Insulin antibodies, performed over a period of 78 weeks show stability of the antibodies over a realistic interval of time. F-E assay series were also performed over 111 weeks, with equivalent results, further demonstrating temporal stability (F-E assays not shown, for brevity).*

Table 8 Stability of positive control antibodies (F-E and D-F)

Condition	Insulin aspart specific antibodies (F-E)				Cross-reacting antibodies (D-F)	
	QC2 low		QC2		QC3	
	%B/T	in % of reference QC[1]	%B/T	in % of reference QC[1]	%B/T	in % of reference QC[1]
3 freeze-thaw cycles	6.1	113	32.6	106	47.7	98
5 h at RT	5.8	107	34.5	112	49.8	102
24 h at RT	5.4	100	***33.5***	108	46	94
Reference from -20°C	5.4	100	30.9	100	48.9	100

Bold and italic: mean value of sample F had a %CV > 75%, therefore only a single determination of F was used for calculating the F-E value (34.9-1.4=33.5) reported in the table.

[1]: In % of reference QC correspond to the % change for the specific sample compared to the same QC sample tested directly without freeze-thaw cycles or incubation at room temperature.

Table 9 Stability of positive control antibodies (D-E)

Condition	Total insulin antibodies (D-E)					
	QC2 low		QC2		QC3	
	%B/T	in % of reference QC[1]	%B/T	in % of reference QC[1]	%B/T	in % of reference QC[1]
3 freeze-thaw cycles	7.1	117	36.8	127	50.1	95
5 h at RT	6.8	112	33.5	116	51.7	98
24 h at RT	6.0	99	31.6	109	48.7	92
Reference from -20°C	6.1	100	28.9	100	53.0	100

[1]: In % of reference QC correspond to the % change for the specific sample compared to the same QC sample tested directly without freeze-thaw cycles or incubation at room temperature

***Reviewer comment**: The %B/T readouts of the various immunoassays using the X14-6F34 and GP anti-Insulin antibodies remain stable after handling at various conditions, including RT for up to 24 hours, and 3 cycles of freeze-thaw (see Table 8 and 9, above). CRL Issue 17 is considered to be satisfied.*

- **1.9 - CRL Issue 18:** *The acceptance criteria used for the QC2 and QC3 suitability controls were calculated for a nominal value for each control ±20%. It is unclear how the nominal values for QC2 and QC3 indicated in Table 1-6 of Section 2.7.1 were calculated or what the upper and lower acceptance limits were for each series. Provide a description of how the calculations were done to establish the acceptance criteria for the suitability controls (including the QCneg) used during the testing of clinical samples.*

The Sponsor responded to CRL Issue 18 with the explanation that the nominal QC2 and QC3 suitability control values were calculated from 6 analytical runs performed prior to analysis of clinical samples (Study CA10238), with acceptance ranges set at ±20% of the mean. This is not consistent with the recommendations of the FDA Guidance for Industry (April 2016), which specifies a 1% rejection rate; however the outcome of the ±20% range-finding calculation results in ranges that are only slightly broader for the QC2 control, and virtually unchanged in the case of the QC3 control; see Table 4, below:

Table 4 Acceptance ranges for QC2 and QC3 using nominal value +/- 20% or 1% rejection rate

	Nominal value +/- 20 %		1% rejection rate		
QC	**Nominal value**	**Range Nominal +/- 20 %**	**Mean value all assay runs**	**SD**	**Range: mean+/- t(0.005;df)xSD one-sided 99.5% (t=2.593)**
QC2	49.43 %B/T	39.54 – 59.31 %B/T	49.11	2.61	42.34 – 55.88 %B/T
QC3	32.83 %B/T	26.26 – 39.39 %B/T	32.28	2.24	26.47 – 38.10 %B/T

During analysis of clinical samples, it was found that the number of accepted assay runs would have been similar, no matter which strategy for calculation of acceptance ranges was used; only one assay run more would have been excluded using the 1% rejection rate calculation. The acceptance range for QCneg was not applied during clinical sample analysis because a fixed cut-point was utilized; therefore the QCneg was not used for cut-point calculation.

Reviewer comment*: The Sponsor's explanation for their derivation of the QC2 and QC3 calculations and ranges are reasonable, as is their reasoning for not calculating the acceptance range for the QCneg. The response to CRL Issue 18 is acceptable.*

- **1.10 - CRL Issue 19:** *Validation data for the labeling efficiency, batch-to-batch consistency, and stability of the radiolabeled insulin aspart tracer were not provided. Provide data validating these attributes of the radiolabeled insulin aspart tracer used in the RIA.*

The Sponsor responded to CRL Issue 19 by supplying data showing results of immunoassays using insulin aspart tracers stored at -20°C up to 3 months after production (one representative graph demonstrating F-E assay data shown below, of four total provided in the CRL Response package materials). Overall, tracer potency degradation was less than 3% over the 3 month period.

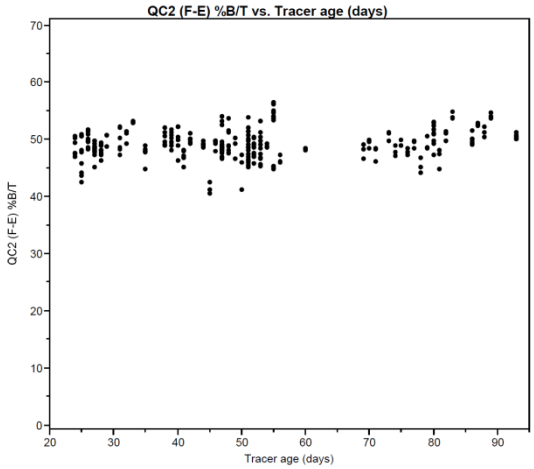


Figure 9 QC2 values (series F-E) obtained versus age of insulin aspart tracer (days) in trial 3852

The Sponsor also stated that 10 different lots of tracer were used over an 18 month testing period in a clinical trial, with batch-to-batch consistency in all lots. One representative graph, of four provided in the CRL Response package materials, showing tracer results of different lots over 90 days, is shown below:

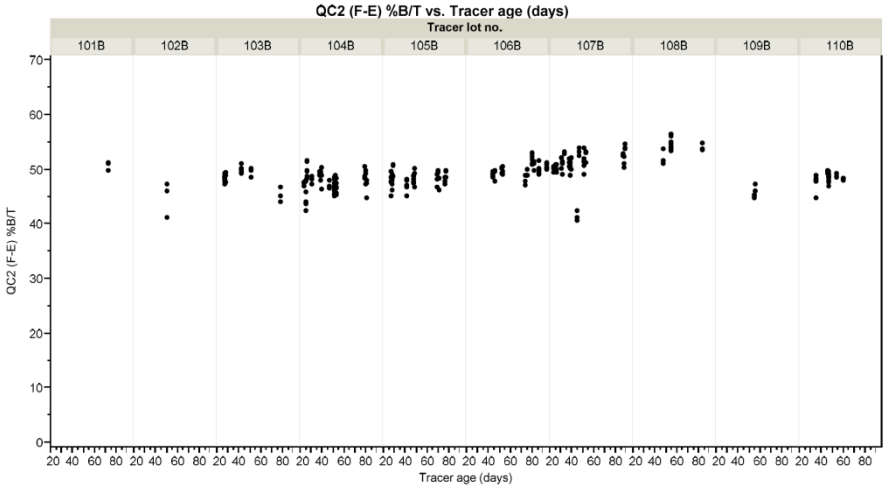


Figure 13 QC2 values (%B/T values for series F-E) obtained using 10 different insulin aspart tracer lots of up to 90 days of age in trial 3852

Reviewer comment*: The graphs showing activity of the tracer up to 90 days demonstrates acceptable stability. Likewise, the graphs showing relative uniformity of tracer activity among different lots supports the acceptable consistency. The lot-to-lot consistency data only shows readings up to 90 days however, in contrast to the actual testing period described as 18 months. Nevertheless, in light of the apparent lack of any downward trend in the activity at 90 days, it is not likely that the tracer uniformity will be severely diminished at 18 months, especially with proper storage at -20°C. The sponsor's response to CRL Issue 19 is acceptable.*

- **1.11 - CRL Additional Comments (Immunogenicity Issue):** *Regarding the analysis of clinical data from Study NN1218-3852, Section 2.7.1 of the NDA notes that most patients*

were positive for ADA at baseline and that no cut-points were established to evaluate treatment-boosted ADA responses. In order to compare the immunogenicity of (b) (4) *and Novolog, the frequency of patients with treatment-emergent and treatment-boosted ADA should be determined. Indicate how treatment-emergent and treatment-boosted patients were mathematically defined in your analysis as well as the frequency of patients in each treatment group with treatment-induced or treatment-boosted ADA.*

The Sponsor responded to the CRL Additional Immunogenicity Comment by defining treatment-induced ADA as occurring in baseline-negative patients which became ADA$^+$ post-baseline. The criteria for Patients experiencing a boost were defined by ADA-positivity at baseline with increase in later readings exceeding the assay variance, calculated as 1.96*√2*SD. The value for SD is the standard deviation of either the QC2low or QC3 results; the condition for usage of the QC2low or QC3 was set as midway between the mean readings of the QC2low and QC3 readings (see Table 5, below):

Table 5 Calculation of the absolute difference between baseline and post baseline samples for treatment boosted patients

QC sample	Mean	SD	Absolut difference in %B/T between baseline and post baseline sample[a]	Range of response at baseline
QC2low	3.9	1.04	3 or more	Cut point - < 18%B/T
QC3	32.43	3.2	9 or more	≥ 18%B/T

[a] Absolute difference calculated as 1.96 x √2 x SD

The midway value between the mean readings of the QC2low and QC3 results was found to be 18%, thus the defined limits for treatment-boosted subjects are as follows:

- Patients with baseline %B/T readings above cut-point, but < 18% B/T, experiencing ≥ 3% B/T increase over baseline
- Patients with baseline %B/T readings > 18% B/T, experiencing ≥ 9% B/T increase over baseline

The calculation strategy shown above was applied to patients in Trial 3852, the results are shown below in Tables 6 and 7 (colored boxes added by reviewer for clarity). The incidence of patients with treatment-induced Fiasp-specific antibodies in each treatment group is shown in the lower half of Table 6; in comparison to NovoLog, the frequency is equivalent. The rate of cross-reacting antibody occurrence (shown in the upper half of Table 6) is initially less in Fiasp when compared to NovoRapid at week 12, but at subsequent time points, a greater percentage of Fiasp patients were found positive for cross-reacting antibodies. The frequency of patients with treatment-boosted Fiasp-specific antibodies in each treatment group is shown in the lower half of Table 7; in comparison to NovoLog, the frequency is equivalent.

Table 6 Incidence of subjects with treatment induced anti-insulin aspart antibodies by visit (trial 3852, 52 weeks)

	Anti-insulin aspart antibody positive									
	Number of subjects	Week 12			Week 26			Week 40			Week 52		
		N	P	(%)	N	P	(%)	N	P	(%)	N	P	(%)
Cross-reacting antibodies													
Faster aspart (mealtime)	38	38	21	(55.3)	34	27	(79.4)	31	28	(90.3)	30	29	(96.7)
NovoRapid	23	23	15	(65.2)	23	16	(69.6)	22	16	(72.7)	21	15	(71.4)
Specific antibodies													
Faster aspart (mealtime)	319	313	14	(4.5)	301	21	(7.0)	280	21	(7.5)	277	21	(7.6)
NovoRapid	308	304	14	(4.6)	302	18	(6.0)	282	21	(7.4)	275	20	(7.3)

N: Number of subjects negative for anti-insulin aspart antibodies at baseline, P: Number of subjects with positive measurements, %: Percentage of subjects with positive measurements, Limits: Cross-reacting antibodies > 0.7 % B/T, Specific antibodies > 1.9 % B/T
NovoRapid is known as NovoLog in the U.S.

Table 7 Incidence of subjects with treatment-boosted anti-insulin aspart antibodies by visit (trial 3852, 52 weeks)

	Anti-insulin aspart antibody boost									
	Number of subjects	Week 12			Week 26			Week 40			Week 52		
		N	P	(%)	N	P	(%)	N	P	(%)	N	P	(%)
Cross-reacting antibodies													
Faster aspart (mealtime)	348	341	123	(36.1)	332	137	(41.3)	313	152	(48.6)	306	152	(49.7)
NovoRapid	353	347	145	(41.8)	345	165	(47.8)	323	173	(53.6)	317	162	(51.1)
Specific antibodies													
Faster aspart (mealtime)	67	66	8	(12.1)	65	9	(13.8)	60	6	(10.0)	58	3	(5.2)
NovoRapid	70	68	2	(2.9)	68	4	(5.9)	65	9	(13.8)	63	8	(12.7)

N: Number of subjects positive for anti-insulin aspart antibodies at baseline, P: Number of subjects with substantially increased measurements,%: Percentage of subjects with substantially increased measurements. For subjects with a baseline measurement below/above the median % B/T of subjects positive at baseline an increase of 5 and 10 percentage points, respectively, is considered substantial.
Limits: Cross-reacting antibodies > 0.7 % B/T, Specific antibodies > 1.9 % B/T
NovoRapid is known as NovoLog in the U.S

***Reviewer comment**: The Sponsor developed a computational strategy to determine the proportion of patients for whom the presence of ADA / cross-reactive immunity was induced by Fiasp treatment, and those for whom pre-existing ADA / cross-reactive immunity were boosted by Fiasp treatment. The calculated results of the assays indicate that the observed rates of treatment-induced and treatment-boosted immunity in patients receiving Fiasp were generally comparable with those of patients receiving NovoRapid. This result supports the assertion of the Sponsor that the difference in the formulation between Fiasp and Novolog (e.g. the addition of nicotinamide and L-arginine hydrochloride as excipients in Fiasp) do not significantly alter the potential for immunogenicity in patients. The response to the CRL Additional Comment (Immunogenicity) is acceptable.*

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/s/

BRUCE K HUANG
09/06/2017

WILLIAM H HALLETT
09/06/2017

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 23, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208751
Product Name and Strength:	Fiasp (insulin aspart), injection, 100 units/mL 1,000 units per 10 mL vial Fiasp FlexTouch (insulin aspart), injection, 100 units/mL 300 units per 3 mL pen
Applicant/Sponsor Name:	Novo Nordisk
Submission Date:	August 16, 2017
OSE RCM #:	2015-2637-2
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised carton and container labeling for Fiasp (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labels for Fiasp are acceptable from a medication error perspective. We have no further recommendations at this time.

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

[a] Conrad A. Revised Label and Labeling Review for Fiasp (NDA 208751). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Aug 7. RCM No.: 2017-2637-1.

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/s/

ARIANE O CONRAD
08/23/2017

HINA S MEHTA
08/24/2017

REVISED 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:	August 7, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208751
Product Name and Strength:	Fiasp (insulin aspart), injection, 100 units/mL 1,000 units per 10 mL vial Fiasp FlexTouch (insulin aspart), injection, 100 units/mL 300 units per 3 mL pen
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novo Nordisk
Submission Date:	March 29, 2017, June 12, 2017, June 26, 2017, and July 11, 2017
OSE RCM #:	2015-2637-1
DMEPA Primary Reviewer:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the resubmitted container labels and carton labeling for Fiasp and Fiasp FlexTouch to determine if they are acceptable from a medication error perspective. The carton and container labeling revisions are in response to recommendations that we made during a previous label and labeling review.[a] In addition, the applicant updated the carton and container labeling to include the proprietary names Fiasp and Fiasp FlexTouch after the names were conditionally approved on June 2, 2017.[b]

1.1 REGULATORY HISTORY

Novo Nordisk submitted NDA 208751 for Fiasp (insulin aspart) on December 9, 2015. The applicant received a Complete Response on October 7, 2016 due to multiple clinical pharmacology and immunogenicity deficiencies. Novo Nordisk submitted a class 2 resubmission in response to the Complete Response on March 29, 2017.

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.

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 our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[a] Vee S. Human Factors, Label and Labeling Review for Fiasp (insulin aspart, NDA 208751). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 July 20. RCM No.: 2015-2637.

[b] Thomas T. Proprietary Name Granted for Fiasp (insulin aspart). Silver Spring (MD): FDA, CDER, OSE; 2017 June 2. NDA 208751.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Novo Nordisk submitted a response to the Complete Response for Fiasp and Fiasp FlexTouch, under NDA 208751, which will be supplied in a multiple dose vial and disposable multiple dose pen injector containing 100 units/mL of insulin aspart, to improve glycemic control in adults with diabetes mellitus. DMEPA previously completed a review of the human factors study results for the pen injector and the proposed labeling submitted by Novo Nordisk for both the pen and vial preparations.[c] The carton and container labeling comments from this review were sent to the applicant on July 21, 2016. However, the review team's labeling comments for the prescribing information (PI) were not sent to the applicant during the previous review cycle because the NDA received a Complete Response in October 2016. Therefore, the comment provided in our previous labeling review for the PI was not addressed in the resubmitted labeling. In addition, we did not provide comment for the Instructions for Use (IFU).

Thus, we performed a risk assessment of the proposed labeling to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We noted several areas that could be clarified within the proposed labels and labeling for Fiasp and Fiasp FlexTouch.

4 CONCLUSION & RECOMMENDATIONS

We noted several areas that could be clarified within the proposed labels and labeling for Fiasp and Fiasp FlexTouch. We provide recommendations in Sections 4.1 for the Division and 4.2 for the Applicant.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

A. Highlights of Prescribing Information: Dosage and Administration
    1. We recommend adding the following as the first bulleted statement in this section: "See Full Prescribing Information for important administration and dosage instructions".
    2. We recommend removing the statement "(b) (4) " from this section.
    3. We recommend revising the statement "Subcutaneous injection: (b) (4) " as follows for improved clarity: "Subcutaneous injection: (b) (4) at the start of a meal or within 20 minutes after starting a meal".

[c] Vee S. Human Factors, Label and Labeling Review for Fiasp (insulin aspart, NDA 208751). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 July 20. RCM No.: 2015-2637.

B. Full Prescribing Information: Section 2.2 General Dosing Instructions

1. This section includes improper dose designations (i.e., trailing zeros). Thus, we recommend revising all instances of trailing zeros throughout the PI (e.g., revise 1.0 unit to 1 unit).
2. We recommend revising the statement [redacted] as follows for improved clarity: "[redacted] at the start of a meal or within 20 minutes after starting a meal."
3. We recommend moving the statement that reads [redacted] Individualize [redacted] the dose of TRADENAME based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal *[see Warnings and Precautions (5.2)]*." so that it is the first bulleted statement in this section.
4. We recommend removing the statement "Patients on basal-bolus treatment who forget a mealtime dose [redacted] to monitor their blood glucose level to decide if an insulin dose is needed. [redacted] resume their usual dosing schedule at the next meal." because this is patient counseling information. Consider moving this statement to Section 17 Patient Counseling.

C. Full Prescribing Information: Section 2.4 Converting to TRADENAME from Other Insulins

1. We recommend revising the statement [redacted] ." to read as follows: [redacted]

D. Full Prescribing Information: Section 3 Dosage Forms and Strengths

1. We recommend revising the statement as follows for improved readability: "[redacted] 100 units of insulin aspart per mL (U-100) is available as a clear and colorless solution for injection in:"

E. Full Prescribing Information: Section 16.1 How Supplied

1. We recommend revising the statement as follows for improved readability: "TRADENAME (insulin aspart injection) 100 units of insulin aspart per mL (U-100) is available as a clear and colorless solution for injection in:"

F. Full Prescribing Information: Section 17 Patient Counseling

1. We recommend revising the statement "[redacted]" to read "Advise the patient to read the FDA-Approved Patient Labeling".
2. [redacted]

(b) (4)

3. Under the (b) (4) heading, we recommend replacing the removed information, noted above in comment F.2., with the following statement:

   "Hypoglycemia due to Medication Errors
   Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products (b) (4) ."

Instructions for Use (IFU)-FlexTouch

A. We recommend revising the statement "**Fiasp FlexTouch Pen ("Pen") is a prefilled disposable pen** containing 300 units of U-100 Fiasp (insulin aspart injection) (b) (4) ." to read as follows for improved clarity: "**Fiasp FlexTouch Pen ("Pen") is a prefilled disposable pen** containing 300 units of U-100 Fiasp (insulin aspart injection)."

4.2 RECOMMENDATIONS FOR NOVO NORDISK

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

A. Carton Labeling and Container Labels
   a. Include the approved routes of administration to the vial carton and container labeling principal display panel per 21 CFR 201.100(b)(3).
B. Carton Labeling and Container Label for Professional Samples
   a. Increase the size and prominence of the "Sample. Not for Resale" statement on the drug sample's label and the "Sample" statement on the drug sample

container's labeling so that it is clear that these are drug samples, per 21CFR 203.38(c). Consider using a different font color or a text box for improved differentiation.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Fiasp that Novo Nordisk submitted on March 29, 2017.

Table 2. Relevant Product Information for Fiasp and Fiasp FlexTouch

Initial Approval Date	n/a
Active Ingredient	insulin aspart
Indication	to improve glycemic control in adults with diabetes mellitus
Route of Administration	subcutaneous and intravenous
Dosage Form	injection
Strength	100 units/mL
Dose and Frequency	• individualized dose administered subcutaneously at the start of a meal or within 20 minutes after starting a meal • individualized dose administered by intravenous infusion under direct medical supervision only
How Supplied	10 mL vials 3 mL FlexTouch pen
Storage	

TRADENAME presentation	Not in-use (unopened)		In-use (opened)	
	Room Temperature (below 30°C)	Refrigerated (2°C to 8°C)	Room Temperature (below 30°C)	Refrigerated (2°C to 8°C)
10 mL vial	28 days	Until expiration date	28 days	28 days
3 mL TRADENAME FlexTouch	28 days	Until expiration date	28 days	28 days

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 29, 2017, we searched the L:drive using the terms, insulin aspart, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review[d] for this insulin aspart (submitted under NDA 208751 and we confirmed that the carton and container labeling comments were implemented; however, the comments for the prescribing information were not implemented because the application received a complete response.

[d] Vee S. Human Factors, Label and Labeling Review for Fiasp (insulin aspart, NDA 208751). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 July 20. RCM No.: 2015-2637.

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,[e] along with postmarket medication error data, we reviewed the following Fiasp labels and labeling submitted by Novo Nordisk on March 29, 2017, June 12, 2017, and June 26, 2017.

- Container labels
- Carton labeling
- Professional Sample Container Labels
- Professional Sample Carton Labeling
- Prescribing Information: \\cdsesub1\evsprod\nda208751\0031\m1\us\prop-ft-ifu.doc

C.2 Label and Labeling Images

Container labels

(b) (4)

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

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

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

/s/

ARIANE O CONRAD
08/07/2017

HINA S MEHTA
08/07/2017

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Therapeutic Proteins
Bethesda, MD 20892
Tel. 301-827-1790

Memorandum of Review

STN: NDA 208751
Subject: Immunogenicity consult: Original NDA for insulin aspart (faster aspart)

Date: 7-26-2016

Primary Reviewer: Steven Bowen, PhD
Secondary Reviewer: Susan Kirshner, PhD

RPM: Callie Cappel-Lynch
Clinical Division: DMEP

Sponsor: Novo Nordisk
Product: Insulin aspart for injection (faster aspart)
Indication: Glycemic control for patients with diabetes mellitus

Submission Date: 12/8/2015
Consult Request Date: 6/3/2016
PDUFA Goal Date: 10/8/2016

Summary of Review: Due to major deficiencies identified in the validation of the anti-drug antibody (ADA) assays and the clinical data submitted as part of NDA 208751, I recommend a Complete Response for this application.

This is a review of information pertaining to the immunogenicity of insulin aspart for injection ("faster aspart"; Novo Nordisk). The primary clinical immunogenicity assessment of "faster aspart" was conducted in a parallel arm study (trial 3852) in comparison with the approved insulin aspart product NovoLog® (Novo Nordisk) in patients with diabetes mellitus. The Sponsor analyzed the incidence of anti-drug antibodies (ADA) in each group and the overall antibody levels in each group. However, the Sponsor did not provide an analysis of treatment-boosted ADA responses in each group.

Samples collected from patients in trial 3852 were tested using a radioimmunoprecipitation assay (RIA) to detect ADA and antibodies that are cross-reactive to human insulin. Two Validation Reports were submitted (960358 and 215373)

and are reviewed here. A six item information request for more information about the development, validation, and routine performance of the assays was sent to the Sponsor on August 1st 2016. The response was received on August 25th, 2016 and will be reviewed in the next review cycle. Due to major deficiencies identified in the validation of the ADA assays as well as the clinical data I recommend a Complete Response for this application.

Comments to Sponsor- *Note that the IR response recieved on August 25th 2016 (Seq 0021) will be reviewed in the next cycle.

Regarding the validation of the radioimmunoprecipitation assay (RIA) for the detection of insulin aspart-specific and cross-reactive anti-human insulin anti-drug antibodies refer to the comments below.

1. Validation Report 215373 describes the QC3 suitability control as a guinea pig polyclonal anti-human insulin (GPα Insulin). Table 1-6 of Section 2.7.1 of the application (Summary of biopharmaceutic studies and associated analytical methods) describes QC3 as a polyclonal anti-insulin aspart antibody. Explain the discrepancy between the two descriptions of QC3 and indicate what immunogen was used to raise the QC3 antibodies used during the testing of clinical samples.

2. It is not clear whether the patient samples were diluted prior to testing. If patient samples are diluted prior to testing, provide data demonstrating the suitability of the minimum required dilution.

3. Serum samples were tested in three parallel conditions: D, E, and F. Conditions E and F involved competition with unlabeled insulin aspart and human insulin respectively. However, the concentrations of unlabeled insulin aspart and human insulin used in the assay are not provided. Indicate the concentrations of unlabeled insulin aspart and human insulin used in the assay as well as the rationale for the selected concentrations.

4. The Sponsor did not provide data demonstrating the tolerance of the assay to on-board insulin aspart. The tolerance of the assay to human insulin was determined during assay development but supporting data was not provided. Provide data demonstrating the assay tolerance of insulin aspart and human insulin to ensure that on-board levels of these protiens will not interfere with assay performance.

5. The levels of total anti-drug antibodies (ADA), insulin aspart-specific antibodies, and antibodies cross-reactive with human insulin are quantitated using the percentage of total radiolabeled tracer (insulin aspart) that is co-precipitated with Ig (%B/T). However, there is insufficient data in the Validation Reports to demonstrate that the assay is quantitative. One approach to address this deficiency

and support the use of the %B/T value as a quantitative measure of antibodies in patient samples would be to demonstrate that there is a linear relationship between the positive control antibody concentration and the %B/T signal. Include a graphical and tabular analysis for each series (D, E, F) and the subtracted (D-E, D-F, F-E) values.

6. Section 2.7.1 Table 1-6 indicates that the two positive suitability controls used for analysis of clinical samples were QC2, monoclonal anti-insulin aspart, 560 ng/ml, and QC3, guinea pig polyclonal anti-human insulin antibody, 23-230 ng/ml. The sensitivity analysis described in Validation Report 215373 indicates that the amounts of both QC2 and QC3 used are close to the upper limit of quantitation of the assay. This raises concerns that your suitability controls are inadequate to ensure the detection of low levels of ADA and suitable assay performance. Low positive controls should be set to have a 1% failure rate based on the assay cutpoint. Indicate how the detection of low levels of ADA was demonstrated during clinical testing. For guidance refer to FDA Draft Guidance: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (2016).

7. Some of the assay parameters, such as intra-assay precision, inter-assay precision, and robustness were validated by analyzing only the D-E series. However, the clinical samples were evaluated using the D-F and F-E series. Therefore, assay parameters validated using only the D-E conditions need to be validated using the D-F and F-E series using appropriate suitability controls to demonstrate that the assay performs appropriately for the detection of insulin aspart specific (D-F) and cross-reactive (F-E) antibodies.

8. The Sponsor did not provide data demonstrating the stability of the positive control antibodies used during the testing of clinical samples. In order to demonstrate that the X14-6F34 and GPa Insulin antibodies remain stable under normal testing conditions assess the performance of the antibodies under long-term storage, freeze-thaw, and benchtop conditions.

9. The acceptance criteria used for the QC2 and QC3 suitability controls were calculated from a nominal value for each control +/- 20%. It is unclear how the nominal values for QC2 and QC3 indicated in Table 1-6 of Section 2.7.3 were calculated or what the upper and lower acceptance limits were for each series. Provide a description of how the calculations were done to establish the acceptance criteria for the suitability controls (including the QCneg) used during testing of clinical samples.

10. Validation data for the labeling efficiency, batch-to-batch consistency, and stability of the radiolabeled insulin aspart tracer were not provided. Provide data validating these attributes of the radiolabeled insulin aspart tracer used in the RIA.

Regarding the analysis of clinical data from Study NN1218-3852 refer to the following comment.

1. Section 2.7.1 of your application notes that most patients were positive for ADA at baseline and that no cutpoints were established to evaluate treatment-boosted ADA responses. In order to compare the immunogenicity of "faster aspart" and NovoRapid® the frequency of patients with treatment-emergent and treatment-boosted ADA should be determined. Indicate how treatment-emergent and treatment-boosted patients were mathematically defined in your analysis as well as the frequency of patients in each treatment group with treatment-induced or treatment-boosted ADA.

Background

Novo Nordisk is seeking approval of insulin aspart (referred to by the sponsor as "faster aspart or FIAsp"), a mealtime insulin to improve glycemic control in adult patients with diabetes mellitus. "Faster aspart" has a different formulation than the currently approved insulin aspart NovoRapid® (Proprietary name NovoLog® in the US), which was approved by the FDA in 2000. The "faster aspart" formulation includes two excipients (nicotinamide and L-arginine hydrochloride) not present in the NovoRapid® formulation that are intended to increase the speed of absorption and to stabilize the protein respectively. Both nicotinamide (also known as niacinamide and vitamin B3) and L-arginine hydrochloride are USP grade.

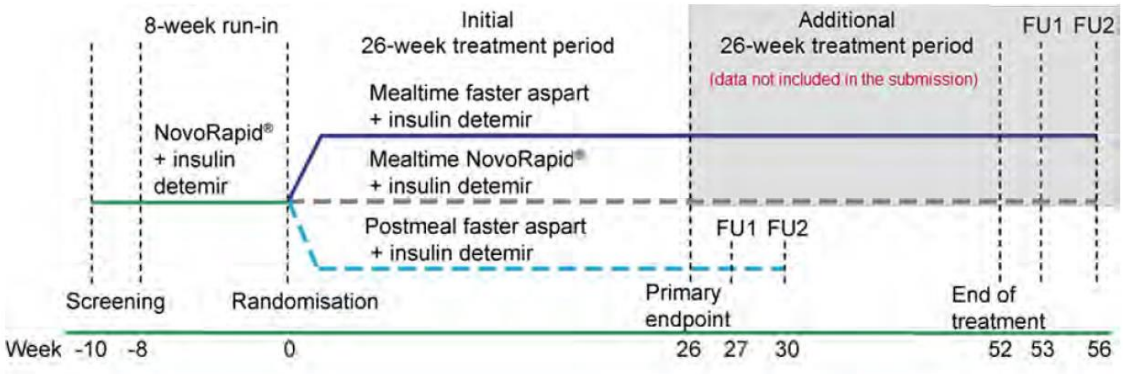
Insulin aspart differs from endogenous human insulin by the substitution of a single proline on the B chain of insulin with aspartic acid. This substitution prevents self-association and increases the availability of the active monomeric form, resulting in more rapid action. Immunogenicity of "faster aspart" compared to NovoRapid® was evaluated in Phase 3a study NN1218-3852: *Efficacy and Safety of FIAsp Compared to Insulin Aspart Both in Combination with Insulin Detemir in Adults with Type 1 Diabetes.* In this study, adult patients with type 1 diabetes mellitus (T1DM) were treated with NovoRapid® in combination with insulin detemir (long-acting insulin) for an 8-week lead-in period followed by randomization into one of 3 parallel arms:

- Mealtime "faster aspart" in combination with insulin detemir
- Mealtime NovoRapid® in combination with insulin detemir
- Postmeal "faster aspart" in combination with insulin detemir

The “mealtime” insulin aspart administrations occur 0-2 minutes before each meal. The “postmeal” administrations occur 20 minutes after the completion of each meal.

All three arms were treated for an initial 26 week period during which immunogenicity samples were collected at week 0, week 12, and week 26. For the mealtime “faster aspart” and mealtime NovoRapid® arms an additional 26-week treatment period was conducted and additional samples were collected at week 40 and week 52.

NN1218-3852 design



Serum samples were analyzed for anti-drug antibodies (ADA) and ADA that cross-react with human insulin using a radioimmunoprecipitation (RIP) assay. The assay was developed at Novo Nordisk and was transferred to (b) (4) for the testing of clinical samples. Initial assay validation was performed in 1997 and is included in Validation Study Report 960358: *Validation of RIA used for the determination of Insulin, X14 and NN304 antibodies*. Insulin aspart is referred to as X14 in many of the validation exercises. Additional validation was performed in 2015 and the data are included in Validation Study Report 215373: *Validation to document assay sensitivity and normal ranges in an anti-insulin aspart antibody RIA method.*

Principle of the Assay

The RIP assay involves the overnight incubation of patient serum samples with a radiolabeled insulin aspart tracer. Ig molecules in the sample are then precipitated with polyethylene glycol (PEG) 6000 (12.6%), washed, and measured on a gamma counter. The level of radioactivity of the precipitated sample is proportional to the level of ADA bound to the radiolabeled tracer. Values for each sample are expressed as %B/T (the percentage of bound tracer after precipitation to total tracer). Each patient sample is measured in three parallel tests:

- With assay buffer and radiolabeled insulin aspart tracer
- With excess unlabeled insulin aspart competitor and insulin aspart tracer
- With excess unlabeled human insulin competitor and insulin aspart tracer

The tests are designated D, E, and F as shown in the table below.

Table 1–5 Antibody against insulin aspart analyses series

Series	Assay mixture	Result represent the sum of:
D	Sample + buffer+ insulin aspart tracer	Background, insulin aspart specific and cross-reacting antibodies
E	Sample + unlabelled insulin aspart + insulin aspart tracer	Background
F	Sample + unlabelled human insulin + insulin aspart tracer	Background, insulin aspart specific antibodies

The determination of total ADA in each serum sample is made by subtracting the signal of the sample competed with insulin aspart competitor (E, referred to by the Sponsor as "background") from the uninhibited sample (D). ADA that cross-react with human insulin are measured by subtracting the signal of the sample competed with unlabeled human insulin (F) from the uninhibited sample (D). Thus, the equations used to derive the ADA values reported for each sample are:

Total ADA= D-E

Insulin Aspart Specific ADA= F-E

Cross reactive ADA=D-F

FDA Comment: The Sponsor does not use a tiered approach for ADA assessment as recommended by FDA guidance. The immunogenicity assessment is based on a single assay where the "background" is determined by competition with cold drug. Although this is not the recommended practice for immunogenicity assessment it is acceptable provided the assay is specific and sensitive.

Assay Cutpoints

Separate cutpoints were determined based on the 99% percentile of series D-E, D-F and F-E based on 50 normal human serum samples. The cutpoints are shown below.

Table 4 99% percentile for series D-E, F-E and D-F

Series	N	Mean %B/T	99% Percentile Col Quantile [%B/T(series) 0.99]
D-E	242	0.5	1.9
F-E	242	0.4	1.9
D-F	262	0.2	0.7

Fifty serum samples from healthy donors ((b) (4)) were tested in series D, E, and F in twelve independent runs by three different analysts. Values for series D-E, D-F, and F-E were calculated for each sample and the distribution of each series was analyzed for outliers by box plot analysis. After removal of outliers the normality of the distribution for each run was tested using a Shapiro-Wilk normality test. The normality results for each series are shown below. The Prob<W value indicates the probability that the value came from a normal distribution. Values > 0.05 are considered normally distributed. For those distributions that were not normal the skewness (another indicator of normality) was tested with values between -1 and 1 considered normal.

All three series had runs that were not normally distributed, and so a non-parametric 99% cutpoint was established for series D-E, D-F and F-E.

Series D-E

Table 6 Assessment of normality (Shapiro-Wilk W test) of data for screening cut point evaluation; summary data, series D-E (Total insulin aspart antibodies)

Set-up	W	Prob<W[1]	Skewness[2]
001	0.942631	0.2687	
002	0.899115	0.0397	0.4991586
003	0.947078	0.381	
004	0.934504	0.1694	
006	0.855247	*0.0082*	*1.1078086*
007	0.872014	*0.0104*	*1.0874787*
008	0.931992	0.135	
009	0.876234	0.0124	0.9811527
010	0.928315	0.1612	
011	0.839725	*0.0036*	*1.3804803*
012	0.880277	0.0148	0.5054164
025	0.914665	0.0783	

1. Prob <W > 0.05, data is normal distributed. Prob <W <0.05, data is not normal distributed

2: Skewness between -1 and 1, data can be regarded as normal distributed.

Italics. Data not normal distributed and skewness factor > 1 or <-1

Series F-E

Table 7 Assessment of normality (Shapiro-Wilk W test) of data for screening cut point evaluation; summary data, series F-E (insulin aspart specific antibodies)

Set-up	W	Prob<W[1]	Skewness[2]
001	0.880837	0.0183	0.6449428
002	0.861378	0.0083	0.6342016
003	0.827625	*0.0038*	*1.4767112*
004	0.931045	0.1445	
006	0.863532	0.0112	0.9767063
007	0.79803	*0.0006*	*1.5272763*
008	0.89901	0.0284	0.8044202
009	0.852055	*0.0046*	*1.2140409*
010	0.933686	0.2024	
011	0.807329	*0.0011*	*1.8510372*
012	0.829335	0.0019	0.6865228
025	0.818216	*0.0016*	*1.2692319*

1. Prob <W > 0.05, data is normal distributed. Prob <W <0.05, data is not normal distributed

2: Skewness between -1 and 1, data can be regarded as normal distributed.

Italics. Data not normal distributed and skewness factor > 1 or <-1

Series D-F

Table 8 Assessment of normality (Shapiro-Wilk W test) of data for screening cut point evaluation; summary data, series D-F (Cross reacting antibodies to HI)

Set-up	W	Prob<W[1]	Skewness[2]
001	0.916918	0.0572	
002	0.939506	0.2347	
003	0.95058	0.376	
004	0.939766	0.2156	
006	0.933111	0.1772	
007	0.961662	0.5236	
008	0.904688	0.0432	0.529691
009	0.951087	0.286	
010	0.957355	0.4377	
011	0.941282	0.1742	
012	0.925349	0.0982	
025	0.937641	0.1599	

1. Prob <W > 0.05, data is normal distributed. Prob <W <0.05, data is not normal distributed

2: Skewness between -1 and 1, data can be regarded as normal distributed.

Although the D-F series were normally distributed the non-parametric 99% CI was used to be consistent with the series D-E and series F-E.

FDA comment: The Sponsor did not Log-transform the data and re-test for normality to potentially allow for the use of a parametric cutpoint as recommended by FDA guidance. Log-transformation could be applied to these data to evaluate the feasibility of a parametric cutpoint. However the non-parametric cutpoints are reasonable and the approach valid. Therefore no further action is recommended.

The concentration of insulin aspart or human insulin used to inhibit the sample in series E and F respectively is not explicitly stated. For this assay it is critical that the concentration of inhibiting drug be at saturation so as to completely bind up the specific antibody in the sample. The Sponsor should provide a dose response curve of the levels of inhibition at various concentrations of inhibitor and provide a rationale for the selected concentrations used in series E and F (see comment to the Sponsor).

Justification of a Fixed Cutpoint

To justify the use of a fixed cutpoint the Sponsor analyzed variation in the means (ANOVA) and variances (Levene's Test) between the 12 runs for each series.

Table 4 Means: Analysis of variance. Equal means (p>0.05)

Series	Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Series D-E	Set-up	11	4.680164	0.425469	1.1241	**0.3429**
	Error	240	90.838407	0.378493		
	C. Total	251	95.518571			
Series F-E	Set-up	11	1.895153	0.172287	0.5104	**0.8955**
	Error	240	81.010045	0.337542		
	C. Total	251	82.905198			
Series D-F	Set-up	11	1.426089	0.129644	1.7952	**0.0554**
	Error	240	17.332442	0.072219		
	C. Total	251	18.758532			

0-hypothesis = equal means
If Prob > F is above 0.05, the 0-hypothesis is accepted
If Prob > F is below 0.05, the 0-hypothesis is rejected

Table 5 Test of equal variances. Equal variances according to Levenes test, (p>0.05)

Series	Test	F Ratio	DFNum	DFDen	Prob > F
Series D-E	**Levene**	**0.9503**	**11**	**240**	**0.4929**
Series F-E	**Levene**	**0.7560**	**11**	**240**	**0.6837**
Series D-F	**Levene**	**1.1859**	**11**	**240**	**0.2974**

0-hypthesis = equal variances
If Prob > F is above 0.05, the 0-hypothesis is accepted
If Prob > F is below 0.05, the 0-hypothesis is rejected

FDA comment: For the ANOVA of mean values and the Levene's test of equal variances the data were not significantly different between runs. This approach to justify the fixed cutpoint is appropriate. These data indicate that the means and variances were similar for the same 50 samples between runs, and therefore a fixed cutpoint is acceptable.

Suitability controls

Three positive system suitability controls were included during assay validation.

QC2low: monoclonal anti-insulin aspart antibody X14-6F34 (50ng/ml)
QC2: monoclonal anti-insulin aspart antibody X14-6F34 (560ng/ml)
QC3: guinea pig polyclonal anti-human insulin (GPα Insulin, 23-230 ng/ml of anti-insulin antibody estimated from 2300 ng/ml of total Ig)

*Only QC2 and QC3 were included for routine sample testing as indicated in the table below.

Table 1–6 Two-system suitability control for determination of antibodies against insulin aspart

System suitability control	Content	Nominal value from at least six assay runs
QC2	560 ng/mL monoclonal anti-insulin aspart antibody in serum	49 %B/T
QC3	23−230 ng/mL polyclonal anti-insulin aspart antibody in serum[A]	32 %B/T

QC2 and QC3: two different system suitability controls. %B/T: percent bound radioactivity (B) of the total amount of radioactivity (T), the %B/T value is proportional to the amount (titer) of anti-insulin aspart antibody present in the sample.

[A] A concentration of 2300 ng/mL total Ig was spiked into serum, corresponding to 23-230 ng/mL anti-insulin aspart antibodies assuming that 1-10 % of the total Ig is anti-insulin aspart antibodies

FDA Comment: The validation report refers to QC3 as anti-human insulin and table 1-6 refers to QC3 as anti-insulin aspart. This point will be communicated to the sponsor for clarification in the CR letter. It is unclear how the nominal value was calculated (i.e. from series D-E, F-E, D-F etc.). This also requires clarification in a CR comment to the Sponsor.

The acceptance criteria for the suitability controls that were used during the testing of clinical samples were the nominal value +/- 20%. This is consistent with the FDA Bioanalytical Method Validation guidance.

QCneg: The negative suitability control consisted of pooled human serum from normal donors ((b) (4)).

Acceptance criteria for suitability controls during validation

Acceptance ranges of the suitability controls were determined for the validation exercises using the **mean +/- t(onesided,0.005,df_{n-1})xSD** over 24 independent runs by 3 different analysts. This represents the range for each suitability control with a 1% failure rate. The acceptance ranges are shown below. These criteria were retroactivly applied to each run after the validation exercises were complete. Runs that were out of range were repeated.

Table 14 QC acceptance ranges

Range	QCNeg (F-E) within or equal to:	QC2 (F-E) within or equal to:	QC2low (F-E) within or equal to:	QCNeg (D-E) within or equal to:	QC2low (D-E) within or equal to:	QC3 (D-E) within or equal to:
Mean ± t(0.005;df)xSD one-sided 99.5%	1.7	37.0	6.3	2.0	7.7	61.4
	-0.4	-1.1	0.0	0.0	0.3	46.5

FDA comment: The approach to establish acceptance ranges for the suitability controls for validation is reasonable. However, the range for QC2 (F-E) is quite wide and includes negative numbers which would allow the series E value (inhibited with insulin aspart) to be greater than the series F value (inhibited with human insulin). For the insulin aspart-specific QC2 antibody this would be counter to the expected result, and

thus would not indicate the proper function of the assay. However, during validation the QC2 was within a reasonable range, and thus is not a major concern.

The rationale for not having suitability controls for the D-F series, which measures antibodies cross-reactive to human insulin, is unclear. The D-F values could be calclulated for the GPa polyclonal antibody against human insulin and acceptance ranges for this series could be established. However, the current suitability controls do provide control over all three conditions, D, E, and F, and so no further action is required.

QC2 was analyzed in the F-E series but not in the D-E series. The Sponsor should include this control in the D-E series because it provides useful QC coverage in the middle range of detection.However, the D-E series has QC2low which provides coverage in the low range and QC3 which provides coverage in the upper range which is acceptable.

Sensitivity

The sensitivities of the assays were calculated by serially diluting the positive QC antibodies X14-6F34 and GP α Insulin as well as a monoclonal anti-human insulin (HUI-001) in normal human serum. The sensitivities are reported as the highest dilution that tested above the assay cutpoint for each series (D-E, F-E, and D-F). The data are shown in the tables below.

X14-6F34

Table 9 Sensitivity of series D-E, Total insulin aspart antibodies and series F-E, insulin aspart specific antibodies using an insulin aspart specific monoclonal antibody X14-6 F34

Assay ID	215373-13	215373-16	215373-19	215373-22	215373-13	215373-16	215373-19	215373-22
Analyst	Tech 3	Tech 1	Tech 3	Tech 1	Tech 3	Tech 1	Tech 3	Tech 1
Concentration X14-6 F34 (µg/ml)	Result (%B/T) D-E series				Result (%B/T) F-E series			
20	53.5	41.8	43.0	69.8	53.1	46.9	44.5	68.7
10	44.3	36.5	33.7	66.8	44.1	37.3	32.3	65.4
5	37.9	29.3	25.4	62.3	37	28	24.8	59.4
2.5	31	23.4	20.4	54.5	34.2	22.7	18.6	57.2
1.25	27.5	19.2	15.8	49.8	25.3	16.6	13.7	45.8
0.625	19.9	14.3	10.8	41.5	18.1	12.6	9.5	38.7
0.313	13.2	11	7.8	28.6	13.1	7.2	6.3	26.4
0.156	8.9	7.4	5.2	18.5	8.4	5.6	4.2	15.9
0.078	5.7	4.5	3.4	10.7	4.7	2.3	2.3	9.1
0.039	3.6	2.3	1.7	6.9	2.7	1.9	1.3	5.8
0.020	2.2	1.6	1.1	5	1.7	1.2	1	3.9
0.010	1.6	1	0.9	2.9	1.5	0.9	0.9	2.3
0.005	1.4	1.2	1.2	2.4	1	0.9	0.7	1.8
0	1	1	0.8	1.6	0.6	0.4	0.4	1.2
99% percentile (Cut point)	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9
Lowest concentration ≥ cut point (µg/ml)	0.020	0.039	0.078	0.005	0.039	0.039	0.078	0.010
Mean concentration ≥ assay cut point (µg/ml)				0.0355				0.04151563
SD concentration ≥ assay cut point (µg/ml)				0.03156475				0.02790872
Sensitivity of D-E series in ng/ml								36
Sensitivity of F-E series in ng/ml								42

GP α Insulin

Table 10 Sensitivity of series D-E (Total insulin aspart antibodies) and D-F (cross reacting antibodies to human insulin) using an Guinea Pig anti-human insulin polyclonal antibody

Assay ID	215373-14	215373-17	215373-20	215373-23	215373-14	215373-17	215373-20	215373-23
Analyst	Tech 3	Tech 1	Tech 3	Tech 1	Tech 3	Tech 1	Tech 3	Tech 1
Concentration GP α insulin (µg/ml)	Result (%B/T) D-E series				Result (%B/T) D-F series			
20	64.4	65.4	54.4	53.5	55.9	54.8	48.5	39.9
10	73.3	72.5	66.1	66	64.7	62.4	56.4	57.7
5	79.6	78	72.5	75.1	73.5	70.3	61.9	68
2.5	63.8	61.8	60.7	62.7	60.4	58.4	56.4	58.1
1.25	33.3	32.9	35.2	33.4	31.9	31.3	32.4	31.5
0.625	15.6	15	17.6	16.1	14.8	14	16.5	14.8
0.313	8.1	8	9.6	8.4	7.5	7.2	8.8	7.6
0.156	4.4	4.5	5	5.2	4.2	3.8	3.9	4.5
0.078	2.5	2.7	3.1	2.9	1.8	2.2	2.7	2.5
0.039	1.9	1.7	2.5	1.9	1.3	1	1.9	1.3
0.020	1.3	1.2	1.6	1.1	0.9	0.7	1.1	0.5
0.010	0.9	1.1	1.3	1.2	0.3	0.6	0.8	0.5
0.005	1.1	1.3	0.8	1.1	0.4	0.7	0.3	0.5
0	0.5	0.9	0.6	0.7	-0.1	0.3	0.1	0.1
99% percentile (cut point)	1.9	1.9	1.9	1.9	0.7	0.7	0.7	0.7
Lowest concentration ≥ cut point (µg/ml)	0.039	0.078	0.039	0.039	0.020	0.020	0.010	0.039
Mean concentration ≥ assay cut point (µg/ml)				0.04875				0.02213281
SD concentration ≥ assay cut point (µg/ml)				0.0195				0.01215215
Sensitivity of D-E series in ng/ml								49
Sensitivity of D-F series in ng/ml								22

HUI-001

Table 11 Sensitivity of series D-E (Total insulin aspart antibodies) and D-F (cross reacting antibodies to human insulin) using an anti-human insulin monoclonal antibody

Assay ID	215373-15	215373-18	215373-21	215373-24	215373-15	215373-18	215373-21	215373-24
Analyst	Tech 3	Tech 1	Tech 3	Tech 1	Tech 3	Tech 1	Tech 3	Tech 1
Concentration HUI-001, (µg/ml)	Result (%B/T) D-E series				Result (%B/T) D-F series			
20	53.5	48.3	45.8	54.7	48.9	44.3	43.8	52
10	54.8	51.9	49.7	52.6	49.1	49.2	45.8	48
5	60	52.3	53.9	55.2	52.3	47.7	52.5	50.4
2.5	61.6	55.9	55.8	56.9	56.2	52.5	51.8	50.6
1.25	66.1	61.7	62.3	61.8	61.5	58.1	55.3	56.3
0.625	66.5	61	62.3	64.4	63.2	58.6	62.6	60.9
0.313	69	64.1	65	66.2	66.5	62.4	60.4	63.3
0.156	64.6	60.3	59.4	60.3	63	59.4	56.9	58.9
0.078	46.7	45.6	43.9	43	45.8	45	42.8	42
0.039	26.3	27.8	25.1	24.9	25.4	27.2	24.2	24.3
0.020	13.4	14.5	11.8	12.9	12.3	13.8	11.9	12.4
0.010	7.1	7.6	6.9	6.4	6.2	6.9	6.4	6.2
0.005	4.3	4.5	4.2	3.3	3.1	3.9	3.6	3
0	1	1	1	0.7	0.4	0.3	0.5	0.1
99% percentile	1.9	1.9	1.9	1.9	0.7	0.7	0.7	0.7
Lowest concentration ≥ plate cut point (µg/ml)	0.005	0.005	0.005	0.005	0.0050	0.0050	0.0050	0.0050
Mean concentration ≥ assay cut point (µg/ml)				0.005				0.005
SD concentration ≥ assay cut point (µg/ml)				0				0
Sensitivity of D-E series in ng/ml								5
Sensitivity of D-F series in ng/ml								5

The X14-6F34 monoclonal anti-insulin aspart gave sensitivity results of 36ng/ml for series D-E (total ADA) and 42ng/ml for series F-E (insulin aspart specific ADA). The assay had a sensitivity to polyclonal GP α Insulin of 49ng/ml for series D-E and 22ng/ml for series F-E. The monoclonal HUI-001 gave a higher sensitivity of 5ng/ml for series D-E and 5ng/ml for series D-F (human insulin cross reactive antibodies).

FDA comment: For GPα Insulin the linear range of the assay appears to be roughly between 2%-60% B/T for each series. For X14-6F34 there is not clear linearity at any concentration range. Since the Sponsor is not using a titering assay to estimate the levels of ADA in patients, it is critical that the Sponsor demonstrate a linear relationship between ADA concentration and %B/T signal. This was demonstrated for the GPa Insulin polyclonal antibody but not for the insulin aspart specific monoclonal X14-6F34. This concern was communicated to the sponsor in the August 1st, 2016 IR but the response was not reviewed in this cycle.

For the testing of clinical samples the two positive suitability controls were X14-6F34 at 560ng/ml and GPα Insulin at 2300ng/ml of total Ig which, based on the dose response curves, are toward the upper limit of quantitation. Thus there was no positive suitability control used for the testing of clinical samples at the lower end of the dose response curve close to the cutpoint. This concern was communicated to the sponsor in the August 1st, 2016 IR but the response was not reviewed in this cycle.

Precision

The precision of the RIA assay was performed as part of the original assay validation in 1997 submitted in Validation Report 960358.

Intra Assay Variability

Intra-assay variability was measured in 10 replicates of low, medium and high concentration of guinea pig polyclonal anti-insulin run in the same setup. The total ADA (series D-E) were measured.

Tracer		X 14	
Sample	Mean D-E	SD	% CV
Guinea Pig low	n = 10 11.79	1.283	10.88
Guinea Pig medium	n = 10 34.93	0.989	2.83
Guinea Pig high	n = 10 70.80	0.573	0.81

FDA Comment: *It is not clear if the guinea pig polyclonal antibody used in this validation exercise is GPa Insulin. However the three dilutions analyzed cover a reasonable range in the assay between ~11%-70% B/T.*

The variability was highest at the lowest concentration of antibody, but all concentrations had reasonable %CV values across the 10 replicates. The intra-assay variability is acceptable.

Inter-assay variability

Inter-assay variability was measured over 16 independent runs for the low, medium, and high antibody concentrations.

Control in series	Mean	n	SD	%CV
Low D-E, X14	9.1	16	0.651	7.2
Medium D-E, X14	32.0	16	3.447	10.8
High D-E, X14	65.6	16	3.185	4.9

FDA comment: The inter-assay variability at the three concentrations of antibody for series D-E are below the 15% CV recommended by FDA guidance and is therefore acceptable.

Drug Tolerance

The tolerance of the assay to insulin was assessed during assay development but the results were not provided in this submission. The Sponsor states that insulin interferes with the assay at 2000pmol/l but does not provide details as to how this was assessed.

According to the clinical study reports for PK studies NN1218-3888 insulin aspart reaches a mean maximal concentration (Cmax) of 250-300pmol/L in children, adolescents, and adults (see table below). The maximum concentration observed was 574.1pmol/L.

14.2.95 Insulin Aspart endpoints - Cmax - Faster Aspart - descriptive statistics - sensitivity analysis - full analysis set

	Children	Adolescents	Adults
Cmax (pmol/L)			
N	12	13	15
Mean (StD)	277.08 (111.83)	279.36 (93.59)	284.20 (95.17)
Median	257.95	276.80	257.70
Geometric mean	260.73	265.61	269.68
Min; Max	160.80; 574.10	165.00; 458.20	149.10; 502.30

N: Number of subjects, StD: Standard deviation
Sensitivity analysis where Cmax for CHILD subject 101041 at V3 (Faster Aspart) is set to the original value 574.1 pmol/L.

FDA comment: The observed levels of "faster aspart" in the PK studies were below the reported insulin tolerance of the assay. However, the levels of drug reported are specific

for insulin aspart and may not reflect the total levels of insulin in the serum, especially for T1D patients also taking longer-acting insulin. Thus, it is possible that total insulin concentrations at the time of sampling

The tolerance of the assay to human insulin is not necessarily reflective of the tolerance to insulin aspart. The tolerance of the assay for insulin aspart is not known and should be assessed using "faster aspart" and human insulin with the cutpoints established during validation.

Positive control stability

The stability of the QC2 and QC3 antibodies used during testing of clinical samples was not assessed. Validation report 960358 includes a -20oC long term storage stability assessment of KIII, a human sample known to have anti-insulin antibodies. A freeze-thaw stability assessment was performed for a guinea pig polyclonal antibody in human serum at low, medium, and high concentrations and no effect was observed after 5 freeze-thaw cycles.

FDA Comment: The long-term, freeze-thaw, and benchtop stability of the QC2 and QC3 antibodies used during the testing of clinical samples was not assessed. This analysis should be done to determine the proper handling of the suitability controls for the SOPs. Since the SOPs were not provided it is not clear how the suitability controls are handled during testing. The relevant SOPs should be provided.

Robustness

Hemolysis

FDA comment: The effect of 5mg/ml of hemoglobin in the sample was tested on the guinea pig polyclonal at the medium dilution and was found to have no effect on the signal in series D-E. This does not raise any concerns about assay interference by hemolysis of the patient samples.

Bilirubin

FDA comment: The effect of 200ug/ml of bilirubin was analyzed with the X14 monoclonal antibody in the D-E series and was found to have no significant effect. This is acceptable.

Lipemia

The effect of lipemia was assessed by analyzing various concentrations of lipid spiked into the guinea pig medium control. The results indicate a significant reduction in signal at 20mg/ml of lipid and a total inhibition of the signal at 40mg/ml (see red boxed area in table below).

Table 1. The influence of lipid on the antibody measurements

Sample with lipid added.	Series A-B %B/T	Series D-E X14 %B/T	Series D-E NN304 %B/T
40 mg/ml	0.5	1.2	0.4
40 mg/ml	0.6	1.2	0.4
40 mg/ml	0.8	1.7	0.8
40 mg/ml	0.7	1.2	0.3
40 mg/ml	0.7	1.1	0.5
40 mg/ml	0.7	1.0	0.3
Mean	**0.7**	**1.2**	**0.5**
SEM	**0.042**	**0.099**	**0.076**
p in comparison to 0 mg/ml	**<0.001**	**<0.001**	**<0.001**
20 mg/ml	17.8	21.8	8.0
20 mg/ml	16.7	21.3	6.4
20 mg/ml	17.4	21.7	7.9
20 mg/ml	17.9	22.6	6.9
20 mg/ml	18.5	22.9	7.9
20 mg/ml	18.1	22.4	6.6
Mean	**17.7**	**22.1**	**7.3**
SEM	**0.254**	**0.250**	**0.298**
p in comparison to 0 mg/ml	**<0.001**	**<0.001**	**<0.001**
10 mg/ml	21.5	25.6	8.6
10 mg/ml	20.8	25.4	9.3
10 mg/ml	20.1	25.3	9.1
10 mg/ml	19.5	25.1	8.8
10 mg/ml	20.4	25.3	9.4
10 mg/ml	21.5	25.6	9.8
Mean	**20.6**	**25.4**	**9.2**
SEM	**0.324**	**0.079**	**0.176**
p in comparison to 0 mg/ml	**0.12**	**0.55**	**0.11**
5 mg/ml	21.7	25.7	7.8
5 mg/ml	21.2	24.7	10.2
5 mg/ml	21.4	24.7	9.4
5 mg/ml	21.1	25.0	9.9
5 mg/ml	21.1	25.2	10.2
5 mg/ml	20.6	24.5	9.7
Mean	**21.2**	**25.0**	**9.5**
SEM	**0.149**	**0.178**	**0.368**
p in comparison to 0 mg/ml	**0.77**	**0.056**	**0.59**
2.5 mg/ml	21.3	25.6	9.0
2.5 mg/ml	21.5	25.7	9.1
2.5 mg/ml	21.5	25.2	8.4
2.5 mg/ml	21.1	26.0	9.2
2.5 mg/ml	21.6	25.7	8.2
2.5 mg/ml	21.1	25.6	8.5
Mean	**21.4**	**25.6**	**8.7**
SEM	**0.089**	**0.105**	**0.171**
p in comparison to 0 mg/ml	**0.59**	**0.52**	**0.014**
0 mg/ml	21.7	24.9	9.7
0 mg/ml	21.2	25.4	9.9
0 mg/ml	20.8	25.6	10.2
0 mg/ml	21.4	26.0	9.9
0 mg/ml	20.8	25.2	8.4
0 mg/ml	21.6	25.9	10.7
Mean	**21.3**	**25.5**	**9.8**
SEM	**0.159**	**0.171**	**0.314**

pH

The effect of altering the pH of the assay was tested by running the medium guinea pig positive control at a lower pH (6.7) and at a higher pH (7.8) compared to the nominal pH. It was found that at lower pH the signal was significantly higher and that at higher pH the signal was significantly lower than the control.

Table 14. The effect on the antibody measurement of lowered pH (pH 6.7) in the sample

Sample	Series A-B %B/T	Series D-E X14 %B/T	Series D-E NN304 %B/T
pH 6.7	27.2	34.1	13.6
pH 6.7	26.3	32.6	14.3
pH 6.7	27.9	33.2	14.4
pH 6.7	27.5	33.7	14.4
pH 6.7	27.9	34.3	13.9
pH 6.7	26.6	33.2	14.7
Mean	**27.2**	**33.5**	**14.2**
SEM	**0.273**	**0.260**	**0.162**
Control	22.7	27.4	11.9
Control	22.4	27.7	11.5
Control	22.1	27.4	12.9
Control	22.4	27.5	12.1
Control	22.4	28.3	12.8
Control	22.4	27.3	12.7
Mean	**22.4**	**27.6**	**12.3**
SEM	**0.077**	**0.151**	**0.232**
p values	**<0.001**	**<0.001**	**<0.001**

Table 15. The effect on the antibody measurement of risen pH (pH 7.8) in the sample

Sample	Series A-B %B/T	Series D-E X14 %B/T	Series D-E NN304 %B/T
pH 7.8	27.2	34.3	14.7
pH 7.8	27.4	33.3	16.2
pH 7.8	26.8	33.8	15
pH 7.8	27.8	33.1	16.1
pH 7.8	27.4	33.4	15.1
pH 7.8	27.2	33.6	15.8
Mean	**27.3**	**33.6**	**15.5**
SEM	**0.134**	**0.174**	**0.257**
Control	29.2	35.3	17.6
Control	27.3	34.6	17.6
Control	27.7	35.1	17.6
Control	27.8	35.1	17.0
Control	28.2	35.3	17.0
Control	28.5	36.1	17.5
Mean	**28.1**	**35.3**	**17.4**
SEM	**0.275**	**0.200**	**0.122**
p values	**0.024**	**<0.001**	**<0.001**

FDA Comment: The effect of altering the pH was small but statistically significant over 6 replicates. This does not raise any concerns about assay performance provided that all samples are run at the same pH.

Stability of Radiolabeled Tracer

The Sponsor analyzed the stability of the radiolabeled X14 tracer by comparing the first setup and last setup from the same batch of tracer in the low, medium, and high positive guinea pig polyclonal controls. The results are shown below.

Table 8 Drifting from start to end of upset with X14 tracer

Sample	% B/T Series D-E First in setup	% B/T Series D-E Last in setup	Difference
Guinea Pig low	9.9	9.6	0.4
Guinea Pig medium	29.6	27.3	2.3
Guinea Pig high	67.2	65.2	2.0
Blind	0.4	0.6	-0.2

FDA comment: There does not appear to be a difference in the magnitude of the signal between the first and last setups. However, it is not stated how much time elapsed between the setups or how the radiolabeled tracer was stored. The labeling efficiency, batch-to-batch variability, and stability of the radiolabeled tracer needs to be validated. A comment to this effect will be included in the CR letter.

Clinical Assessment of Immungenicity in Study NN1218-3852

The 120-day safety update received on 4/04/2016 included immunogenicity data through the 52 week sampling timepoint. The Sponsor calculated the incidence of ADA positive patients in the "faster aspart" and NovoRapid treatment arms for both cross-reactive antibodies (D-F) and insulin aspart specific antibodies (F-E). As shown in the table below >90% of patients tested above the assay cutpoint for cross-reactive antibodies at baseline and >99% of patients tested positive for cross-reactive antibodies at some point during the trial. >98% of patients had a response that was considered sustained, meaning that they tested positive at more than one visit during the trial or were positive at the last visit. Both treatment arms exhibited the same incidence of cross-reactive antibodies using this analytical approach. The incidence of insulin aspart-specific antibodies was lower, with >17% testing positive at baseline, >26% testing positive at some point in the trial and >23% having a sustained response. The two treatment arms were similar for insulin-aspart specific antibody incidence.

2: Incidence of anti-insulin aspart antibody positive subjects at 52 weeks - summary - trial 3852 52 weeks - safety analysis set

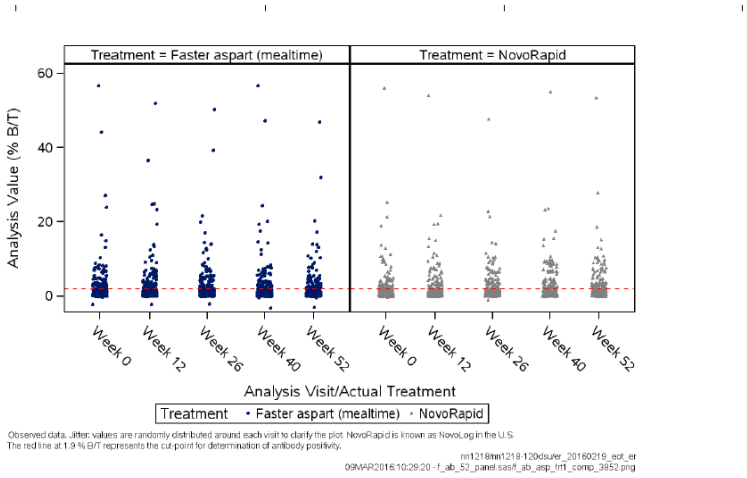
		Anti-insulin aspart antibody positive		
	Safety Set	Baseline N (%)	Anytime N (%)	Sustained N (%)
Cross-reacting antibodies				
Faster aspart (mealtime)	386	348 (90.2)	382 (99.0)	379 (98.2)
NovoRapid	380	352 (92.6)	377 (99.2)	376 (98.9)
Specific antibodies				
Faster aspart (mealtime)	386	67 (17.4)	103 (26.7)	91 (23.6)
NovoRapid	380	70 (18.4)	104 (27.4)	91 (23.9)

N: Number of subjects, %: Percentages of subjects
Limits: Cross-reacting antibodies > 0.7 % B/T, Specific antibodies > 1.9 % B/T
Baseline: antibody sample above limit at baseline. Anytime: at least one antibody sample above limit during the trial.
Sustained: More than one antibody sample above limit during the trial or above at last observation.
NovoRapid is known as NovoLog in the U.S.

The semi-quantitative %B/T values for the insulin aspart specific (D-F) and cross-reactive (F-E) antibodies are used to indicate antibody levels in patient samples. In the

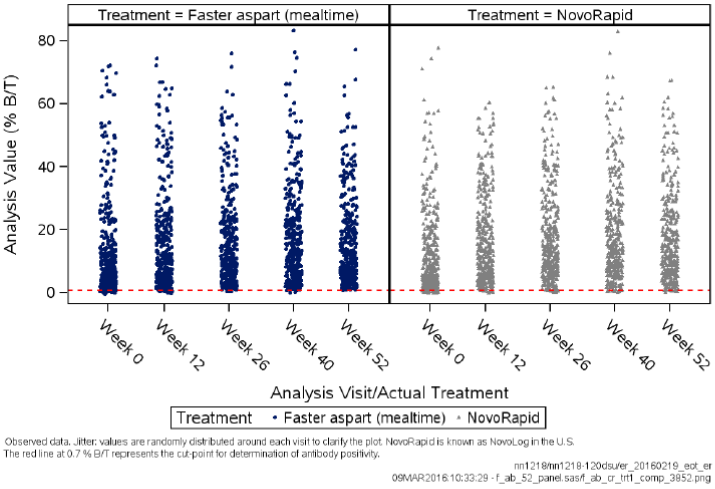
graph below the %B/T levels for each patient sample are shown at each visit for the "faster aspart" (mealtime) and NovoRapid treatment arms. The assay cutpoint is indicated by the red dotted line.

Insulin Aspart-Specific ADA



19: Anti-insulin aspart specific antibodies in subjects by analysis visit week - panel dot plot with jitter - Faster aspart (mealtime) - NovoRapid - trial 3852 52 weeks - safety analysis set

ADA Cross-Reactive to Human Insulin

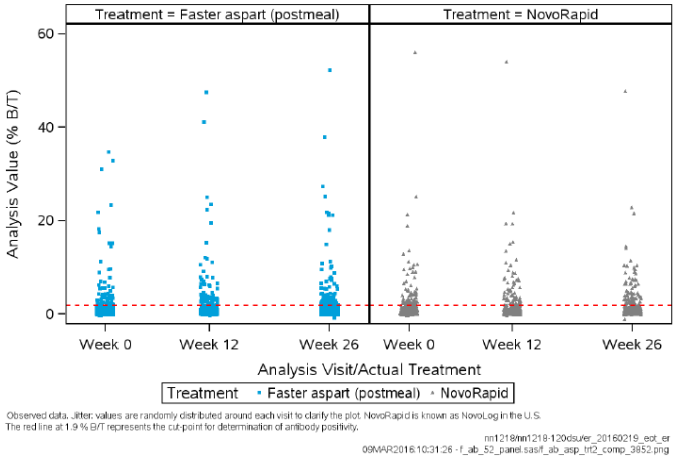


21: Cross-reacting antibodies to human insulin in subjects by analysis visit week - panel dot plot with jitter - Faster aspart (mealtime) - NovoRapid - trial 3852 52 weeks - safety analysis set

FDA comment: In general the antibody levels in patients from patients in each arm appear comparable. The Sponsor did not provide data on the frequency of treatment-boosted ADA in each treatment arm or the strategy for defining treatment-boosted ADA responses. This was communicated to the Sponsor in the 8-1-2016 IR, however the response was not reviewed in this cycle.

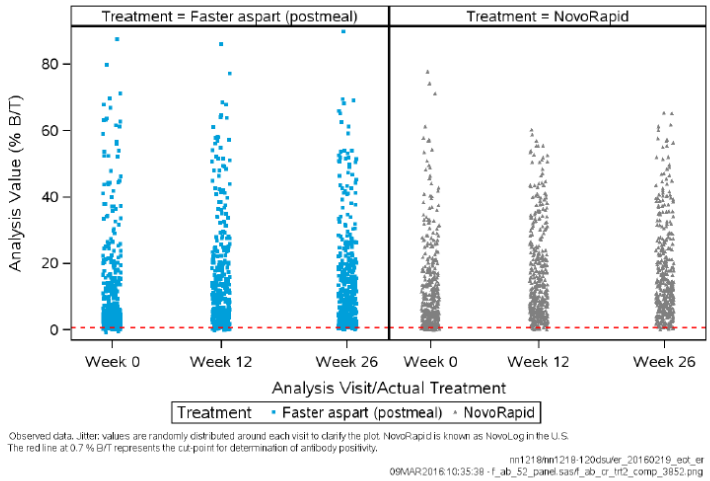
The Sponsor also compared antibody levels between the "faster aspart" (post-meal) and NovoRapid arms at the baseline, week 12, and week 26 timepoints.

Insulin Aspart-Specific ADA



20: Anti-insulin aspart specific antibodies in subjects by analysis visit week - panel dot plot with jitter - Faster aspart (postmeal) - NovoRapid - trial 3852 52 weeks - safety analysis set

ADA Cross-Reactive to Human Insulin



22: Cross-reacting antibodies to human insulin in subjects by analysis visit week - panel dot plot with jitter - Faster aspart (postmeal) - NovoRapid - trial 3852 52 weeks - safety analysis set

FDA Comment: The insulin aspart specific and cross-reactive antibody responses appear similar between the "faster aspart" (postmeal) and NovoRapid treatment arms. However, as noted in the comment above, the incidence of treatment-boosted ADA responses is not provided.

FDA comment: Correlations between antibody levels and adverse events and HbA1c were analyzed. There appeared to be no correlation between the levels of ADA and AEs or changes in HbA1c. This is acceptable.

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/s/

STEVEN E BOWEN
09/23/2016

SUSAN L KIRSHNER
09/29/2016

OFFICE OF DEVICE EVALUATION
DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL, RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM

Date: September 9, 2016

To: Anika Lalmansingh, RPM
OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI

From: Carolyn Cochenour
CDRH/ODE/DAGRID/GHDB

Through: CDR Alan Stevens, Branch Chief
General Hospital Devices Branch

Subject: Consult for NDA 208751, ICC 1500680

Applicant	Novo Nordisk Inc
Indication for Use	FIASP is a rapid-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus
Drug / Biologic Constituent	Fiasp® insuin aspart injection
Device Constituent	FlexTouch, Vial, (b) (4)

Recommendation:
The FlexTouch FIASP Pen-injector of the Combination Product is Approvable.

(b) (4)

See Section 12 for Outstanding Deficiencies

Digital Signature Concurrence Table	
Reviewer	Carolyn T. Cochenour -S 2016.09.09 14:24:37 -04'00'
Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2016.09.09 14:31:51 -04'00'

TABLE OF CONTENTS

1. PURPOSE/BACKGROUND

1.1. Scope

CDER has requested that CDRH provide review for the NDA 208751 submitted by Novo Nordisk Inc for the combination product Fiasp ® (insulin aspart injection) 100units/mL. The proposed multi-dose product will be available in 10 mL vials and 3mL prefilled pen presentations. (b) (4)

Faster aspart was developed as a mealtime insulin for the treatment of patients with diabetes mellitus, with the aim of providing a faster glucose-lowering effect which mimics more closely the physiological mealtime insulin response than NovoRapid®/NovoLog®. Faster aspart is intended to be used both for basal-bolus therapy in combination with basal insulin (± oral antidiabetic drugs (OADs)), (b) (4) Glycaemic control is to be optimised through individual titration.

Faster aspart 100 units/mL will be provided in a pre-filled disposable PDS290 Faster Aspart peninjector (3 mL), in Penfill® cartridges (3 mL) for use in Novo Nordisk insulin delivery systems (outside of the U.S.), and in Vials (10 mL). The prefilled pen-injector has a dose range of 1−80 units in increments of 1 unit.

The goal of this review memo is to evaluate the safety and effectiveness for the device constituent components of this submission as well as evaluation the use of the drug (b) (4). This includes the AI pen that is within this submission (b) (4)

This review will cover a full review of the device constituent of the combination auto-injector insulin pen. The pen review will not cover the pre-filled cartridge for use with the pen or the drug pathway. This review will look at the critical tasks for the Human Factors data, but the final review of the Human Factors studies is deferred to DMEPA.

This review will encompass a review of the device related attributes for the clinical studies used to support this NDA.

1.2. Prior Interactions

None

1.3. Indications for Use

Product	Indications for Use
Fiasp® insuin aspart injection	FIASP is a rapid-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus
Fiasp Flex Touch Pen	Incorporates a design containing 3 ml cartridges to assist in the subcutaneous injection of Fiasp ® (insulin aspart) drug product for the treatment of individuals with diabetes mellitus (b) (4)

2. ADMINISTRATIVE

2.1. Documents Reviewed

Document Title	Date - Version	Location
Proposed FlexTouch Trade Carton	n/a	Sequence 0000 GSR/1.14.1.1. Draft Carton and Container Labels
Proposed FlexTouch Trade Container	n/a	Sequence 0000 GSR/1.14.1.1. Draft Carton and Container Labels
Proposed FlexTouch Sample Container	n/a	Sequence 0000 GSR/1.14.1.1. Draft Carton and Container Labels
Proposed FlexTouch Rx Sticker	n/a	Sequence 0000 GSR/1.14.1.1. Draft Carton and Container Labels
Proposed FlexTouch IFU & PPI	n/a	Sequence 0000 GSR/1.14.1.3. Draft Labeling Text
Proposed Physician Insert	n/a	Sequence 0000 GSR/1.14.1.3. Draft Labeling Text
Proposed FlexTouch IFU	n/a	Sequence 0000 GSR/1.14.1.3. Draft Labeling Text
PDS290 Pen-injector 100U/ml – Technical Description	August 4, 2015; v3	Sequence 0000 GSR/3.2.P.7 Container Closure System
PDS290 Faster Aspart Pen-Injector – Dose Accuracy Data	January 23, 2015 v1	Sequence 0000 GSR/3.2.P.7 Container Closure System
PDS290 Faster Aspart Pen-Injector – Summary Report of Qualification Testing	March 10, 2015 v1	Sequence 0000 GSR/3.2.P.7 Container Closure System
PDS290 Pen-Injector – Validation of route of administration and injection	January 26, 2015 v1	Sequence 0000 GSR/3.2.P.7 Container Closure System

depth		
PDS290 Faster Aspart Pen-Injector – Validation of Device Use: Summative Usability Testing Report	May 28, 2015 v1	Sequence 0000 GSR/3.2.P.7 Container Closure System
PDS290 Faster Aspart pen-injector – Risk Management Analysis Input to Usability Test	November 13, 2015, v2	Sequence 0000 GSR/3.2.P.7 Container Closure System
(b) (4)		
Tabular Listing	November 3, 2015, v1	Sequence 0000 GSR/5.2 Tabular Listing of all Clinical Studies
Response to Day 74 Letter – Device	March 9, 2015, v1	Sequence 0006 GSR/1.11.1 Quality Information Amendment
PDS290 Faster Aspart pen-injector – Essential device performance and safety requirements	March 9, 2016 v2	Sequence 0006 GSR/3.2.P.7. Container Closure System
PDS290 Faster Aspart pen-injector – Document inspection summary report	March 9, 2016 v1	Sequence 0006 GSR/3.2.P.7. Container Closure System
PDS290 pen-injector – inspections of PDS290 Insulin Devices – 290-AF-R893	December 22, 2015 v1	Sequence 0006 GSR/3.2.P.7. Container Closure System
PDS290 pen-injector – Dirt and Dust – 290-AF-R875	July 28, 2015 v1	Sequence 0006 GSR/3.2.P.7. Container Closure System
PDS290 Faster Aspart pen-injector – Shelf Life data	March 9, 2016 v2	Sequence 0006 GSR/3.2.P.7. Container Closure System
PDS290 Faster Aspart pen-injector – Product Qualification Testing according to ISO 11608-1	May 14, 2014 v1	Sequence 0006 GSR/3.2.P.7. Container Closure System
PDS290 Faster Aspart pen-injector – Gage R&R report for Dose Accuracy Measurement	June 8, 2012 v1	Sequence 0006 GSR/3.2.P.7. Container Closure System
PDS290 Faster Aspart pen-injector – Summary Report of (b) (4) – 290-AF-S501	March 9, 2016 v1	Sequence 0006 GSR/3.2.P.7. Container Closure System
PDS290 pen-injector – Design Verification 290.QA.066.R.	February 20, 2012 v1	Sequence 0006 GSR/3.2.P.7. Container Closure System
PDS290 pen-injector – Tolerance stack	March 8, 2016 v1	Sequence 0006 GSR/3.2.P.7. Container

up verifications		Closure System
PDS290 Faster Aspart pen-injector Product Risk Management Summary	March 9, 2016 v1	Sequence 0006 GSR/3.2.P.7. Container Closure System

2.2. CDRH Review Team

Team Member	Role	Deficiencies
Carolyn Cochenour CDRH/ODE/DAGRID/GHDB	Lead Reviewer – {Engineering}	CDRH Comments 1 and 3
Patricia Beaston CDRH/ODE/DAGRID/GHDB	Consultant – Clinical	CDRH Comment 2
Sarah Mollo CDRH/ODE/DAGRID/GHDB	Biocompatibility Consultant	None

3. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The following is summarized from:
Sequence 0000 GSR/3.2.P.7 Container Closure System - PDS290 Pen-injector 100U/ml – Technical Description (August 4, 2015; v3);

PDS290 pen-injector 100 U/ml is a pen-shaped, prefilled device containing a 3 ml cartridge with insulin, see Figure 1. Therefore the drug is not in contact with the device. The pen-injector is designed and tested to function with a standard (b) (4) needle (b) (4)

Physical characteristics:

- Length and thickness: Approximately 138 mm without cap and 156 mm with cap. Thickness is approximately Ø19 mm
- Dose button displacement: Approximately 2 mm, (b) (4)
- (b) (4)
- Components: (b) (4)
- (b) (4)
- End-of-dose click

PDS290 pen-injector 100 U/ml is developed to fulfil the international standard for drug injectors, ISO 11608-1 Needle-based injection systems for medical use – Requirements and test methods - Part 1: Needle-based injection systems.

Figure 1 PDS290 Faster Aspart pen-injector (arbitrary label design)

The pen-injector mechanism can be considered as two interacting systems:

- Dose system
- Dial system

During dose setting, the dial mechanism consisting of dial, [redacted] (b) (4)

When the dose button is pushed down, [redacted] (b) (4) dial mechanism back to the starting point (0 U) [redacted] (b) (4) the dose system which enables delivery of the dose selected.

Device Characteristic	Description / Specification
Injector Name	PDS290 Faster Aspart pen-injector
Injector Platform Name	FlexTouch
Priming Dose / Volume	2 Units
Dose accuracy	ISO11608-1; [redacted] (b) (4) % at 50 units ie 500g [redacted] (b) (4)
Injection Time	Variable
Injection Site	Upper Arm, Thigh, Abdomen
Injection tissue and depth of injection	Subcutaneous, [redacted] (b) (4) mm
Audible / visual feedback	End of Dose Click
Cap Removal Force	[redacted] (b) (4) N
Activation Force	[redacted] (b) (4) N
Visibility of medication container	3mL cartridge window
Last Dose Specifications and Safety	[redacted] (b) (4)

Features	(b) (4)
Needle Specifications • Length(s) • Gauge(s) • Connection type o ISO 11608-2:2012 o Prestaked	sterile single-use needles with (b) (4) NovoFine®, NovoFine® Plus and NovoTwist® needles up to a length of 8 millimetres. The needle-based injection system (pen injector and single-use needle) is tested for functional compatibility according to ISO 11608-2: 2012: "Needle based injection systems for medical use – Requirements and test methods – Part 2: Needles". The system is also tested for flow-rate according to ISO 11608-2: 2012.
Type of Use (e.g. single use, disposable, reusable, other)	Reusable, single patient (multi-dose)
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Self or caregiver administration, (b) (4) Adults (age 18-64) who are able to perform their own injections
Injection mechanism (e.g., manual piston, spring, gas, etc.)	(b) (4)
Method of actuation	(b) (4) Button
Automated Functions	None
Residual Medication	Multi-dose, up to 3mL
Delivered Volume (for single dose or selectable volume range for multidose pens)	dose range of 1−80 units in increments of 1 unit
Drug Container Type	Pre-filled glass 3mL cartridge
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	Units
Environments of use	Home, Clinic
Storage conditions and expiry	Once a FIASP FlexTouch is punctured, it can be stored for 28 days at room temperature (below 86°F (30°C)) or in a refrigerator (36°F to 46°F; 2°C to 8°C) without the needle

	attached, but should not be exposed to excessive heat or light. Device Shelf-Life=30 months
Graduation marks / fill lines	On plastic housing of pen ((b) (4) unit increments)
Preparation and administration (describe all that are applicable) • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc.	Pen cap removal Needle mounting Priming Set dose Remove needle Place cap on store
Safety Features • Needle safety	none
Electronics / Data transmission • Display • Control functions • Data transmission technology • Data being transferred	None
Material composition of injector	(b) (4)

4. CLINICAL DEVELOPMENT

4.1. PDS290 Faster Aspart Pen-Injector Clinical Development

Reference Documents

- *Sequence 0000 GSR/5.2 Tabular Listing of all Clinical Studies*
  - *Tabular Listing (November 3, 2015, v1)*
- *Sequence 0006 GSR/1.11.1 Quality Information Amendment*
  - *Response to Day 74 Letter – Device (March 9, 2015, v1)*

The PDS290 Faster Aspart pen-injector has been used in three therapeutic confirmatory trials and seven clinical pharmacology trials of the Faster Aspart clinical development program. The clinical trials where the PDS290 Faster Aspart pen-injector has been used are listed in Table 1. For trial design, see Module 5.2 Tabular listing of all clinical trials.

Table 1 Clinical Trials using the PDS290 Faster Aspart pen-injector

Trial ID	PDS290 pen-injectors used	No of subjects randomised	No of subjects exposed to the PDS290 Faster Aspart or Insulin Aspart pen-injector	No of adverse events related to a PDS290 pen-injector technical complaint
Clinical pharmacology trials				
Trial 3887	PDS290 Faster Aspart PDS290 Insulin Aspart	46	46 PDS290 Faster Aspart 44 PDS290 Insulin Aspart	0
Trial 3888	PDS290 Faster Aspart PDS290 Insulin Aspart	41	40 PDS290 Faster Aspart 38 PDS290 Insulin Aspart	0
Trial 3889	PDS290 Faster Aspart PDS290 Insulin Aspart	36	35 PDS290 Faster Aspart 36 PDS290 Insulin Aspart	0
Trial 3891	PDS290 Faster Aspart PDS290 Insulin Aspart	67	66 PDS290 Faster Aspart 66 PDS290 Insulin Aspart	0
Trial 3949	PDS290 Faster Aspart	22	21 PDS290 Faster Aspart	0
Trial 3921	PDS290 Faster Aspart PDS290 Insulin Aspart	33	33 PDS290 Faster Aspart 32 PDS290 Insulin Aspart	0
Trial 3918	PDS290 Faster Aspart PDS290 Insulin Aspart	50	43 PDS290 Faster Aspart 42 PDS290 Insulin Aspart	0
Therapeutic confirmatory trials				
Trial 3852	PDS290 Faster Aspart PDS290 Insulin Aspart	1143	763 PDS290 Faster Aspart 380 PDS290 Insulin Aspart	2 (one for PDS290 Faster Aspart and one for PDS290 Insulin Aspart)
Trial 3853	PDS290 Faster Aspart PDS290 Insulin Aspart	689	341 PDS290 Faster Aspart 341 PDS290 Insulin Aspart	0
Trial 4049	PDS290 Faster Aspart	236	115 PDS290 Faster Aspart	0

In Trial 3852, two (2) adverse events (AEs) were reported as being related to technical complaints in 2 subjects: blood glucose fluctuation (NovoRapid®/NovoLog®) and hyperglycaemia (mealtime faster aspart). Both were non-serious AEs. In both cases the device was returned to Novo Nordisk for investigations, and nothing abnormal was found (Trial 3852 (M 5.3.5.1), Section 12.3.2.4).

CDRH Reviewer Comments:
CDRH finds the response to provide where the pen was used in the clinical trials. The 2 adverse events were not device related. There were no device failures in the trials using the faster aspart insulin pen-injector.

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

(b) (4)

6. DESIGN CONTROL REVIEW

6.1. Design Review Summary

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	x		Sequence 0006 GSR/3.2.P.7. Container Closure System - PDS290 Faster Aspart pen-injector – Essential Device Performance and Safety Requirements
Design Verification Data included in the NDA / BLA or adequately cross-referenced to	x		Sequence 0006 GSR/3.2.P.7. Container Closure System - PDS290 pen-injector – Design Verification 290.QA.066.R. Sequence 0006 GSR/3.2.P.7. Container Closure System -

a master file.			PDS290 pen-injector – Tolerance Stack up verifications
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	x		Sequence 0006 GSR/3.2.P.7. Container Closure System - PDS290 Faster Aspart pen-injector Product Risk Management Summary Sequence 0000 GSR/3.2.P.7. Container Closure System - PDS290 Faster Aspart pen-injector – Risk Management Analysis Input to Usability Test
Validation Data • Human factors • Clinical data	x		Sequence 0000 GSR/3.2.P.7. Container Closure System - PDS290 Faster Aspart pen-injector – Risk Management Analysis Input to Usability Test Sequence 0000 GSR/3.2.P.7. Container Closure System – PDS290 Faster Acting Pen-injector Summative Differentiation Usability Test Plan Sequence 0000 GSR/3.2.P.7. Container Closure System - PDS290 Faster Acting Pen-injector Summative Differentiation Usability Test Report Sequence 0000 GSR/3.2.P.7. Container Closure System - PDS290 Faster Acting Pen-injector Validation of device Use
		x	
Traceability Documentation	x		Located throughout the documents within Sequence 0006 GSR/3.2.P.7. & Sequence 0000 GSR/3.2.P.7.

***Sponsor may derive the regulatory requirements from 21 CFR 820.30 into multiple sets of documents. For example, injectors containing software may include separate software requirements and specification documents. In these circumstances, additional rows may need to be added to the table.**

7. DESIGN VERIFICATION AND VALIDATION REVIEW

7.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing		x	
To-be-marketed device was used in the pivotal clinical trial?	x		
Verification methods relevant to specific use conditions as described in design documents and labeling	x		

Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)		x		
Traceability demonstrated for specifications to performance data		x		
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility	X		
	Sterility			X
	Software / Cybersecurity			X
	Electrical Safety / EMC			X
	Human Factors	X		

Clinical Studies using the to-be-marketed device are listed in Section 4 Clinical Studies of this memo. Only 2 adverse events related to the device were reported, this is further discussed in Section 4. Clinical Studies of this memo.

Simulated Use studies were conducted in the form of the Usability Testing. A full list of the critical tasks can be found in eCTD Module 3.2.P.7. PDS290 Faster Acting Pen-injector Summative Differentiation Usability Test Report. These critical tasks and use errors are further discussed in section 8 Risk Analysis of this memo.

The following table identifies any standards or relevant FDA guidance documents not listed in the above table that might be referenced by the sponsor or determined to be relevant by the CDRH / ODE reviewer in the course of the design review.

Standard/Guidance	**Description**	**Documentation Adequate**	
		Yes	**No**
ISO 11608-1	Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems.	x	
ISO 14971	Medical devices - Application of risk management to medical devices	x	
ISO 10993-1	Biological evaluation of medical devices - Part 1: Evaluation and testing.	x	
FDA Guidance Document	Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products	x	

7.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase III Study utilized the to-be-marketed device	x		
Bioequivalence Study utilized to-be-marketed device			x
Simulated Actual Use Study utilized to-be-marketed device	x		

7.2.1. Design Verification Review

Document References:

Sequence 0006 GSR/3.2.P.7. Container Closure System –

PDS290 Faster Aspart pen-injector – Essential Device Performance and Safety Requirements
PDS290 Faster Aspart pen-injector – Shelf Life data
PDS290 Faster Aspart pen-injector – Product Qualification Testing according to ISO 11608-1
PDS290 Faster Aspart pen-injector – Gage R&R report for Dose Accuracy Measurement
PDS290 Faster Aspart pen-injector – Summary Re[prt of (b) (4) – 290-AF-S501
PDS290 pen-injector – Design Verification 290.QA.066.R.
PDS290 pen-injector – Tolerance stack up verifications

Sequence 0000 GSR/ 3.2.P.7. Container Closure System

PDS290 Faster Aspart Pen-Injector – Dose Accuracy Data
PDS290 Faster Aspart Pen-Injector – Summary Report of Qualification Testing
PDS290 Pen-Injector – Validation of route of administration and injection depth
PDS290 Faster Aspart Pen-Injector – Validation of Device Use: Summative Usability Testing Report

Essential Performance Requirement	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Injection Depth	(b) (4)	Yes	Yes	No	Yes	No
Injection Time		Yes	No	No	No	No
Dose Accuracy		Yes	Yes	Yes	Yes	Yes
Visual/Audible Feedback		Yes	Yes	No	No	No
Activation Force		Yes	Yes	No	No	No
Needle Connection Type		Yes	No	Yes	Yes	No
Torque NovoFine® needle- Mounting [Nmm] - Demounting [Nmm] - Destructive [Nmm]		Yes	No	Yes	Yes	No
Torque NovoTwist® needle-Mounting [Nmm] - Demounting [Nmm] - Destructive [Nmm]		Yes	No	Yes	Yes	No
Cap Removal Force		Yes	No	No	No	No
Torque to rotate cap		Yes	N0	No	No	No
Torque when setting dose		Yes	No	No	No	No
Torque when resetting dose		Yes	No	No	No	No

7.2.1. Dose Accuracy

In accordance with FDA recommendations, the following injection dose accuracy testing for the final drug/device combination product, PDS290 Faster Aspart pen-injector, in its approved dosage form for injection was performed:

- Testing to demonstrate that the volume/weight of drug product expelled through the injector is the same as the set dose
- Testing to ensure that multi-dose (variable dose) cartridge injectors are designed to accurately deliver each successive randomly set dose
- Testing to ensure that dose settings/markings correlate with the volume of drug product delivered

The Design Verification test was carried out according to ISO 11608-1 Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems. The dose accuracy was investigated at three dose sizes; dose 10 µl, 400 µl and 800 µl (1 increment, 40 increments and 80 increments) representing the minimum, midpoint and maximum dose, respectively.

The Design Verification test of the PDS290 Faster Aspart pen-injector complies with the dose accuracy acceptance criteria according to ISO 11608-1. Furthermore, the PDS290 Faster Aspart pen-injector meets the specifications for total content of device, dose accuracy of last dose, dose accuracy after free fall and vibration pre-conditioning and visual inspection according to ISO 11608-1.

From: "*Summary Report of Qualification Testing*"

The dose accuracy must comply with ISO 11608-1:2012. The mean value and the standard deviation are calculated based upon the results from weighing out of each of the 3 dose sizes 1 unit, 40 units and 80 units (10 µl, 400 µl and 800 µl). Furthermore, the statistical minimum and maximum weighing out of the doses are calculated.

The requirement is fulfilled when:

Dose accuracy (n=60):

Lower Acceptance criteria < Average value – (b) (4) *standard deviation and
Average value + (b) (4) *standard deviation < Upper Acceptance criteria

Dose accuracy (n=21):

Lower Acceptance criteria < Average value – (b) (4) *standard deviation and
Average value + (b) (4) *standard deviation < Upper Acceptance criteria

Dose accuracy (n=20):

Lower Acceptance criteria < Average value – (b) (4) *standard deviation and
Average value + (b) (4) *standard deviation < Upper Acceptance criteria

Data in Table 4 below shows density, weighing and acceptance limits when carrying out dose accuracy on PDS290 Faster Aspart pen-injectors according to ISO 11608-1:2012 (1).

Table 4 Acceptance criteria according to ISO 11608-1:2012 and ISO 11608-1:2014

Drug Type	Faster-acting insulin aspart 100 U/ml
Tempera-ture	(b) (4)
Density [g/ml]	
Dose size [µl]	
Dose size [mg]	
Limit acc. to ISO11608-1:2012	
Accepted Lower Limit [mg]	
Accepted Upper Limit [mg]	

Per ISO 11608-1, the system falls within designation C with no electronics – "multi dose needle-based injection device with integrated nonreplaceable container and no electronics"

Pages 11-12 shows that the PDS290 pen-injector complies with the following sections of ISO 11608-1: 5.5a,b,d,e,f,g,h,j,l,m. Data is shown in Tables 5:

Table 5 Total content test results

Total content [units]			
Pen 1 = (b) (4)	Pen 6 = (b) (4)	Pen 11 = (b) (4)	Pen 16 = (b) (4)
Pen 2 =	Pen 7 =	Pen 12 =	Pen 17 =
Pen 3 =	Pen 8 =	Pen 13 =	Pen 18 =
Pen 4 =	Pen 9 =	Pen 14 =	Pen 19 =
Pen 5 =	Pen 10 =	Pen 15 =	Pen 20 =
Acceptance criteria fulfilled for all 20 devices? Min. (b) (4) units [Yes/No]		Yes	

Pages 13- shows that the PDS290 pen-injector complies with the following sections of ISO 11608-1: 10.2, 10.1, 10.5b, 10.6, 10.9 11.1, 11.2, 11.3. Data is shown in Tables 6-9:

Table 6 Results of visual inspection on all visually inspected pen-injectors

ISO 11608-1:2012 section:	Inspect for:	The number of devices that do not pass the inspection will be noted down:
11.1a	Markings that are no longer visible or easily legible (that impact safe functioning).	No faults found
11.1b	Cracks in the body and/or component of the NIS that might impact safe functioning.	No faults found
11.1c	Compromised assembly bonds, joints and alignments that might impact safe functioning.	No faults found
11.2	Container inspection: if the container is completely fractured or has lost its contents in such a way that is obvious to the user, replace the container in order to complete the testing.	No faults found

Table 7 Dose accuracy test results at standard atmosphere

Dose size [µl]	10		400		800	
ISO 11608-1 section/ Name of test	Acceptance criteria (b) (4) mg		Acceptance criteria (b) (4) mg		Acceptance criteria (b) (4) mg	
	Avg-*k**std.dev	Avg+*k**std.dev	Avg-*k**std.dev	Avg+*k**std.dev	Avg-*k**std.dev	Avg+*k**std.dev
10.2/ Standard atmosphere n=60	7.94	11.68	393.45	405.48	789.71	810.54
Avg; std.dev.	9.81; 0.6995		399.46; 2.2522		800.13; 3.9004	
10.3/ Last dose n=60	6.10	11.77	-	-	-	-
Avg; std.dev.	8.94; 1.0619		-		-	
10.5/ After free fall n=21	7.77	11.69	394.52	405.42	791.23	811.94
Avg; std.dev.	9.73; 0.7170		399.97; 1.9961		801.59; 3.7916	
10.6/ Dry heat storage pre-condition n=60	7.78	12.19	393.26	406.87	788.41	812.88
Avg; std.dev.	9.98; 0.8256		400.06; 2.5473		800.65;4.5822	
10.6/ Cold storage pre-condition n=60	7.81	11.87	393.06	406.30	790.44	811.83
Avg; std.dev.	9.84; 0.7609		399.68; 2.4797		801.14; 4.0053	
10.9/ After vibration n=20	8.41	11.42	390.80	405.59	788.06	810.17
Avg; std.dev.	9.92; 0.5461		398.20; 2.6779		799.12; 4.0066	

Table 8 Dose accuracy test results at cool atmosphere

Dose size [µl]	10		400		800	
ISO 11608-1 section/ Name of test	Acceptance criteria (b) (4) mg		Acceptance criteria (b) (4) mg		Acceptance criteria (b) (4) mg	
	Avg-*k**std.dev	Avg+*k**std.dev	Avg-*k**std.dev	Avg+*k**std.dev	Avg-*k**std.dev	Avg+*k**std.dev
10.2/ Cool atmosphere test n=60	8.31	12.11	393.23	406.62	789.92	811.60
Avg; std.dev.	10.21; 0.7106		399.93; 2.5090		800.76; 4.0598	

Table 9 Dose accuracy test results at warm atmosphere

Dose size [µl]	10		400		800	
ISO 11608-1 section/ Name of test	Acceptance criteria (b) (4) mg		Acceptance criteria (b) (4) mg		Acceptance criteria (b) (4) mg	
	Avg-*k**std.dev	Avg+*k**std.dev	Avg-*k**std.dev	Avg+*k**std.dev	Avg-*k**std.dev	Avg+*k**std.dev
10.2/ Warm atmosphere test n=60	7.87	12.48	392.54	406.45	788.51	810.18
Avg; std.dev.	10.17; 0.8631		399.50; 2.6032		799.34; 4.0574	

The Design Verification test according to protocol 290.QA.111P has been passed. The PDS290 Faster Aspart pen-injector complies with the dose accuracy tolerance limits according to ISO 11608-1:2012 and ISO 11608-1:2014. Furthermore, the PDS290 Faster Aspart pen-injector meets the specifications for total content of device, dose accuracy of last dose, dose accuracy after free fall and vibration pre-conditioning and visual inspection according to ISO 11608-1:2012 and ISO 11608-1:2014.

In addition, according to the drug/device specification for release of the product 3.2.P.5.1 Specification for 3 ml cartridge the analytical testing program of dose accuracy testing has been performed in accordance with 3.2.P.5.2 Analytical Procedure A29001a Dose Accuracy, and the results of dose accuracy test of the assembled batches “complies” with the specification limits.

From : “*Analytical Procedure A29001a Dose Accuracy*”

Dose Accuracy was determined by weighing the samples. All measurements are performed at standard conditions:

- Temperature from 18 °C to 28 °C
- Relative humidity: from 25% RH to 75% RH.

The pen-injectors must be stored at the standard conditions prior to testing. Conditions are according to ISO11608-1 “Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems”.

For all pen-injectors in the sample, one dose (the first dose) is measured: for each pen-injector the dose of 50 units (for PDS290 pen-injector containing a drug product with a concentration of 100 U/ml) or 100 units (for PDS290 pen-injector containing a drug product with a concentration of 200 U/ml) is dialed and the dose is delivered to the electronic balance. The measurement is recorded.

Acceptance criteria:
The specification limits are (b) (4)% at 50 units for PDS290 pen-injector 100 U/ml and (b) (4)% at 100 units for PDS290 pen-injector 200 U/ml according to ISO 11608-1 "Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems". For batch release (the routine determination of dose accuracy) ISO3951-1:2005 or ISO3951-2:2006 is used to sample when testing if the specification limits of (b) (4)% are fulfilled.

Table 1 Release of batches according to dose accuracy of PDS290 Faster Aspart pen-injector

Batch no.	Drug product	Specification limit (b) (4) at 50 units i.e. 500 mg*	Mean value [mg]	Standard Deviation [mg]	Result
DV40228	Faster-acting insulin aspart	(b) (4)	498.9	2.92	Complies
DV40229			499.7	2.92	Complies
DV40230			500.0	3.01	Complies

* According to ISO 11608-1 Needle-based injection systems for medical use - Requirements and test methods - Part 1: Needle-based injection systems.

As the results for dose accuracy of batches assembled in Brennum Park, Hillerød, Denmark comply with the specification limits, the results confirms the quality of the PDS290 Faster Aspart peninjector.

The PDS290 Faster Aspart pen-injector was used in the Phase 3a clinical program for faster acting insulin aspart. For the phase 3 clinical program, all the PDS290 pen-injectors used conformed to the ISO 11608-1 dose accuracy requirements. In the three long-term efficacy and safety trials, nearly 2000 diabetes subjects were exposed to the PDS290 pen-injector. The safety and efficacy is described in
Module 5.3.5.1

Comments 9 and 10 of the 74-Day Letter pertain to the dose accuracy testing:
Comment 9:
For the PDS290 Pen-Injector, you have provided a risk analysis, identification and verification of safety and essential performance characteristics, including test protocols. There is compliance with all the specifications and test methods according to ISO 11608-1. However, the submission does not appear to contain information supporting a conclusion that the dose accuracy requirements proposed in ISO 11608-1 do not present any additional risks for this particular faster-acting insulin aspart. Please provide a justification as to why the dose accuracy requirements in the ISO11608-1 standard are applicable to the PDS290 Pen-Injector and this new faster-acting insulin aspart.

Sponsor Response

Novo Nordisk would like to clarify that ISO 11608-1 has been used by Novo Nordisk since 2000 in the development of pen-injectors for Novo Nordisk insulin products. For the prefilled insulin peninjectors, this includes Levemir® FlexPen®, NovoLog® FlexPen®, Tresiba® FlexTouch®, Ryzodeg® FlexTouch®, Levemir® FlexTouch® and NovoLog® FlexTouch®; all approved in US.

Faster Aspart is intended to be dosed according to the actual blood glucose levels, insulin sensitivity and insulin requirement. The dose estimate should include contributions from other factors, which might have an effect on the outcome of an over- and underdose such as changes in diet, exercise, concomitant disease (e.g. infections), alcohol consumption, concomitant medication or lack of understanding of the prescribed dose regimen, in order to avoid inappropriate adjustments of insulin dose.

The with-in and between subject variability for the glucose lowering effect of insulin is included as an inherent pre-condition of insulin therapy (1) that hereby sets the limits for the optimal glucose control which goes beyond the technical dose accuracy of a pen-injector for insulin delivery.

Furthermore, there is evidence from the literature that when comparing pen-injectors with conventional insulin delivery via syringe and vial, dosing accuracy is higher with pen-injectors, especially for doses below 5 units (2).

In the clinical trial program for Faster Apart, subjects were exposed to the PDS290 Faster Aspart pen-injectors. All the PDS290 Faster Aspart pen-injectors used conformed to the ISO 11608-1 dose accuracy requirements.

In the three therapeutic confirmatory trials for Faster Aspart, the bolus insulin dose ranged from 0 to 172 units per meal (Trial 3852 CTR, 14.2.13, Trial 3853 CTR, 14.2.11, and Trial 4049 CTR, 14.2.11) covering the full dose range of 1-80 units of the PDS290 Faster Aspart pen-injector. The safety and efficacy of Faster Aspart is described in Module 5.3.5.1. Two Technical Complaints related to AEs have been reported during the clinical trial program (see response to question 8 above). The PDS290 pen-injectors were returned to Novo Nordisk, examined and nothing abnormal was found (Trial 3852 (M 5.3.5.1), Section 12.3.2.4).

Furthermore, no safety signals on dose accuracy have been identified in the Post Marketing Surveillance of Novo Nordisk prefilled insulin pen-injectors (FlexPen® and FlexTouch®) which all are developed and verified according to ISO 11608-1.

Based on the above arguments, it is the Novo Nordisk position that the ISO 11608-1 dose accuracy requirements are acceptable for the PDS290 Faster Aspart pen-injector and will not present any additional risk.

Comment 10

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

Sponsor Response

The dose accuracy testing of the PDS290 Faster Aspart pen-injector at the min, mid and max doses of 1, 40, 80 units respectively is described in 3.2.P.7 PDS290 Faster Aspart pen-injector Summary Report of Qualification Testing. The PDS290 Faster Aspart pen-injector complies with the dose accuracy tolerance limits according to ISO 11608-1 'Needle-based injection systems for medical use
- Requirements and test methods - Part 1: Needle-based injection systems'. All measurements were carried out at conditions described in, and the measured data were calculated according to, ISO 11608-1. The test methods are described in the test protocol 3.2.P.7 PDS290 Faster Aspart pen injector
- Protocol Qualification Testing according to ISO 11608-1. Gauge R&R test results that demonstrate that the provided test protocol for dose accuracy is adequate are provided in 3.2.P.7 PDS290 pen-injector - Gauge R&R report for Dose Accuracy Measurement.

Novo Nordisk has additionally provided the requested information on dose accuracy for the min, mid and max doses of 1, 40, 80 units respectively for both time zero product and aged product in the updated version of 3.2.P.7 PDS290 Faster Aspart pen-injector Shelf life data, Section 2.3. The tests were conducted according to test methods specified in ISO 11608-1 as mentioned above. The test results verify that the PDS290 Faster Aspart pen-injector complies with the requirements specified in ISO 11608-1

CDRH Comments:

CDRH finds the responses to comments 9 and 10 of the 74 day letter to adequate to support the complete review of the dose accuracy.

The dose accuracy testing for the pen injector and the batch release criteria show that the subject device performs within the stated specifications in ISO 11608-1. The protocol and acceptance criteria are appropriate for this combination product as the testing was completed at various temperatures. CDRH finds the dose accuracy and batch release criteria acceptable.

7.2.2. Shelf-Life

Sequence 0006 GSR/3.2.P.7. Container Closure System
PDS290 Faster Aspart pen-injector – Essential device performance and safety requirements

March 9, 2016 v2

The PDS290 Faster Aspart pen-injector drug product has a shelf life of 30 months. The shelf life of the pen-injector is supported by testing the essential device performance requirements i.e. visual inspection of the pen-injector, torque for attachment and removal of the two types of needles (NovoFine® and NovoTwist®) and dose accuracy of 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. Shelf life data for the PDS290 Faster Aspart pen-injector are provided in 3.2.P.7 PDS290 Faster Aspart pen-injector – Shelf life data.

Sequence 0006 GSR/3.2.P.7. Container Closure System
PDS290 Faster Aspart pen-injector – Shelf Life Data
March 9, 2016 v2

The following essential device performance requirements are considered relevant for determination of the shelf life of PDS290 Faster Aspart pen-injector and are covered in this document:

- ☐ Visual inspection of the pen-injector, section 2.1
- ☐ Attachment and removal of needle, section 2.2

Table 1 Torque of NovoFine® needle

n=20	Attachment torque	Removal torque	Result
Acceptance criteria [Nmm]	(b) (4)	(b) (4)	-
Max peak [Nmm]	72	81	**Complies**
Min peak [Nmm]	70	56	**Complies**

Table 2 Torque of NovoTwist® needle

n=20	Attachment torque	Removal torque	Result
Acceptance criteria [Nmm]	(b) (4)	(b) (4)	-
Max peak [Nmm]	84	56	**Complies**
Min peak [Nmm]	58	36	**Complies**

- ☐ Dose accuracy of the pen-injector, section 2.3

Table 3 Dose accuracy (n=60) at cool atmosphere 5 C and t=0

Dose size	1 U / 10 µl		40 U / 400 µl		80 U / 800 µl	
Acceptance Criteria[1] ISO 11608-1:2012 [mg]	LSL:	USL:	LSL:	USL:	LSL:	USL:
						(b) (4)
Mean ± Stdev. X *k* factor	Mean – stdev*k	Mean + stdev*k	Mean – stdev*k	Mean + stdev*k	Mean – stdev*k	Mean + stdev*k
Results [mg]	9.14	10.94	393.20	405.13	788.89	808.28
Stdev.	0.3366		2.2352		3.6317	
Mean	10.04		399.17		798.59	
Used *k* factor						(b) (4)
Accept criteria fulfilled? (Yes/No)	Yes		Yes		Yes	

As seen from the obtained results above the test verifies that the dose accuracy at cool atmosphere at 1, 40 and 80 units complies with requirement in ISO 11608-1.

Table 4 Dose Accuracy (n=60) at warm atmosphere 40 C and t=0

Dose size	1U / 10 µl		40 U / 400 µl		80 units / 800 µl	
Acceptance Criteria[1] ISO 11608-1:2012 [mg]	LSL:	USL:	LSL:	USL:	LSL:	USL:
		(b) (4)				(b) (4)
Mean ±Stdev. X *k* factor	Mean – stdev*k	Mean + stdev*k	Mean – stdev*k	Mean + stdev*k	Mean – stdev*k	Mean + stdev*k
Results [mg]	8.15	11.32	391.47	404.75	785.26	808.93
Stdev.	0.5937		2.4860		4.4335	
Mean	9.74		398.11		797.09	
Used *k* factor						(b) (4)
Accept criteria fulfilled? (Yes/No)	Yes		Yes		Yes	

Table 5 Dose Accuracy (n=60) at cool atmosphere 5 C and t=30 months

Dose size	1 U / 10 µl		40 U / 400 µl		80 U / 800 µl	
Acceptance Criteria[54] ISO 11608-1:2012 [mg]	(b) (4)					
Mean ±Stdev. X *k* factor	Mean – stdev*k	Mean + stdev*k	Mean – stdev*k	Mean + stdev*k	Mean – stdev*k	Mean + stdev*k
Results [mg]	7.7	11.0	392.4	405.2	788.8	809.6
Stdev	0.6239		2.3882		3.8999	
Mean	9.33		398.77		799.18	
Used *k* factor	(b) (4)					
Acceptance criteria fulfilled? (yes/no)	Yes		Yes		Yes	

Table 6 Dose Accuracy (n=60) at warm atmosphere 40 C and t=30 months

Dose size	1U / 10 µl		40 U / 400 µl		80 U / 800 µl	
Acceptance Criteria[56] ISO 11608-1:2012 [mg]	(b) (4)					
Mean ±Stdev. X *k* factor	Mean – stdev*k	Mean + stdev*k	Mean – stdev*k	Mean + stdev*k	Mean – stdev*k	Mean + stdev*k
Results [mg]	8.1	10.9	390.5	404.2	785.3	808.2
Stdev.	0.5175		2.5731		4.2858	
Mean	9.51		397.34		796.79	
Used *k* factor	(b) (4)					
Accept criteria for dose accuracy fulfilled? (Yes/No)	Yes		Yes		Yes	

CDRH Reviewer Comments:

The data from the shelf life and aging protocols are in line with the proposed shelf life for the drug and device as well as expected use conditions. The testing performed shows no deterioration in performance of the essential functions for the pen-injector. The shelf-life testing is reasonable for this device.

7.2.3. Biocompatibility

A biocompatibility consult was obtained from Sarah Mollo (CDRH/DAGRID/GHDB). The following summary is from her memo. The full memo is appended to this memo.

The sponsor states that the intended use of PDS290 Faster Aspart pen-injector implies brief, repeated handling of the device and consequently contact to intact skin by handling of the device; therefore, the PDS290 Faster Aspart pen-injector is categorized as a surface device with contact to intact skin, Category C – permanent (> 30 d). Based on this contact classification the sponsor has considered the following biological endpoint: Cytotoxicity, Sensitization, Irritation or intracutaneous reactivity.

Device Materials

Table 1 Components of the PDS290 Faster Aspart pen-injector and the user contact

Component	(b) (4) vendor and type	Masterbatch (MB), Novo Nordisk naming, vendor	User contact
Housing and cap	(b) (4)		Brief, repeated contact to intact skin during handling of the device
Cartridge holder			
Dial			
Dose button			

The sponsor states that the intended use of PDS290 Faster Aspart pen-injector implies brief, repeated handling of the device and consequently contact to intact skin by handling of the device; therefore, the PDS290 Faster Aspart pen-injector is categorized as a surface device with contact to intact skin, Category C – permanent (> 30 d). Based on this contact classification the sponsor has considered the following biological endpoint: Cytotoxicity, Sensitization, Irritation or intracutaneous reactivity.

In vitro cytotoxicity testing was performed on samples representative of the final finished PDS290 Faster Aspart pen-injector components.

The (b) (4) including the color masterbatch (b) (4) used for the h**ousing and cap components** of the FlexTouch® pen-injector is identical to the housing and cap component of the NovoLog FlexPen pen-injector as it was approved in NDA 20986/S-001, January 19, 2001 in formulation, processing, and sterilization, and no other chemicals have been added (e.g., (b) (4), etc.).

(b) (4) including the color masterbatch (b) (4) used for the **dial component** of the PDS290 Faster Aspart pen-injector is identical to the dial component of NovoLog FlexTouch® pen-injector as it was approved in NDA 20986/S-061, October 31, 2013 in formulation, processing, and sterilization, and no other chemicals have been added (e.g., (b) (4) , etc.).

The (b) (4) used for the **cartridge holder** and the **dose button** in PDS290 Faster Aspart pen-injector consist of identical materials compared to the currently approved NovoLog FlexTouch® pen-injector. The **color masterbatches in the cartridge holder and dose button** are the only materials in PDS290 Faster Aspart pen-injector which differ from the currently approved NovoLog FlexTouch® pen-injector. To address cytotoxicity endpoint for the color masterbatches of these components the sponsor has performed cytotoxicity testing on components representative of the final finished components. To address the sensitization and irritation endpoints the sponsor has performed a risk assessment based on data from the literature, supplier data, Quantitative Structure-Activity Relationship (QSAR) assessments and/or a worst case exposure assessment, it was concluded that the color additives do not contain any constituent with a potential to cause skin irritation or sensitization reactions.

The sponsor has provided a discussion of how the manufacturing and processing of the materials will not impact the biocompatibility of the components. The sponsor states that the components of the PDS290 Faster Aspart pen-injector that come in direct or indirect contact with the user are all based on commercially available (b) (4) materials designed for (b) (4) purposes. Further, the components are (b) (4) processes within validated process parameters in agreement with recommendations from suppliers. The sponsor also states that the assembly processes (b) (4) do not change the chemical properties of the materials.

The sponsor provided the below overview of the biological documentation basis and location of the documentation in this report for components and materials of the PDS290 Faster Aspart peninjector that come in direct or indirect contact with the user.

Table 4 The biological documentation basis for components and materials in the PDS290 Faster Aspart pen-injector with direct or indirect contact to the user

Component	Material	Biological evaluation basis	Section
Housing and cap	(b) (4)	Identical material composition to currently marketed prefilled FlexTouch® and FlexPen®; toxicologically equivalent.	7.1.1
Cartridge holder		Identical to currently marketed prefilled FlexTouch® and the housing of currently marketed prefilled FlexPen®; toxicologically equivalent. Information on the chemical composition of the masterbatch and literature data for the constituents assessed as potential leachables; no further biological evaluation necessary.	7.1.2
Dial		The material meets USP Class VI requirements and has passed tests for irritation and delayed-type hypersensitivity in accordance with ISO 10993-10 [10]; no further biological evaluation necessary. (b) (4) has passed an *in vitro* cytotoxicity test – see Appendix G; no further biological evaluation necessary.	7.1.3
Dose button		(b) (4) with a long history of safe use in medical devices and has passed an *in vitro* cytotoxicity test - see Appendix G . Information on the chemical composition of the masterbatch and literature data for the constituents assessed as potential leachables, a passed *in vitro* cytotoxicity test for a dose button including CAS no. (b) (4) – see Appendix G; no further biological evaluation necessary.	

The biocompatibility evaluation is adequate for the intended use of device.

8. RISK ANALYSIS

8.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified	x		
Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities	x		

8.2. Summary of Risk Analysis

Reference Documents

- *Sequence 0006 GSR/3.2.P.7. Container Closure System*
  - *PDS290 Faster Aspart pen-injector Product Risk Management Summary (March 9, 2016 v1)*
- *Sequence 0000 GSR/3.2.P.7. Container Closure System*
  - *PDS290 Faster Aspart pen-injector – Risk Management Analysis Input to Usability Test (November 13, 2015, v2)*

The product risk management process complies with the requirements of ISO 14971 (1), IEC 62366 (2), ISO 13485 (3) and ISO 10993-1 (4). The product risk management process is described in internal Novo Nordisk procedures and the PDS290 Faster Aspart pen-injector is developed according to these procedures to ensure development of a safe device.

The following analyses and test have been performed:

- An Failure Mode Effects and Criticality Analysis (FMECA),
- A Use Error Risk Analysis (UERA)-This includes analysing the consequences of mixing up the PDS290 Faster Aspart pen-injector with other drug delivery products available on the market.
- A usability test, which investigates whether the PDS290 Faster Aspart pen-injector is adequately safe and effective for use and the chosen mitigations address the hazards as intended. The test is based on the Use Error Risk Analysis and analyses of the intended use, the user groups, and environment in which the pen-injector will be used.

The Sponsor asserts that the use-related risks identified with regard to the handling of the PDS290 Faster aspart pen-injector are the same as the use-related risks previously identified for the PDS290 insulin pen-injectors (e.g. NovoLog® FlexTouch®). There were no additional risks identified specific for the PDS290 Faster aspart pen-injector. Therefore, the risk analysis and risk evaluation that was utilized for the insulin FlexTouch® /NovoLog® FlexTouch® human factors program with regard to handling was also determined to be applicable to the PDS290 Faster aspart pen-injector.

The risk control measures, comprising risk control option analysis and additional mitigations for the Instructions for Use (IFU) / ancillary instructional video, which were implemented and approved by the Agency for Levemir® FlexTouch® /NovoLog® FlexTouch®, were evaluated for incorporation into the PDS290 Faster aspart pen-injector. Novo Nordisk evaluated that the IFU and ancillary instructional video mitigations, based on the use of the PDS290 insulin pen-injector, should be incorporated into the corresponding IFU and ancillary instructional video for the PDS290 Faster aspart pen-injector in alignment with the Levemir® FlexTouch® /NovoLog® FlexTouch®.

The Use Error Risk Analysis identified mitigations for each of the use related hazards related to differentiation. The mitigations are grouped into the following categories: Pen-injector design, pen-injector label design, carton design, requirements to the IFU, and ancillary instructional video.

- Pen-injector design
    - Different colors of dose button, cartridge holder, and label for different drug products enhance differentiation between the pen-injectors.
- Pen-injector label design
    - The design and color of the pen-injector label is chosen to enhance differentiation and to clearly define pen-injector type, type of drug, and drug strength. The drug brand name and the pen-injector brand name are placed in a prominent position together with the product strength.
- Carton design
    - Mitigations to carton design are implemented to maximize differentiation at the time of dispensing the product e.g. at the pharmacy and home environment.
- Requirements to the IFU
    - These requirements specify the information contained in the IFU. The IFU and the information contained therein will be used as the basis of pen-injector specific training, which is given to the patient.
- Ancillary instructional video
    - The ancillary instructional video is an additional training tool that will be available to support HCPs, caregivers, and patients online if needed. It is aligned with the content in the IFU and will help ensure alignment in training and correct use of the PDS290 Faster aspart pen-injector.
- Key formative testing results and mitigations implemented
    - Novo Nordisk previously assessed PDS290 Faster Aspart pen-injector differentiation during formative usability test, DV3313-UT134-2014 (UT134). The test demonstrated that the pen-injector with label and carton designs facilitated the users' ability to differentiate the PDS290 Faster aspart pen-injector from other similar pen-injectors.

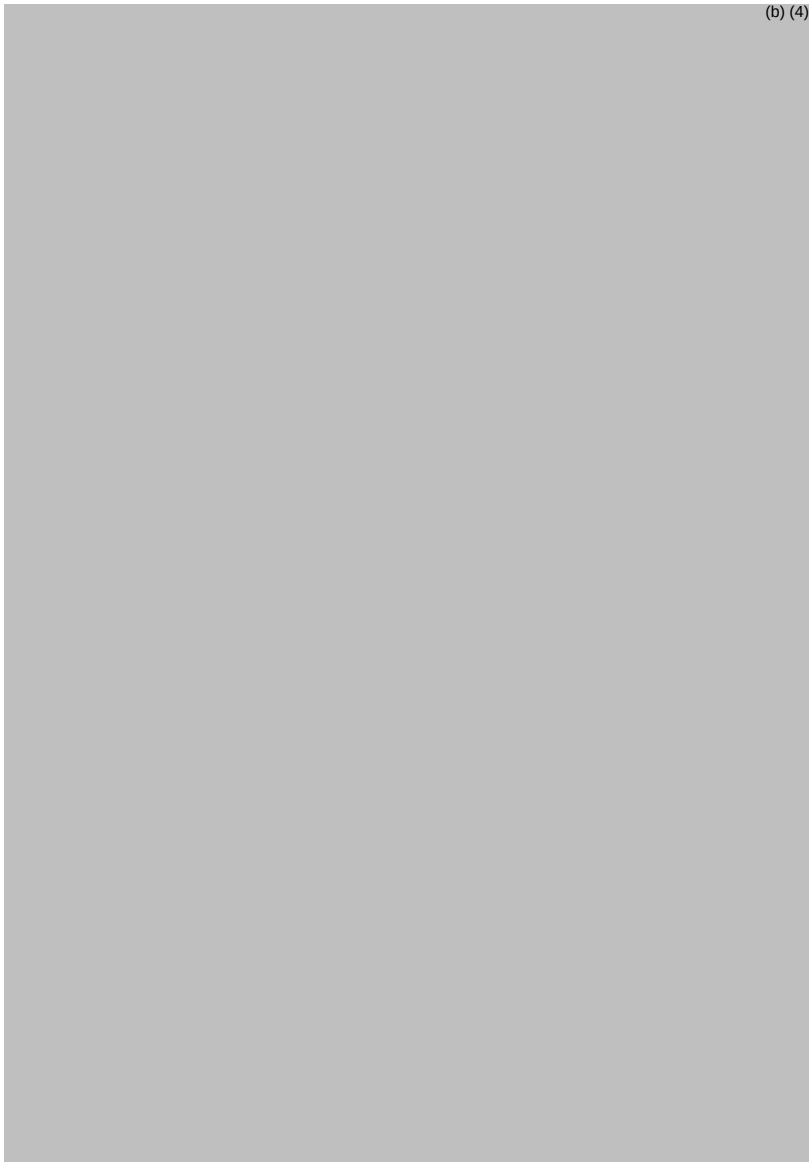
The risk management process for the PDS290 Faster aspart pen-injector also determined that no further design optimizations, labeling, or training mitigations would further reduce risk. The overall residual risk was found to be acceptable and is outweighed by the clinical/device benefits that are derived from the use of the PDS290 pen-injector as designed.

CDRH Reviewer Comments:
The information provided supports that fact that there are no additional risks specific to the PDS290 Faster aspart pen-injector over the other PDS290 pen-injectors. Therefore the same mitigation strategies previously implemented are acceptable for this device. A review of the human factors studies to ensure differentiation from the other similar pen-injectors is deferred to DMEPA.

9. LABELING

Document References:

- *Sequence 0000 GSR/1.14.1.1. Draft Carton and Container Lables*
  - *Proposed FlexTouch Trade Carton*
  - *Proposed FlexTouch Sample Carton*
  - *Proposed FlexTouch Trade Container*
  - *Proposed FlexTouch Sample Container*
  - *Proposed FlexTouch Rx Sticker*
- *Sequence 0000 GSR/1.14.1.3. Draft Labeling Text*
  - *Proposed FlexTouch IFU & PPI*
  - *Proposed Physician Insert*
  - *Proposed FlexTouch IFU*


(b) (4)

CDRH Reviewer Comments:
All draft labeling for the Faster Aspart Pen-Injector is appropriate for the device. **The final labeling has not been determined at the time of the memo. The review is based on what has been provided and the opinion of the reviewer might change if new labeling is submitted**. Adequacy of the final labeling, including consistency with the drug labeling and the naming is deferred to CDER.

10.DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

Document References:

- *Sequence 0006 GSR/3.2.P.7. Container Closure System*
  - *PDS290 Faster Aspart pen-injector – Essential device performance and safety requirements (March 9, 2016 v2)*
  - *PDS290 Faster Aspart pen-injector – Document inspection summary report (March 9, 2016 v1)*
  - *PDS290 pen-injector – inspections of PDS290 Insulin Devices – 290-AF-R893 (December 22, 2015 v1)*
  - *PDS290 pen-injector – Dirt and Dust – 290-AF-R875 (July 28, 2015 v1)*

Attribute	Specification	Test Method
Dose Accuracy	(b) (4)% at 50 units ie 500g ((b) (4)	3.2.P.5.2 Analytical Procedure

	(b) (4)	A29001a Dose Accuracy

The list of parameters for batch release testing covers both in-line process controls and visual inspections and are discussed below. In-line process controls consists of both tests and inspections as follows:

Description of tests:

- Check of correct code on Cartridge
- Check of correct color on Dose button
- Check of correct color of Cartridge holder
- Check of correct assembled components

The visual inspection of the final device includes:

- Dirt/spots
- Wrong/missing print
- Scratches
- Chips and Cracks

All batches complies with the visual in-line visual inspections (see reference documents).

CDRH Reviewer Comments
Batch Release Attributes are acceptable

11.INFORMATION REQUESTS

11.1. Day 74 Letter sent February 16, 2016

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

FDA Question 7
The labeling for the this product indicates (b) (4)

(b) (4)

(b) (4)

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

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

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

accuracy testing of the PDS290 Pen-Injector for the min, mid and max doses. Please provide this information for both time zero product and aged product part of shelf life testing.

11.2. Information Request Sent June 10, 2016

FDA Question 10

(b) (4).

FDA Question 11

PDS290 Pen-Injector Design Verification:

In the Design Verification Report, you state: "PDS290 pen-injectors U100 1U have been used in this study as a representative of the PDS290 platform." It is unclear if any changes were made between the version of the pen-injector used in the design verification activities versus the peninjector you intend to market. Please provide a detailed history of all design changes between the test article and the commercial device. Additionally please provide a risk analysis for the impact of each of these changes. This information is needed to determine if the performance data provided is applicable to the commercial version of the device.

FDA Question 12

PDS290 Pen-Injector Biocompatibility:

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

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

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

b. You have added new materials for the cartridge holder, dial, and dose button components. The biocompatibility evaluation of the delivery device referenced testing conducted on the raw material.

However, medical device manufacturing processes can adversely affect biocompatibility by altering the chemical and physical properties of materials. Therefore, FDA and the ISO10993-1 recommend that biocompatibility testing is performed on the final finished device or component. Please provide cytotoxicity, sensitization, and irritation testing on the final finished components that have changed from your previous device.

12.OUTSTANDING DEFICIENCIES

12.1. CDRH Comment – Outstanding Device Issue

CDRH Comment 1

(b) (4)

12.2. CDRH Comment – Clinical Deficiencies

CDRH Comment 2

(b) (4)

(b) (4)

12.3. CDRH Comment – (b) (4)

CDRH Comment 3

(b) (4)

13.POST-MARKET COMMITMENTS/POST-MARKET REQUIREMENTS

CDRH Reviewer Comment

Post Market Commitments will need to be made for continued shelf life stability of the device constituent of the combination product in accordance with the accelerated stability testing performed as part of the validation

studies once the NDA is ready for approval. This will be communicated to the Sponsor when the other CR issues are resolved.

14.RECOMMENDATION

CDRH is recommending approval for the FIASP insulin aspart Pen-Injector.

CDRH has outstanding deficiencies related to the safe use of the device in Section 12 of this memo and therefore requests that a Complete Response Letter be sent to the Sponsor containing the outstanding deficiencies.

Additionally, since this is a combination product (b) (4)

15.APPENDIX

15.1. Biocompatibility Consult

Consult Memo: ICC1500680_NDA208751

Date:	September 9, 2016
From:	Sarah Mollo, DAGRID/GHDB
To:	Carolyn Cochenour, Lead Reviewer, DAGRID/GHDB
Type of Product:	pen injector
Product Name:	3mL Fiasp FlexTouch
Intended Use:	subcutaneous injection of Fiasp® (insulin aspart injection)
Sponsor:	Novo Nordisk
Consult Review:	Biocompatibility of the Device Constituent

I. Scope of Consult

This consult is a review of the biocompatibility of the patient contacting components of the pen injector. The toxicological assessment of the primary container closure is reviewed by CDER.

II. Documents Reviewed

NDA208751 Biological Evaluation Report

III. Biocompatibility Review

The sponsor states that the intended use of PDS290 Faster Aspart pen-injector implies brief, repeated handling of the device and consequently contact to intact skin by handling of the device; therefore, the PDS290 Faster Aspart pen-injector is categorized as a surface device with contact to intact skin, Category C – permanent (> 30 d). Based on this contact classification the sponsor has considered the following biological endpoint: Cytotoxicity, Sensitization, Irritation or intracutaneous reactivity.

Device Materials

Table 1 Components of the PDS290 Faster Aspart pen-injector and the user contact

Component	(b) (4) vendor and type	Masterbatch (MB), Novo Nordisk naming, vendor	User contact
Housing and cap	(b) (4)	(b) (4)	Brief, repeated contact to intact skin during handling of the device
Cartridge holder			
Dial			
Dose button			

The sponsor has provided the following statement:

> *All manufacturing processes with a potential to change the chemical properties of materials with user contact listed in section 6.1.4 of ISO/TR 15499 (2) are identical to the currently marketed FlexPen® and FlexTouch® pen-injectors, and are without any use of additional processing aids. The PDS290 IDegLira pen-injector is not subject to sterilization.*

The sponsor states that all the device components which come in direct or indirect contact with users consist of identical materials compared to the currently marketed prefilled disposable FlexPen and FlexTouch peninjectors with the exception of the **dial and dose button and the colour masterbatch in the cartridge holder** (differs from FlexPen) and the **dose button and colour masterbatch in the cartridge holder** (differs from FlexTouch).

Additionally, the sponsor states that the intended use of the subject device is identical to the currently marketed FlexPen and FlexTouch.

Biocompatibility Evaluation

Housing and cap – (b) (4)

The sponsor has provided the following certifications statement:

> *The* (b) (4) *including the color masterbatch* (b) (4) *used for the housing and cap components of the FlexTouch® pen-injector is identical to the housing and cap component of the NovoLog FlexPen® pen-injector as it was approved in NDA 20986/S-001, January 19, 2001 in formulation, processing, and sterilization, and no other chemicals have been added (e.g.,* (b) (4) *, etc.).*

Reviewer Comment
The reviewer agrees that if the materials and manufacturing of the housing and cap are identical to the currently marketed FlexPen, no further biocompatibility evaluation is necessary for these components.

Cartridge holder – (b) (4)

The sponsor has provided the following certifications statement:

> *Novo Nordisk would like to clarify that the* (b) (4) *including the color masterbatch* (b) (4) *used for the dial component of the PDS290 Faster Aspart pen-injector is identical to the dial component of NovoLog FlexTouch® pen-injector as it was approved in NDA 20986/S-061, October 31, 2013 in formulation, processing, and sterilization, and no other chemicals have been added (e.g.,* (b) (4) *, etc.).*
>
> *The colour masterbatch of the cartridge holder (* (b) (4) *is a medical grade material manufactured under change control. The chemical composition of the colour masterbatch is listed in Appendix B. With the exception of insoluble substances* (b) (4) *the colour masterbatch, all constituents were evaluated for their potential to cause irritation and sensitisation based on toxicological data in the scientific literature published on four publicly available websites [6,7,8,9] in addition to supplier data. Results are listed in Table 2. In conclusion, based on literature data the colour masterbatch* (b) (4) *does not contain any component with a potential to cause skin irritation and skin sensitisation.*

Table 2 Potential leachables from (b) (4)

Cas no.	Substance	Skin irritation	Skin sensitisation	Sources
(b) (4)		No potential	No potential	[6,7]
		No potential	No potential	[7]

Dial – (b) (4)

The (b) (4) of the dial consists of (b) (4) The material is based on (b) (4) meeting the requirements for (b) (4) [4]. This implies that polar and nonpolar extracts of the material have passed the in vivo systemic injection test, along with the in vivo implantation test of the solid material. Also, (b) (4) has been tested for irritation and delayed-type hypersensitivity in accordance with ISO10993-10 [10].

The colour masterbatch of the dial (b) (4) is a medical grade material manufactured under change control. The (b) (4) including the colour masterbatch (b) (4) has passed an in vitro cytotoxicity test in cultured mammalian cells (L929 mouse fibroblasts) see Appendix G. The concordance between in vivo irritation and in vitro cytotoxicity is considered well-established [11]. Although the mechanism of skin sensitisation is more complex than that of cytotoxicity and irritation, the weight of evidence shows that epidermal inflammation caused by cytotoxicity is a prerequisite in the sensitisation pathway [12,13]. Therefore a negative in vitro cytotoxicity test is considered sufficient to rule out any relevant hazard for skin irritation and sensitisation caused by dermal exposure to leaching substances.

Reviewer Comment
The reviewer does not agree with the rationale that a negative cytotoxicity score negates the need for an irritation or sensitization test. Non-cytotoxic chemicals can be irritating or sensitizing. An IR has been sent in previous submissions to the sponsor requesting an evaluation of the irritation and sensitization endpoints as this rationale is inadequate. An IR was sent to the sponsor in this submission requesting testing on the final finished device. The sponsor instead provided a rationale stating that all constituents of the color additives (masterbatches) with a potential to migrate were evaluated for their potential to cause irritation and sensitization based on QSAR assessments and/or worst case exposure assessments.

Dose button - (b) (4)

In the response to the IR sent June 10, 2016, the sponsor clarified that the (b) (4) from the dose button consists of identical materials compared to the currently approved NovoLog FlexTouch pen-injector. The color masterbatches in the cartridge holder and dose button are the only materials in PDS290 Faster Aspart pen-injector which differ from the currently approved NovoLog FlexTouch® pen-injector.

The sponsor provided the following information in their biological evaulation of the colour masterbatch of the dose button ((b) (4)):

The colour masterbatch of the dose button ((b) (4) is a medical grade material manufactured under change control. The chemical composition of the masterbatch is listed in Appendix B. With the exception of insoluble substances ((b) (4)) in the colour masterbatch, all constituents were evaluated for their potential to cause irritation and sensitisation based on toxicological data in the scientific literature published on four publicly available websites [6,7,8,9], supplier data and QSAR assessments for specified substances. Results are listed in Table 3.

For all the constituents listed in Table 3, except for (b) (4) it is concluded that there is no inherent potential to cause skin irritation or sensitisation.

Based on test data, (b) (4) are irritating to skin [7]. In accordance with EU rules for health and environmental classification of chemicals, the lower concentration limit for classification of chemical mixtures containing skin irritating

substances is ≥ 10 % [14]. Based on the fact that the concentration of the colour masterbatch (b) (4) *in the dose button is* (b) (4) *(w/w), the maximum concentration of* (b) (4) *in the dose button is <* (b) (4) *(w/w) (*(b) (4)*). Furthermore,* (b) (4) *in the dose button. Based on this, it is concluded that* (b) (4) *do not pose a potential to cause skin irritation or sensitisation during the intended use of the pen-injector.*

Table 3 Potential leachables from (b) (4)

Cas no.	Substance	Skin irritation	Skin sensitisation	Sources
(b) (4)		No potential	No potential	[6,7]
		No potential	No data	QSAR: DEREK negative – see also Appendix H. Non-irritating to skin and eyes according to MSDS for (b) (4) – see also Appendix C.
		No potential	No potential	Non-irritating to skin and eyes and non-sensitizing to skin according to MSDS for (b) (4) – see also Appendix D.
		Irritating	No potential	[7]
		No potential	No potential	[7,8]
		No potential	No potential	Non-irritating to skin and eyes and non-sensitizing to skin (negative GPMT) according to MSDS for (b) (4) see also Appendix E.

Manufacture and processing

In an IR sent on June 10, 2016, the sponsor was asked to provide testing on the final, finished device components as the manufacture and processing can impact the chemistry and therefore, biocompatibility of the device. The following response was provided:

The manufacturing and processing of the PDS290 Faster Aspart pen-injector do not impact the biocompatibility of the cartridge holder and dose button components. A scientific rationale is provided below.

According to section 6.1.4 in ISO/TR 15499:2012 Biological evaluation of medical devices -

Guidance on the conduct of biological evaluation within a risk management process, the following aspects of the manufacturing process may have a potential to change the chemical properties of materials and should therefore be considered when test data on the final finished device is not available:

- *Intended additives, e.g. colorants, lubricants, pigments, surface treatments, ink;*
- *Potential process aids, e.g. cleaning/disinfection/sterilization agents, etching agents, mould release agents, cutting fluids and particles, machine contaminants such as lubricants;*
- *Potential process residuals of chemicals and additives;*
- *Degradation during manufacturing and processing*

All manufacturing processes for the PDS290 Faster Aspart pen-injector with a potential to change the chemical properties of materials with user contact listed above per section 6.1.4 of ISO/TR 15499 are identical to the currently marketed FlexPen® and FlexTouch® pen-injectors

The components of the PDS290 Faster Aspart pen-injector that come in direct or indirect contact with the user are all based on commercially available (b) (4) *materials designed for* (b) (4) *purposes. Further, the components are* (b) (4) *processes within validated process parameters in agreement with recommendations from suppliers and without use of any additional processing aids or chemicals apart from different color additives as described above. Also, the assembly processes* (b) (4) *do not change the chemical properties of the materials. Finally, the PDS290 Faster Aspart pen-injector is not subject to sterilization.*

In conclusion, the PDS290 Faster Aspart pen-injector does not pose a risk of cytotoxicity, skin irritation or sensitization, or any other biological hazard as defined in ISO 10993-1, as a consequence of its intended use.

IV. Biocompatibility Summary

The sponsor states that the intended use of PDS290 Faster Aspart pen-injector implies brief, repeated handling of the device and consequently contact to intact skin by handling of the device; therefore, the PDS290 Faster Aspart pen-injector is categorized as a surface device with contact to intact skin, Category C – permanent (> 30 d). Based on this contact classification the sponsor has considered the following biological endpoint: Cytotoxicity, Sensitization, Irritation or intracutaneous reactivity.

In vitro cytotoxicity testing was performed on samples representative of the final finished PDS290 Faster Aspart pen-injector components.

The (b) (4) including the color masterbatch (b) (4) used for the h**ousing and cap components** of the FlexTouch® pen-injector is identical to the housing and cap component of the NovoLog FlexPen pen-injector as it was approved in NDA 20986/S-001, APPEARS THIS WAY ON ORIGINAL January 19, 2001 in formulation, processing, and sterilization, and no other chemicals have been added (e.g., (b) (4) , etc.).

The (b) (4) including the color masterbatch (b) (4) used for the **dial component** of the PDS290 Faster Aspart pen-injector is identical to the dial component of NovoLog FlexTouch® pen-injector as it was approved in NDA 20986/S-061, October 31, 2013 in formulation, processing, and sterilization, and no other chemicals have been added (e.g., (b) (4) , etc.).

The (b) (4) used for the **cartridge holder** and the **dose button** in PDS290 Faster Aspart pen-injector consist of identical materials compared to the currently approved NovoLog FlexTouch® pen-injector. The **color masterbatches in the cartridge holder and dose button** are the only materials in PDS290 Faster Aspart pen-injector which differ from the currently approved NovoLog FlexTouch® pen-injector. To address cytotoxicity endpoint for the color masterbatches of these components the sponsor has performed cytotoxicity testing on components representative of the final finished components. To address the sensitization and irritation endpoints the sponsor has performed a risk assessment based on data from the literature, supplier data, Quantitative Structure-Activity Relationship (QSAR) assessments and/or a worst case exposure assessment, it was concluded that the color additives do not contain any constituent with a potential to cause skin irritation or sensitization reactions.

The sponsor has provided a discussion of how the manufacturing and processing of the materials will not impact the biocompatibility of the components. The sponsor states that the components of the PDS290 Faster Aspart pen-injector that come in direct or indirect contact with the user are all based on commercially available (b) (4) materials designed for (b) (4) purposes. Further, the components are (b) (4) processes within validated process parameters in agreement with recommendations from suppliers. The sponsor also states that the assembly processes (b) (4) do not change the chemical properties of the materials.

The sponsor provided the below overview of the biological documentation basis and location of the documentation in this report for components and materials of the PDS290 Faster Aspart peninjector that come in direct or indirect contact with the user.

Table 4 The biological documentation basis for components and materials in the PDS290 Faster Aspart pen-injector with direct or indirect contact to the user

Component	Material	Biological evaluation basis	Section
Housing and cap	(b) (4)	Identical material composition to currently marketed prefilled FlexTouch® and FlexPen®; toxicologically equivalent.	7.1.1
Cartridge holder		Identical to currently marketed prefilled FlexTouch® and the housing of currently marketed prefilled FlexPen®; toxicologically equivalent. Information on the chemical composition of the masterbatch and literature data for the constituents assessed as potential leachables; no further biological evaluation necessary.	7.1.2
Dial		The material meets USP Class VI requirements and has passed tests for irritation and delayed-type hypersensitivity in accordance with ISO 10993-10 [10]; no further biological evaluation necessary. (b) (4) (b) (4) has passed an *in vitro* cytotoxicity test – see Appendix G; no further biological evaluation necessary.	7.1.3
Dose button		(b) (4) with a long history of safe use in medical devices and has passed an *in vitro* cytotoxicity test - see Appendix G . Information on the chemical composition of the masterbatch and literature data for the constituents assessed as potential leachables, a passed *in vitro* cytotoxicity test for a dose button including CAS no. (b) (4) – see Appendix G; no further biological evaluation necessary.	

V. Conclusion

The biocompatibility evaluation is adequate for the intended use of device.

15.2. Clinical Consult

See Attachment

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/s/

CALLIE C CAPPEL-LYNCH
09/21/2016
signing for Carolyn Cochenour

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

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

Memorandum

Date: September 9, 2016

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

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Request

NDA 208751 FIASP (insulin aspart injection)

OPDP acknowledges receipt of your December 11, 2015, consult request regarding the proposed labeling for FIASP (insulin aspart injection). Final labeling negotiations were not initiated during this review cycle and DMEP plans to issue a Complete Response letter. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DMEP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these materials.

If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

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/s/

ANKUR S KALOLA
09/09/2016

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:	September 8, 2016
To:	Jean-Marc Guettier, MD Director **Division of Metabolism and Endocrinology Products (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:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Information (PPI) and Instructions for Use (IFU)
Drug Name (established name):	FIASP (insulin aspart injection)
Dosage Form and Route:	Solution for subcutaneous and intravenous injection
Application Type/Number:	NDA 208751
Applicant:	Novo Nordisk

1 INTRODUCTION

On December 8, 2015, Novo Nordisk submitted for the Agency's review an Original NDA submission for FIASP (insulin aspart injection) solution for subcutaneous and intravenous injection with a proposed indication to improve glycemic control in adults with diabetes mellitus.

On December 14, 2015, the Division of Metabolism 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 FIASP (insulin aspart injection).

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for FIASP (insulin aspart injection).

2 CONCLUSIONS

Due to outstanding clinical pharmacology deficiencies, DMEP plans to issue a Complete Response (CR) letter. 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/

AMANPREET K SARAI
09/08/2016

MARCIA B WILLIAMS
09/08/2016

Clinical Inspection Summary

Date	8/15/2016
From	Cynthia F. Kleppinger, M.D., OSI/DCCE/GCPAB Susan D. Thompson, M.D.,OSI/DCCE/GCAB acting for Janice Pohlman, M.D., M.P.H., OSI/DCCE/GCPAB, Team Leader Kassa Ayalew, M.D., M.P.H., OSI/DCCE/GCPAB, Branch Chief
To	Hyon J. Kwon, Pharm.D., M.P.H., Senior Clinical Analyst Lisa B. Yanoff, M.D., Clinical Team Leader Callie Cappel-Lynch, Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA/BLA #	NDA 208751
Applicant	Novo Nordisk, Inc.
Drug	Insulin aspart
NME (Yes/No)	No
Therapeutic Classification	Antidiabetic
Proposed Indication(s)	Treatment of diabetes mellitus
Consultation Request Date	1/29/2016
Summary Goal Date	8/19/2016
Action Goal Date	10/7/2016
PDUFA Date	10/8/2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of four domestic clinical sites as well as the sponsor. The inspection of two clinical investigators listed below revealed regulatory violations. The inspection of the sponsor and the remaining two clinical investigators revealed no regulatory violations.

While the inspectional findings based on the inspections of the two clinical sites represent observed regulatory deficiencies, these findings are unlikely to have a significant impact on overall results. The study data generated are considered acceptable and may be used in support of this NDA.

The classification for Drs. Lucas and Sandberg is Voluntary Action Indicated (VAI). Although regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from these sites is acceptable for use in support of the indication for this application. The full Establishment Inspection Reports (EIRs) were submitted for review.

The classification for Drs. Chow, Vance and the sponsor is No Action Indicated (NAI). Data from these sites and the sponsor are considered reliable based on the available information. The full EIRs were submitted for review.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending EIRs.

II. BACKGROUND

Novo Nordisk submitted an original New Drug Application (NDA) for faster-acting insulin aspart injection solution (Fiasp®) to improve glycemic control in adults with diabetes mellitus. Insulin aspart is marketed worldwide as NovoRapid® (NovoLog® in the US) and is a fast-acting insulin analogue indicated for the treatment of diabetes.

Inspections were requested for the following two studies:

NN1218-3852 Efficacy and Safety of FIAsp* Compared to Insulin Aspart Both in Combination with Insulin Detemir in Adults with Type 1 Diabetes (*FIAsp is an earlier abbreviation for faster-acting insulin aspart used in the protocol).

The trial was conducted at 165 sites in nine countries (92 U.S. sites). The trial began August 26, 2013 and completed the initial 26-week period December 13, 2014. The data cut-off was March 10, 2015. A total of 1692 subjects were screened, 1290 subjects entered the run-in period of the trial, and 1143 subjects were randomized. A total of 1062 of the randomized subjects completed the initial 26 weeks of this trial.

The primary objective was to confirm efficacy of treatment with mealtime faster-acting insulin aspart in terms of glycemic control as measured by change from baseline in HbA1c after 26 weeks of randomized treatment by comparing it to mealtime NovoRapid®/NovoLog® both in combination with insulin detemir. The primary endpoint was change from baseline in HbA1c after 26 weeks of randomized treatment.

NN1218-3853 Efficacy and Safety of FIAsp* Compared to Insulin Aspart in Combination with Insulin Glargine and Metformin in Adults with Type 2 Diabetes (*FIAsp is an earlier abbreviation for faster-acting insulin aspart used in the protocol).

The trial was conducted at 128 sites in nine countries (63 U.S. sites). The trial began September 9, 2013 and completed January 22, 2015. Data cut-off was February 12, 2015. There were 1367 subjects screened, 689 subjects randomized, and 606 subjects that completed the trial.

The primary objective was to confirm efficacy of treatment with mealtime faster aspart in terms of glycaemic control measured by HbA1c after 26 weeks of randomized treatment, by comparing to mealtime NovoRapid®/NovoLog®, both in combination with once-daily insulin glargine and

metformin. The primary endpoint was change from baseline in HbA1c after 26 weeks of randomized treatment.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 208751 in accordance with Compliance Programs 7348.810 and 7348.811. General instructions were also provided with this assignment.

Sites were chosen based on the OSI site selection tool. There was enough domestic data to focus on domestic sites only. Two of the sites were chosen as they had never been inspected. Dr. Lucas was selected as she was the highest enroller in study NN1218-3852 although the site is located in a small town.

III. RESULTS (by Site):

Name of CI/ Address Site#	**Protocol # and # of Subjects Randomized**	**Inspection Date**	**Classification**
Kathryn J. Lucas, M.D. 611 N. 35th Street Morehead City, NC 28557 Site 14842 / 704	NN1218-3852 32 subjects	04/05 – 04/08/2016	Voluntary Action Indicated (VAI)*
Jay Sandberg, D.O. 115 E Long Lake Rd Troy, MI 48085-5524 Site 15426 / 102	NN1218-3853 9 subjects	04/12 – 04/20/2016	Voluntary Action Indicated (VAI)*
Christopher Chow, M.D. 18433 Roscoe Blvd. Suite 208 Northridge, CA 91325-4108 Site 15231 / 106	NN1218-3853 12 subjects	03/08 – 03/10/16	No Action Indicated (NAI)
Carl D. Vance, M.D. 3910 Washington Parkway Idaho Falls, ID 83404-7596 Site 2284 / 790	NN1218-3852 23 subjects	2/25 – 03/03/2016	No Action Indicated (NAI)
Novo Nordisk Inc. 800 Scudders Mill Road Plainsboro, NJ 08536	NN1218-3852 NN1218-3853	03/21 – 04/12/2016	No Action Indicated (NAI)*

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
*Pending = Preliminary classification based on information in 483 (if applicable) and preliminary communication with the field; final classification is pending letter to site.

NOTE: Site inspections focused on 100% review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1. Kathryn Lucas/ Site 14842 / 704

There were 37 subjects screened, 32 subjects randomized, and 25 subjects who completed the study. Seven subjects terminated early (two were inadvertently randomized, one became pregnant during the study, two were lost to follow-up, one expired, and one could not tolerate investigational product). All 37 subject records were reviewed for informed consent and eligibility of Type 1 DM diagnosis. All screen failures and twenty-one (21) enrolled subject records were fully reviewed. The first two subjects were screened on September 4, 2013. (b) (4) Institutional Review Board served as the IRB of record.

Subjects were prepped to be in clinical research studies at the site, being placed on and off several different medications as needed to qualify for enrollment. These visits were called "Drug Study Prep Visits". The subjects were being "prepped" prior to getting informed consent. Many subjects were seen and had medications adjusted and laboratory testing repeated in order to fulfill inclusion/exclusion criteria but were not considered being screened. For example, Subject (b) (6) had a diagnosis of DM since age 8 years old. The subject was seen for "Drug Study Prep" (b) (6) and had a HbA1c of 11.2% (HbA1c inclusion criterion was 7.0-9.5%). The subject was seen again on (b) (6) for "Drug Study Visit" and the HbA1c was 10.6%. The subject was seen on (b) (6) for "3852 Prep" and HbA1c was 10.1%. The subject was seen again (b) (6) for "Drug Study Prep", and the HbA1c was 9.4%. Repeat (b) (6) was 9.0%. A subject signed informed consent on (b) (6) and was randomized (b) (6).

Many subjects had been in several studies. Many subjects were documented to be on opioids and other abuse potential medications. Subject (b) (6) had an adverse event of cardiac arrhythmia and died. A copy of the autopsy report dated (b) (6) noted needle track marks; The subject had a prescription for hydromorphone and hydrocodone. Medications listed in the records included Dilaudid (hydromorphone), Flexeril, and hydrocodone with a history of drug seeking behavior.

Electronic health records (EHRs) are used in the practice. Medical histories were obtained from existing patients using their electronic medical record. For new patients, records were requested from previous medical facilities and placed into the EHR. All clinical research records were printed out and placed into binders. Only records needed for the current study were present in the binder. Worksheets were used as source records.

Source records were compared to the sponsor supplied data line listings. No significant discrepancies were noted. Medical events of special interest (MESIs), serious adverse

events (SAEs), and non-serious adverse events were captured appropriately. The primary efficacy endpoint was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigation was not conducted in accordance with the investigational plan.
    a. Specifically, the protocol states that Type 1 diabetes must be diagnosed clinically ≥12 months at the time of screening (Visit 1).
        i. **Subject** (b) (6) was a 46 year old screened (b) (6) and randomized on (b) (6). The subject was diagnosed with Type 2 Diabetes Mellitus in (b) (6) Records from his previous doctor dated (b) (6) list three oral hypoglycemic medications (glyburide, metformin, and pioglitazone). Dr. Lucas' clinic records dated (b) (6) list the diagnosis of Diabetes Mellitus, Type 2, uncontrolled; clinic records dated (b) (6) list the diagnosis of Diabetes Mellitus, Type 2, uncontrolled. At the (b) (6) visit, Dr. Lucas told the subject to continue the metformin and Actos and placed him on glimepiride. On (b) (6), the subject had a C-peptide of 1.2 ng/mL (low normal) and a GAD-65 of 20.8 U/mL (normal range 0–1.5 U/mL). Dr. Lucas' encounter diagnosis on (b) (6) and (b) (6) was "Diabetes Mellitus Type 2, Uncontrolled". The subject saw his private physician on (b) (6) and was still taking the same oral hypoglycemic agents. Dr. Lucas' encounter diagnosis on (b) (6) changed to "Unspecified Diagnosis". It remained "Unspecified Diagnosis" until (b) (6) when it waschanged to "Diabetes Mellitus, Type 1". Dr. Lucas stated that the subject was misdiagnosed and is a Type 1 Diabetic.
        ii. **Subject** (b) (6) was a 57 year old diagnosed with Type 2 DM in 2007. Subject was initially put on metformin and then insulin. He was then off insulin for 6 months and placed back on insulin in 2009. All medical records from his private doctor have the diagnosis of Type 2 DM. Records in the clinic dated (b) (6) had the diagnosis of Diabetes Mellitus, Type 2, uncomplicated. He was on Lantus and Humalog. At his screening visit on (b) (6), Dr. Lucas changed his diagnosis to Type 1 DM. The subject was randomized on (b) (6). Dr. Lucas stated that the subject was misdiagnosed and is a Type 1 Diabetic.
        iii. **Subject** (b) (6) was a 44 year old who was diagnosed with Type 2 diabetes mellitus in (b) (6) He had been on metformin initially then Lantus and Apidra then Lantus and Humalog. He had not been taking his insulin consistently since (b) (6) as he could not afford it. Records from a visit to Dr. Lucas' office on (b) (6) list the diagnosis of Type 2 DM, uncontrolled. The subject was started on metformin and glimepiride along with his insulin. A follow-up clinic visit on (b) (6) has the diagnosis changed to Type 1 diabetes.

Dr. Lucas stated that the subject was misdiagnosed and is a Type 1 Diabetic. A C-peptide result was obtained for this subject from another trial on (b) (6) recorded as 0.06 ng/mL (normal range 0.51 to 2.72 ng/mL). The subject was screened on (b) (6) and enrolled.

iv. **Subject** (b) (6) was diagnosed with diabetes in (b) (6) per chart notes treated with oral hypoglycemic medications. His weight was 250 pounds and with diet and exercise, his weight went down and his blood glucose improved. He was subsequently put on Glucophage and then Glucotrol. He was placed on insulin in (b) (6) Several records were reviewed with documented metformin usage. Medical records from a private physician dated (b) (6) document that the subject was taking metformin 500 mg twice a day. The subject was seen for the first time at the site on (b) (6) and was taking metformin. He was seen by Dr. Lucas on (b) (6) and she also documented the subject's metformin use but records the subject as Type 1 DM and then "Unspecified diagnosis". A C-Peptide non-fasting was reported as 0.8 ng/mL (normal range 0.51 to 2.72 ng/mL) on (b) (6). The subject was seen (b) (6) to "prep for" study NN1218-3852. Subject was still on metformin. The subject was initially screened (b) (6). Records at that time state "He restarted metformin, when he was taking the Prednisone. BS went up to the 500s but they are back down now; has been off Prednisone and metformin for 3 weeks". The subject returned to the site on (b) (6) to be rescreened for the study and was enrolled.

b. The protocol states that eligible subjects could not have use of any anti-diabetic drug other than insulin within the last 3 months prior to screening (Visit 1). **Subject** (b) (6) was diagnosed with diabetes in (b) (6) per study records and was treated with oral anti-diabetic drugs. Progress notes dated (b) (6) shows the subject to be taking metformin. The subject was consented and screened for the study on (b) (6).

<u>OSI Reviewer Comment</u>: Prior to the inspection, there was concern by OSI that ineligible subjects may have been enrolled into the trial as the site was the highest enroller in the study even though it was located in a small town with a population of approximately 9300 and a county population of approximately 69,000 people. The observations in the 483 were based on the protocol deviation that all Type 1 diagnoses had to be made at least a year before enrollment into the study and that the medical records did not reflect that fact. However, due to the change of diagnoses from Type 2 to Type 1, Novo Nordisk was asked during the inspection what information was sent to them regarding the subjects whose diagnosis of Type 2 DM was changed to Type 1. Their monitor had also questioned the changing diagnoses during the trial. There was only one subject ((b) (6) *) who had any diabetes-related (islet) autoantibody i testing. Novo Nordisk sent the following table of what Dr. Lucas had provided to them to support her changing of the diagnoses:*

Subject	Age at V1	Age at original diagnosis of diabetes	Duration of Multi-Daily Injections (MDI) before V1	Clinical data/presentation suggestive of Type 1 disease	Supportive lab findings	Confirmatory testing (GAD65, IA-2, IAA, other)
(b) (6)	44	38	6 years	Non-response to any oral agent. (*not supported in records*)	Low C-peptide (*normal level found in chart*).	(+) GAD65 Ab *(No repeat confirmatory test seen and no other antibody testing).*
(b) (6)	57	51	6 years	Extreme insulin sensitivity		
(b) (6)	43	29	14 years	DKA when omits insulin (*one episode seen in chart when off meds*)	Low C-peptide (*Patient was taking insulin, which would suppress*)	
(b) (6)	63	41	14 years	Extreme insulin sensitivity	Low C-peptide (*normal level found in chart*).	

The sponsor stated that they left the diagnosis of Type 1 DM up to the investigator.

Dr. Lucas responded inadequately to the observations on April 19, 2016. Although documentation in the source records of Type 1 DM diagnosis is < 12 months before the subjects were enrolled into the study, Dr. Lucas stated that she used her clinical judgment and thinks the disease of Type 1 DM "was in evidence" for > 12 months before enrollment. This is a misunderstanding of the protocol requirement.

The changing diagnoses were discussed with the review team and OSI defers to the review division as to the adequacy of Dr. Lucas' diagnoses of Type 1 DM. Otherwise, the audit did not

indicate serious deviations/findings that would impact the validity or reliability of the submitted data. The data from this site appear acceptable.

2. Jay Sandberg/ Site 15426 / 102

There were 16 subjects screened and nine subjects enrolled into the study; eight subjects completed the study (one subject withdrew consent). There were 16 subject records reviewed. The first subject consented 12/16/13. (b) (4) Institutional Review Board served as the IRB of record.

Source records were paper based. Hand-writing was, at times, illegible. Changes were often made by writing over the previous entry. Source data was then entered into the eCRF. Source records were compared to the sponsor supplied data line listings. No significant discrepancies were noted.

Subject (b) (6) had a UTI event not reported; all other adverse events were reported. The primary efficacy endpoint was verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigation was not conducted in accordance with the investigational plan.
    a. A pregnancy test was not performed at screening for Subject (b) (6).
    OSI Reviewer Comment: Source records documented that the husband was surgically sterile. No subsequent pregnancy reported.

    b. Subject (b) (6) was re-screened and did not sign a second informed consent and given another subject number as required by the protocol.

2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.
    a. The diary for Subject (b) (6) had ID # (b) (6) on multiple forms and was not corrected until December 2014.
    b. Multiple titration forms for Subject (b) (6) had ID # (b) (6). *The subject initials at the bottom of the form match Subject* (b) (6).
    c. The serial number of the glucose monitor for Subject (b) (6) was also written for Subject (b) (6). *Sponsor later noted the error during the study and made corrections.*

    OSI Reviewer Comment: Isolated transcription errors noted.

3. Informed consent was not properly documented in that the written informed consent used in the study was not approved by the IRB. Specifically, a change in the run-in period visit schedule was reflected in the revised consent document approved by the IRB on 1/14/14. Subjects (b) (6), (b) (6), (b) (6), (b) (6) were not provided with the revised version at the time of consent.
    OSI Reviewer Comment: The site utilized a consent form checklist that was

developed to track consent versions. However, the site continued to provide the wrong consent to subjects throughout the trial as the form did not include the IRB approval date to appropriately determine if subjects had received the most current copy of the consent.

Dr. Sandberg submitted a response to the 483 items on April 24, 2016 with corrections and preventive actions deemed to be acceptable.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

3. Christopher Chow/ Site 15231 / 106

There were 30 subjects screened and 12 subjects enrolled into the study; 10 subjects completed the study. Subject (b) (6) was withdrawn about 17 weeks into the study when it was noted that they should have been excluded for a high creatinine value. Subject (b) (6) was withdrawn about 30 weeks into the study when their basal dose was changed. All 30 informed consent documents were reviewed. There were 12 subject records reviewed. The first subject ((b) (6)) consented on (b) (6). (b) (4) IRB was the IRB of record.

There were hardcopy case report forms (CRFs) and source documents on site that were organized and available. Each enrolled subject had an individual binder. The subject records for screen failures and run-in failures were kept in separate individual folders.

The complete (b) (4) laboratory reports for the HbA1c values for all 12 enrolled subjects were compared against the electronic data listing provided by Novo Nordisk. There were no discrepancies. The primary efficacy endpoint was verifiable.

There was no under-reporting of adverse events.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

4. Carl Vance/ Site 2284 / 790

There were 29 subjects screened and 23 subjects enrolled into the study; 22 subjects completed the study. Subject (b) (6) withdrew from the study early due to a pregnancy. The pregnancy was not seen in the data listings; however, all required paperwork was submitted by the site to the sponsor. All 29 informed consents were reviewed. There were nine subject records reviewed. (b) (4) IRB was the IRB of record.

Each subject had their own binder for source records and worksheets, a separate binder for the questionnaires, and then an accordion folder full of the subject diaries. The records were organized and in good condition. Each subject had typed progress notes explaining the visit and activities performed. Also included were concomitant medication logs, adverse event logs, test results, and medical history records.

During the study, the formulation for the Ensure meal beverages that were used during the meal test changed. The site provided the appropriate amount of the beverage to equal 80 g of carbohydrates, per protocol.

Source documents were compared against the data listings provided with the assignment, and a few discrepancies were noted. There were some adverse event and concomitant medication documentation errors. Most had been reported by the site in the EDC records but were not seen in the sponsor data listings. *Review of the discrepancies show OTC meds not reported and events such as sinusitis, cold, burn to right finger, elective surgical events.* The only significant adverse event reported by the site and not on the data line listings is for Subject (b) (6) who was reported by the site (b) (6) to have right colon tubular adenoma.

The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

5. Novo Nordisk Inc./ Sponsor

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO, deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and investigator agreements, the interactive voice/web response system, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, selection criteria for all committee members, oversight of committees, data management, escalation of issues, and clinical trial oversight.

Files for eight sites were reviewed (NNI218-3852: Sites 704, 719, 760, and 790, and NNI218-3853: Sites 102, 106, 156, and 208).

The majority of the functions for the clinical studies were handled within Novo Nordisk. The sponsor appeared to have SOPs for all areas at the initiation of the study. The SOPs

were reviewed and compared to the firm's practice. The Contracts and Transfer of Obligations (TOO) for all vendors were reviewed and appeared adequate.

The sites outside of the USA were not under the IND. The sponsor did not utilize the 1572 for non-USA sites, but instead utilized the protocol agreement signature page.

The sponsor utilized their own monitors and monitors which were under contract to the sponsor from (b) (4). Although the Monitoring Guideline was to be finalized before any site initiation, this did not occur until several sites had already been initiated. *The Monitoring Guide had been completed and was in the process of being signed at the time of enrollment of subjects and was in draft format at the time of the site initiation visit (SIV).*

As noted in the Clinical Study Report (CSR), in October 2014, Novo Nordisk was alerted that the manufacturer of the liquid meal replacement, Ensure, which was utilized for the meal tests, had changed the formulation. This was investigated during the inspection. The original formulation contained 40 grams of carbohydrates per bottle which was changed to 32 grams of carbohydrates per bottle. Thus the meal test which was required by the protocol to be 80 grams of carbohydrates was now 64 grams. The sponsor researched the issue and discovered that the manufacturer of Ensure, Abbott, had changed the formulation in March of 2014. Novo Nordisk sent out several messages to the sites as well as a special newsletter and poster. It was determined that 28 sites received the new formulation and that 18 of the sites conducted 28 meal tests on a total of 26 subjects. During the investigation they determined that the following subjects received 2 bottles of Ensure, but cannot confirm that they received the correct amount of carbohydrates: (b) (6) V34 and V36, (b) (6) V36, (b) (6) V36, (b) (6) V36, (b) (6) V36, (b) (6) V36, (b) (6) V36, (b) (6) V36, (b) (6) V36, (b) (6) V36, and (b) (6) V36. A trial level protocol deviation was filed. The sponsor appeared to have appropriately handled the deviation.

The accidental unblinding reported in the CSR was investigated during the inspection. The firm identified that on December 20, 2013 that the vendor (b) (4), who was responsible for shipment of the investigational products to test sites, accidently sent an electronic mail shipping order to Novo Nordisk staff which contained unblinded investigational product information which affected four sites (724, 748, 790, and 802). Only one site (790) had randomized subjects at the time and only one subject who had received and taken the product was potentially affected. The affected products were made unavailable through the IV/WRS and new shipments were dispatched. All who received the electronic mail message were requested to delete the message. The sponsor provided an electronic mail communication explaining the breach and the blinding plan. The affected products were returned to (b) (4) for destruction. Novo Nordisk created two non-conformities, and (b) (4) created an SOP for communication of potentially unblinded information and retrained the employees. A trial level protocol deviation was created. The sponsor appeared to have appropriately handled the deviation.

During the inspection, the case book re-signing outlined in the CSR was investigated. The electronic data capture system (EDC) was developed through a contract with Oracle with user acceptance performed by the firms' trial team. During user acceptance testing it was identified that the casebook signature affidavit text and the CRF signature affidavit texts on the AE form , safety

information form (SIF), medical event of special interest (MESI) form and Technical Complaints were not according to the sponsor requirements as specified in the System Configuration Settings document for either study. The issues were corrected; however, it reappeared in July 2014 due to a replacement of the tests with the default affidavit when updates were made to the user signature groups. The issue was again fixed and there were no other issues identified. Investigators who had already signed the case book with the incorrect text were requested to resign the casebooks. If technical complaints, AE, SIF, and MESI forms had been signed with the incorrect text, a memo was created listing the forms and the incorrect text which the PI signed indicating that they accepted their signature with the sponsor required correct text. For the NN1218-3853 study all the casebooks, technical complaints, AE, SIF, and MESI forms were resigned by the PI.

Once the firm had been informed about the sign-off issue they investigated and on February 12, 2014 the sign-off feature was implemented and electronic mail messages were sent to all staff to instruct them how to obtain electronic signatures for SIF and MESI forms. Additionally, electronic signatures were obtained by 10/7/14 for all forms which had been entered prior to 2/12/14. The sponsor did acknowledge that the process should have been completed sooner but they had difficulty getting all the sites to sign-off. The sponsor appeared to have appropriately handled the deviation.

The sponsor contracted (b) (4) to oversee the Event Adjudication Committee (EAC). (b) (4) contracted the adjudication group chaired by (b) (4) ; the committee was comprised of physicians from (b) (4) group. The committee functioned independently of all individuals associated with the studies and acted in an independent expert advisory capacity to monitor subject safety and the conduct of the study. The FDA inspector requested the EAC meeting minutes and was informed that since the two primary adjudicators were in agreement for all events that the committee did not meet and hence there were no minutes. The reviewer's documents are contained in their adjudication eCRF entries.

The changing diagnosis at Dr. Lucas' site from Type 2 DM to Type 1 DM was evaluated. Novo Nordisk's criterion for type 1 diabetes is clinical diagnosis by the physician as per American Diabetes Association (ADA) Practice Recommendations (Reference: Diabetes Care (suppl 1) January 2013). There is no requirement for biochemical or biomarker confirmation. The Medical Monitor was not consulted and was not aware of the changes that were made at Dr. Lucas' site. The site monitor was responsible for checking that the documentation existed for the clinical diagnosis of type 1 disease for all NN1218-3852 patients.

A request was made for a list of all subjects who had been on oral hypoglycemics in the past. Novo Nordisk did not require that past use of oral anti-diabetic agents were captured in EDC so such a list could not be provided.

It was asked if there were any other such instances of a changed diagnosis at any of the other sites. Novo Nordisk said they were not aware of any other instances but could not confirm that such changes had not occurred.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional

Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this sponsor appear acceptable.

{See appended electronic signature page}

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/s/

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08/15/2016

SUSAN D THOMPSON
08/15/2016

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08/15/2016

HUMAN FACTORS, LABEL AND LABLING 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 19, 2016
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208751
Product Name and Strength:	Insulin aspart injection, 100 units/mL
Product Type:	Combination
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novo Nordisk
Submission Date:	December 9, 2015
OSE RCM #:	2015-2637
DMEPA Primary Reviewer:	Sarah K. Vee, PharmD
DMEPA Team Leader (Acting):	Hina Mehta, PharmD
DMEPA Assoc. Director for Human Factors (Acting):	QuynhNhu Nguyen, MS
DMEPA Deputy Director:	Lubna Merchant, PharmD, MS

1 REASON FOR REVIEW

The Division of Metabolism and Endocrinology Products (DMEP) requested DMEPA to evaluate container label, carton labeling, instructions for use (IFU), and human factors (HF) validation study results for insulin aspart injection, NDA 208751, submitted on December 9, 2015. Our analysis of the findings from the HF validation studies informed our review of the proposed container labels, carton labeling and IFU.

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.

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	N/A
Human Factors Study	B
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other: Response to Information Request (IR)	C
Labels and Labeling	D

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 reviewed the labels and labeling and the human factors differentiation study results provided by Novo Nordisk on December 9, 2015. The study focused only on the differentiation tasks and not every aspect of use. We agreed with this approach as the Applicant was relying on the HF validation data and post-marketing information gathered from the currently marketed Flextouch pen injectors for the injection process. We agree that the use-related risks and risk control measures implemented for the PDS290 platform (i.e. Levemir® FlexTouch® /NovoLog® FlexTouch) applies to the proposed pen injector for insulin aspart and no additional human factors testing is required with regard to the steps associated with product handling.

3.1 HUMAN FACTORS DIFFERENTIATION STUDY

The Applicant conducted a human factor differentiation study with a total of 47 patients and 31 healthcare providers (30 untrained adult patients, 31 untrained healthcare professionals, and 17 trained children patients (see Appendix for details on participants). The study focused on

product differentiation in respect to correct carton and correct pen-injector selection. The Applicant lists three steps as outlined in Appendix B. We requested clarification whether or not each step was included as a separate task in their study. In their response to our IR, the Applicant stated that steps 1, 2, and 3 were not divided into separate tasks for the pen-injector retrieval, thus the failures occurred at step 1 (See Appendix C for details).

The study results showed that 8[*]/78 participants picked a pen-injector carton other than the requested PDS290 Faster Aspart pen-injector carton from the refrigerator. We also noted that seven of these eight participants selected the same pen-injector as the carton they selected during carton retrieval task. Per the protocol, the participant was not told that s/he selected the incorrect product during the carton retrieval task. The root cause analyses of these errors indicated that these participants failed the task due to incorrect perception of the task. Most of the participants indicated that they misunderstood the task instructions and retrieved the product that they use to treat their diabetes or the product most recently ("newly") prescribed to them. None of the participants indicated that they were confused due to similar colors or labels or labeling. Therefore, we consider these failures to be study artifacts.

3.2 LABEL AND LABELING

We also reviewed the prescribing information, container label, and carton labeling and identified some areas that should be improved such as the Dosing and Administration Section which includes the use of improper dose designations, the lack of NDC code, and the proximity of the net quantity and strength. Our recommendations for the Applicant are in section 4.1.

4 CONCLUSIONS & RECOMMENDATIONS

Our review of the human factors differentiation study showed that some patients and healthcare providers selected the wrong carton and pen injector. However, these errors were due to study artifacts. The rest of the study participants were able to differentiate the proposed pen from other currently marketed insulin pens. In addition, our review indicates that the prescribing information, container label, and carton labeling can be improved to increase the prominence of important information to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR NOVO NORDISK

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

A. Prescribing Information (PI)

[*] [1 child, 3 adults, 4 elderly: C10 (trained, pen-experienced), A5 (untrained, pen-naïve), A6 (untrained pen-experienced), A9 (untrained pen-experienced), E8 (untrained, pen-naïve), E9 (untrained, pen-naïve), E11 (untrained pen-experienced), E14 (untrained pen-experienced)]

1. The Dosing and Administration Section includes the use of improper dose designations[1]. Dangerous dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations[1] appear throughout the package insert. As part of a national campaign to avoid the use of dangerous dose designations, FDA agreed not to approve such error prone dose designations in the approved labeling of products. Thus, revise all instances of trailing zeros throughout the PI (e.g. 1.0 unit/mL).

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

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

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

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

[1] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 April 2]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for insulin aspart injection that Novo Nordisk submitted on December 9, 2015.

Table 2. Relevant Product Information for insulin aspart injection

Initial Approval Date	N/A
Active Ingredient	Insulin aspart
Indication	rapid-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus
Route of Administration	Subcutaneous injection, (b) (4) or intravenous infusion
Dosage Form	Injection
Strength	100 units/mL
Dose and Frequency	Individualized dose based on type of diabetes, metabolic needs, blood glucose monitoring results and glycemic control goal
How Supplied	10 mL vials and 3 mL FlexTouch prefilled pen
Storage	APPEARS THIS WAY ON ORIGINAL [nested table]
Container Closure	10 mL glass vial The 3 ml glass cartridge is closed in the one end with a rubber plunger and in the other end with an aluminium cap with a (b) (4).

FIASP presentation	Not in-use (unopened)		In-use (opened)	
	Room Temperature (below 30°C)	Refrigerated (2°C to 8°C)	Room Temperature (below 30°C)	Refrigerated (2°C to 8°C)
10 mL vial	28 days	Until expiration date	28 days	28 days
3 mL FIASP FlexTouch	28 days	Until expiration date	28 days	28 days

APPENDIX B. HUMAN FACTORS

4.2.2 Risk analysis/risk evaluation - Differentiation

The HFE/Risk Management Process for the PDS290 Faster aspart pen-injector also determined for the following user steps related to the scenario *The user does not receive the correct drug due to a mix-up (differentiation)* that summative usability testing regarding differentiation was required to validate the safe and effective use:

Step 1: Pick the correct carton/pen-injector

Step 2: Pen cap removal

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

Table 2 List of user steps and test priority based on severity

Condition	Step to test	Test priority**	Severity class*
Use Scenario – User does not receive the correct drug due to mix-up (all user groups tested)			
Steps are performed at dispensing, e.g. at the pharmacy, and at home: Normal test conditions, Untidy or illogical storage system (only for pharmacies)	Step 1: Pick the PDS290 Faster aspart carton/pen-injector	1	S3
	Step 2: Pen cap removal (Not pharmacists)	3 (*Not safety-related)*	S1 – S2
	Step 3: Verify via label and cartridge holder it is the correct pen (Not pharmacists)	1	S3

*The severity class is based on the worst case scenario of each step

** No steps are S4 or S5 therefore priority 1 is given to the S3 steps. Priority 3 is kept for the S1-S2 steps as they are not safety related

Table 4 Number and type of participants

User groups	Distinct user groups	Age, range (mean)	Trained	Untrained	Experienced	Naïve	Total
Patients	Children (age 10-17)	11-17 (14)	17	N/A	3	14	17
	Adults (age 18-64)	25-63 (55.5)	N/A	15	12	3	15
	Elderly (age 65+)	65-76 (69.4)	N/A	15	11	4	15
HCPs	Physicians/nurses	37-66 (53.7)	N/A	16	N/A	N/A	16
	Pharmacists	27-56 (36.3)	N/A	15	N/A	N/A	15
Total			17	61	26	21	78

During training, the trained participants participated in a one-on-one training session with a trainer (i.e., CDE). All training sessions were video recorded. Training sessions included the following:

- Introduction to the PDS290 Faster Aspart pen-injector
- Identifying the PDS290 Faster Aspart pen-injector and cartons, by highlighting the importance of noticing the:
    - Name of the product
    - Number of units per mL
    - Colouring of the carton and pen-injector label
    - Type of insulin including risk of mixing insulin and insulin types
- Question and answer period

To represent real life use, the test was executed with a delay between training and the actual test (at least 30 minutes after the end of the training session). Following training and throughout the delay period, participants did not have access to the IFU and ancillary instructional video of the PDS290 Faster aspart pen-injector. As such, participants were not able to prepare for the test beyond participating in their training session (i.e., they could not study or refresh their memory).

Results:

Task failure occurrences

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

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

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

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

1. C10: did not pay attention, selected what she uses several times a day (Humalog Mix 75/25)
2. E11: Selected carton located on top of the left-most stack (Humalog Mix 75/25) because that's what he does at home with his current product arranged by expiration date. Did not pay close attention during the presentation.
3. A9: Misinterpreted the task to mean retrieve his current medication (Levemir)
4. E14: Selected Levemir out of habit
5. A5: Misinterpreted "newly" to mean to select the medication that he was most recently prescribed (Lantus).
6. A6: Did not focus on product name but when she saw "Novo Nordisk" she concluded she retrieved the correct carton. She only has one product at home so she does not need to pay attention to product name.
7. E8: Misinterpreted "newly" to mean what was new to the market and selected two cartons (NovoLog Mix 70/30 and Lantus). Also misinterpreted "choose the right product" to mean to choose the correct product for his own diabetes treatment.
8. E9: Chose NovoLog Mix 70/30 because he remembered reading "Novo" on the PDS290 Faster Aspart carton. He questioned himself because the NovoLog Mix labels were blue and he was expecting them to be yellow. However, he believed he made the correct selection because he believed remembering NovoLog in the presentation. Notably, the participant correctly selected the PDS290 Faster Aspart pen-injector with the yellow label during the subsequent task (Task 2 – Pen-injector retrieval).

APPENDIX C. RESPONSE TO INFORMATION REQUEST DATED July 18, 2016

1 FDA Question 1

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

Novo Nordisk Response

In the Summative Usability Test UT135 performed as part of the validation of device use for NDA 208751 submitted on December 8, 2015, Step 1, 2 and 3 were not divided into separate tasks for the pen-injector retrieval. As such, the participants were not prompted to specifically perform Step 2 or 3. Therefore, the task failures for Task 2a (pen-injector retrieval – patient participants) occurred as the participants picked the pen-injector from the container. The summative test protocol was agreed to by the FDA in the July 17, 2014 Type C Written Response (WR) (Reference ID: 3594972).

The root cause analysis in Section 6.7.2.1 of the validation of device use report (see 3.2.P.7 PDS290 Faster Aspart pen-injector - Validation of Device Use: Summative Usability Testing Report) demonstrates that the task failures observed for Task 2a were a consequence of the participants choice of carton in the previous task (Task 1a (carton retrieval - patient participants)) or related to a deliberate choice of picking the patients' current medication. The two tasks were performed consecutively and the participants were not told in between tasks if they committed a use error.

As shown in 3.2.P.7 PDS290 Faster Aspart pen-injector - Summative Differentiation Usability Test Plan UT135, Appendix A, Step 1, 2 and 3 are used to describe the actions that may be involved in performing Task 2 pen-injector retrieval. Thus Step 2 and 3 are optional, the participant may confirm the selection by removing the pen cap and/or inspect the pen-injector label to confirm the selection, but they are not prompted to do so as this could bias the results. If they pick the correct pen-injector, it is not a task failure or a use error if they do not perform Step 2 or 3. If they pick the wrong pen-injector it is a task failure no matter they perform Step 2 or 3 or not.

In conclusion, the task failures occurred at Step 1.

APPENDIX D. LABELS AND LABELING

D.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following insulin aspart injection labels and labeling submitted by Novo Nordisk on June 10, 2016 in their request for proprietary name review for (b) (4)

- Container label
- Carton labeling
- Instructions for Use

D.2 Label and Labeling Images

(b) (4)

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

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

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

/s/

SARAH K VEE
07/19/2016

HINA S MEHTA
07/19/2016

LUBNA A MERCHANT on behalf of QUYNHNHU T NGUYEN
07/20/2016

LUBNA A MERCHANT
07/20/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Division of Pediatric and Maternal Health Memorandum

Date: May 6, 2016 **Date consulted:** February 8, 2016

From: Jane Liedtka, M.D. Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Director
Division of Pediatric and Maternal Health

To: Division of Metabolic and Endocrine Products (DMEP)

Drug/NDA: Fiasp (insulin aspart), NDA 208751

Applicant: Novo Nordisk Inc.

Subject: Pregnancy and Lactation Labeling

Indication: To improve glycemic control in adults with diabetes mellitus

Materials Reviewed:

- Applicant's submitted background package for NDA 208751.
- DPMH consult request dated February 8, 2015, DARRTS Reference ID 3884163.
- DPMH review of pioglitazone, NDA 021073/S-048. Miriam Dinatale D.O., Medical Officer. April 28, 2016. DARRTS Reference ID 3921521.
- DPMH review of pioglitazone, NDA 021073/S-048. Miriam Dinatale D.O., Medical Officer. March 9, 2016. DARRTS Reference ID 3898973.
- DPMH review of Humulin R, NDA 18780. Upasana Bhatnagar, MD and Leyla Sahin, MD, Medical Officers. January 5, 2011. DARRTS Reference ID 2886696.

Consult Question:

DMEP requests that DPMH "Determine if the PLLR format and content in the proposed PI is acceptable."

INTRODUCTION

The Division of Metabolic and Endocrine Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) on February 8, 2016, to provide input for appropriate labeling of the pregnancy and lactation subsections of NDA 208751 to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

REGULATORY HISTORY

On February 8, 2016, Novo Nordisk, Inc. submitted a new NDA 208751 for Fiasp® (insulin aspart), solution for subcutaneous and intravenous injection. Fiasp is indicated to improve glycemic control in adults with diabetes mellitus. This NDA is for a faster acting formulation of insulin aspart that was developed under IND 106878. The original NDA 20986 for NovoLog® (insulin aspart-US) was approved on June 7, 2000. This application cross-references to the full drug substance section and nonclinical program that was submitted under NovoLog NDA 20986. NovoLog® was approved for use in pregnancy (category B) in NDA 20986/S-037 on January 26, 2007. The insulin aspart molecule in NDA 208751 and in NovoRapid®(insulin aspart-outside US) /NovoLog® is identical and therefore - once systemically absorbed - it has the same biological action at the insulin receptor as NovoRapid®/NovoLog®.

DMEP sent Novo Nordisk an information request on February 16, 2016 requesting that the applicant convert labeling to the PLLR format and provide a review of published literature and a summary of their pharmacovigilance database to support changes to the Pregnancy and Lactation sections of labeling. The response to this IR was received on March 3, 2016 and was adequate.

BACKGROUND

Diabetes Mellitus and Pregnancy

Diabetes mellitus (DM) complicates approximately 4% of all pregnancies in the Unites States.[1] Poorly controlled DM during pregnancy increases the risk for maternal complications, including diabetic ketoacidosis, preeclampsia, spontaneous abortions (SAB), preterm delivery, stillbirth and cesarean section (due to fetal macrosomia). In addition, poorly controlled DM during pregnancy increases the risk for fetal malformations, including neural tube defects (anencephaly, open spina bifida, and holoprosencephaly), cardiovascular anomalies (ventricular septal defects and transposition of the great vessels), oral clefts, genitourinary abnormalities (absent kidneys, polycystic kidney, and double ureter), and sacral agenesis or caudal regression, and fetal complications, including macrosomia-related injuries (brachial plexus injury, hypoxia) and fetal hyperglycemia. Infants born to mothers with poorly-controlled DM are at an increased risk for hypoglycemia and respiratory distress. However,

[1] Mills JL. Malformations in infants of diabetic mothers. Teratology.1982:25;385-94

achieving and maintaining maternal euglycemia prior to conception and throughout pregnancy decreases the risk of adverse outcomes for both the mother and the infant.[1,2,3]

Insulin aspart and Drug Characteristics

Insulin aspart (Novolog; Novorapid) is a recombinant human insulin in which a proline has been substituted by an aspartate on the B-chain and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae*[4]. Insulin aspart has a more rapid onset of action and shorter duration of action than regular insulin. The applicant states that Fiasp is a faster acting formulation of insulin aspart in which the addition of niacinamide (vitamin B3) results in a faster initial absorption of the product, leading to an even earlier onset of action and greater early glucose-lowering effect compared to the original formulation. Fiasp was developed under IND 106878. The insulin aspart molecule in Fiasp and NovoLog® is identical and therefore - once systemically absorbed - it has the same biological action. Preclinical studies showed no difference in the activity of insulin aspart compared to regular insulin in experimental animal studies[4]. Clinical trials showed pregnancy outcome in diabetic women treated with insulin aspart to be similar to outcome after treatment with regular insulin[4]. Insulin is a protein hormone produced by the pancreatic beta cells. Insulin regulates glucose metabolism and is involved in many other metabolic processes in the body. Insulin is administered parenterally in the treatment of diabetes mellitus. Insulin aspart is a large peptide with a molecular weight of ≈ 5825 Da[5]. Insulin aspart has a low binding affinity to plasma proteins (<10%), similar to that seen with regular human insulin[5]. The half-life of the Fiasp formulation of insulin aspart after subcutaneous administration is (b) (4) [5]. Serious Adverse Reactions that have occurred with Fiasp include hypoglycemia and allergic reactions.

Pregnancy and Nursing Mothers Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[6] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[7] format to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR went into effect on June 30, 2015.

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[2] Persson, M. and Fadi, H. Perinatal outcome in relation to fetal sex in offspring to mothers with pre-gestational and gestational diabetes- a population-based study. Diabetes Med. 2014; 31(9): 1047-54.
[3] www.cdc.gov. Problems of Diabetes in Pregnancy. Accessed 12/30/2015.
[4] Novolog. Product Labeling. 4/17/2015.
[5] Proposed FIASP Product Labeling.
[6] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[7] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

LITERATURE REVIEW

The applicant performed a literature search concerning the use of insulin aspart in pregnant and lactating women in PubMed and included publications written in the English language from all years. The following terms were used: Search ((((aspart[Title/Abstract]) OR novolog [Title/Abstract]) OR novorapid[Title/Abstract])) AND (((((((pregnancy[MeSH Terms]) OR abortion[MeSH Terms]) OR pregnancy outcomes[MeSH Terms]) OR abnormalities, congenital[MeSH Terms]) OR "pregnancy complications"[MeSH Terms]) OR lactation[MeSH Terms]) OR stillbirths[MeSH Terms]) OR fetal death[MeSH Terms])))))))). The search resulted in a total of 44 publications. Four publications captured in the search did not include any information on the use of insulin aspart in pregnancy were excluded. DPMH also conducted a review of PubMed, Embase, ReproTox[8], Shepard's and TERIS[9] for published literature regarding insulin aspart and use in pregnancy, lactation and females of reproductive potential. DPMH findings were similar to those of the applicant with the exception of one article in Bulgarian discussing insulin aspart and lactation and one article in Chinese discussing insulin aspart and pregnancy (both articles with an English translation of the abstract). A review of data is included below.

Insulin Aspart

Nonclinical Experience

The Fiasp application cross-references to the full nonclinical program that was submitted under NovoLog NDA 20986 approved on June 7, 2000. Fertility, embryo-fetal and pre-and postnatal development studies have been performed with subcutaneous insulin aspart (NovoLog) and regular human insulin in non-diabetic rats and rabbits. In a fertility and embryo-fetal development study, insulin aspart was administered to female rats before mating, during mating, and throughout pregnancy. Further, in a pre- and postnatal development study insulin aspart was given throughout pregnancy and during lactation to rats. In an embryo-fetal development study insulin aspart was given to female rabbits during organogenesis. The effects of insulin aspart did not differ from those observed with subcutaneous regular human insulin. Insulin aspart, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 units/kg/day (approximately 32 times the human subcutaneous dose of 1.0 unit/kg/day, based on human exposure equivalents) and in rabbits at a dose of 10 units/kg/day (approximately three times the human subcutaneous dose of 1.0 unit/kg/day, based on human exposure equivalents). No significant effects were observed in rats at a dose of 50 units/kg/day and in rabbits at a dose of 3 units/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 unit/kg/day for rats and equal to the human subcutaneous dose of 1.0 unit/kg/day for rabbits, based on human exposure equivalents. The effects are considered secondary to maternal hypoglycemia.

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of insulin aspart. In 52-week studies, Sprague-Dawley rats were dosed

[8] ReproTox database, Truven Health analytics, Micromedex solutions, 2016
[9] TERIS database, Truven Health Analytics, Micromedex Solutions, 2016.

subcutaneously with insulin aspart at 10, 50, and 200 units/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 units/kg/day, based on units/body surface area, respectively). At a dose of 200 units/kg/day, insulin aspart increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for insulin aspart was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. Insulin aspart was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, in vivo micronucleus test in mice, and in ex vivo UDS test in rat liver hepatocytes. In fertility studies in male and female rats, at subcutaneous doses up to 200 units/kg/day (approximately 32 times the human subcutaneous dose, based on units/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed.

In standard biological assays in mice and rabbits, one unit of Fiasp has the same glucose-lowering effect as one unit of NovoLog. In humans, the effect of Fiasp is more rapid in absorption and onset of appearance, compared to NovoLog, due to its faster absorption after subcutaneous injection.

See nonclinical review of Fiasp NDA 208751 by Miyun Tsai-Turton and original nonclinical review of Novolog NDA 20986 by Indra Antonipillai for further details.

Pregnancy

Literature Review

There were 40 publications cited by the applicant in their literature search concerning insulin aspart in pregnant and lactating women. I found three additional articles in my search; one in Bulgarian, one in Chinese (both with an English translation of the abstract) and a report of a nonrandomized study in India. The table below presents details on the randomized controlled trials (RCTs) comparing insulin aspart to regular human insulin for mealtime dosing (in most cases in conjunction with NPH insulin qhs) in pregnant women with diabetes mellitus.

Table 1: RCT's of Insulin Aspart versus Regular Human Insulin in Pregnant Women with DM

Trial #/ Author/ Year Published	Type of Trial	Population/ Total # subjects	Arms/# of Subjects	Duration	Results/Outcomes
Trial #1- sponsored by Novo Nordisk (ANA -1474) Mathiesen reported on maternal outcomes 2007	Open-label (OL), Multi-Center (MC), Prospective (P), Parallel group (PG), Randomized(R), Controlled (C) Trial (T) for the bolus component of a basal-bolus regimen (with NPH insulin)	Pregnant Women (PW), Type 1 Diabetes Mellitus (TIDM), 322 subjects	Insulin Aspart (IA)= 157 vs Regular Human Insulin (RHI)=165	Followed through 6 weeks post-partum	No statistically significant differences were seen in maternal outcomes such as major hypoglycemic episodes-trend favoring IA for lower hypoglycemic episodes, nocturnal hypoglycemia and post-prandial glucose levels, No statistically significant differences were seen in fetal outcomes such as fetal loss, perinatal mortality, congenital malformations and pre-term delivery, trend favoring IA for pre-term delivery
Trial #1- sponsored by Novo Nordisk (ANA -1474) (same trial as above) Hod reported on fetal outcomes 2008	Same as above	Same as above	Same as above	Same as above	**IA**=137 live births, 14 fetal losses, perinatal mortality = 14/1000 births, pre-term delivery = 20%, congenital malformations = 6 **RHI** = 131 live births, 21 fetal losses, perinatal mortality = 22/1000 births, pre-term delivery = 31%, congenital malformations = 9
Trial #2- sponsored by Novo Nordisk (ANA-2067) Pettitt 2007	OL, PG, single-center, RCT for the bolus component of a basal-bolus regimen (with NPH insulin)	Women with gestational DM (GDM), $HbA_{1c} < 7$ 27 subjects	IA= 14 vs RHI=13	From diagnosis of GDM (18-28 weeks) to 6 weeks post-partum	Both treatment groups maintained good overall glycemic control, No major hypoglycemic events in either arm, Overall safety and effectiveness of IA were comparable to RHI in pregnant women with GDM. Pregnancy outcomes (the neonatal assessment: weight, length and PE findings) were similar in both treatment groups. One fetal death in IA arm at week 40 (unrelated to drug - cord strangulation), one down's

					syndrome case in RHI arm
Trial #3 Balaji 2010	Single-center, RCT in India	GDM, 152 subjects	A= 76 Premixed IA* 30 units (BIAsp30) B= 76 Premixed Human Insulin** 30 units (BHI30)	From diagnosis of GDM (20-26 weeks) to delivery	No difference in glycemic control or insulin dose, Birth weight>90th percentile: A = 6.8% vs B = 9.2%, Proportion with macrosomia not statistically significantly different
Trial #4 Balaji 2012 (subjects unique compared with above Balaji trial 2010)	OL, PG, single-center RCT in India	GDM, 323 subjects	A=163 Premixed IA* 30 units (BIAsp30) B=157 Premixed Human Insulin** 30 units (BHI30)	2nd Trimester through delivery	Similar glycemic control, required insulin dose lower for A than B, Comparable fetal outcomes, Proportion with macrosomia not statistically significantly different: A = 6.3% vs B = 6.9%
Trial #5 Di Cianni 2007	P, RCT comparing 3 different rapid-acting insulins at mealtime, Bedtime NPH added PRN (added to 23 RHI, 18 Lis and 16 IA) for ↑FBS	GDM, 96 subjects-3 arms	IA=31 Insulin Lispro (Lis)=33 RHI=32	28 weeks gestation through delivery	At week 38, no differences for the duration of insulin therapy, insulin dose, weight gain, fasting plasma glucose, and A1C were noted. Birth weight higher in RHI, macrosomia in 16% HI, 12% Lis, 10% IA
Trial #6 Zhou 2012 (Chinese)	Limited information available from abstract	Women with GDM - 80 subjects	IA vs RHI	unknown	There was no significant inter-group difference in the outcomes of pregnant women and their babies.

*Premixed insulins combine a rapid acting and a long acting component in a single formulation, biphasic insulin aspart= BIAsp 30=30:70 ratio of insulin aspart: protamine crystallized insulin aspart
** Biphasic human insulin=BHI30=30% short-acting and 70% intermediate –acting human neutral protamine hagedorn (NPH)
Source: Reviewer's Table

In addition to the six RCT presented in the above table, there was a meta-analysis published in 2015 by Lv entitled "Safety of insulin analogs during pregnancy: a meta-analysis"[10]. It is unclear whether the meta-analysis includes all of the individually cited articles in the above table. The

[10] Lv S et. al. Safety of insulin analogs during pregnancy: a meta-analysis. Arch Gynecol Obstet. 2015;292(4):749-56.

author describes results from six RCT in 1143 women with GDM, 567 on insulin aspart and 516 on regular human insulin. The author concludes there were "No increased complications for the mother or the fetus with use of insulin aspart" and that "no difference in rates of cesarean section (C-section) and macrosomia" were seen.

The nonrandomized trial performed in India reported by Deepaklal[11] was a prospective, open-label observational study of 276 subjects with GDM and an additional 76 subjects with pre-gestational DM. The subjects received insulin aspart ± neutral protamine hagedorn insulin once medical nutrition therapy for 2 weeks failed to achieve control. The final outcome was assessed in terms of incidence of macrosomia (>3.5 kg body weight) between the two groups and episodes of confirmed (blood glucose <56 mg/dL) minor or major maternal hypoglycemia. Results showed the incidence of maternal and fetal complications in GDM is similar to pre-GDM patients.

The rest of the published literature included secondary and/or exploratory analyses of the previously described randomized controlled trials, two pharmacokinetic trials, and 6 trials investigating basal insulin in which insulin aspart was used as a bolus but was not the focus of the study. There were also two case reports, details available on the case reports are provided below:

- A 31year old multiparous woman with type 2 diabetes mellitus (T2DM) who used insulin aspart at conception and during the first 6 weeks of pregnancy, had a baby with multiple congenital anomalies[12]including ambiguous genitalia due to 5-α reductase enzyme deficiency, anomalous course of left coronary artery, hemi-vertebra and horseshoe kidney. The authors concluded that since the patient's pre-gestational and gestational glucose regulation were well-controlled a "possible embryotoxic effect of insulin aspart cannot be ruled out in this case".
- A 27 year old morbidly obese (BMI=43) gravida 4 para 0 (h/o 3 SAB in 1st trimester likely due to poor glycemic control) with poorly controlled Type II DM treated successfully during pregnancy with U-500R (concentrated regular insulin) combined with aspart insulin delivered a 2955 g female infant with Apgars 6 and 8 at one and five minutes[13]. The neonate was born without complications.

Summary

Available information from randomized controlled trials in 441 pregnant women with diabetes mellitus treated during the latter part of pregnancy that have been reported in the published literature on insulin aspart, the active ingredient of FIASP, did not identify a drug-associated risk with use during pregnancy.

[11] Deepaklal MC et al. Insulin aspart in patients with gestational diabetes mellitus and pre-gestational diabetes mellitus. Indian J Endocrinol Metab. 2015; 19:658-662.
[12] Kanat M, Tahtaci M. Possible fetal outcome of insulin aspart. J Endocrinol Invest. 2008; 31(9):841.
[13]Okeigwe I et al. U-500R and aspart insulin for the treatment of severe insulin resistance in pregnancy associated with pregestational diabetes. J Perinatol. 2013; 33(3):235-8.

Summary of the Applicant's Pharmacovigilance Database

The Novo Nordisk safety database contains information from various sources including clinical trials, non-interventional and observational studies, patient support programs etc. (solicited cases), literature and spontaneously reported cases (unsolicited cases). The usual limitations (under-reporting, variable quality, insufficient information) apply to the spontaneously reported cases.

A total of 5,219 case reports of exposure of insulin aspart (NovoRapid®/NovoLog® or faster aspart) during pregnancy and lactation have been identified from all reporting sources cumulatively up till 31st December 2015. The majority (71%) of the cases were non-serious. Out of the cases of exposure during pregnancy, the fetal outcome was available for approximately 2,300 cases – in the case of multiple pregnancies (e.g., twins or triplets) one outcome per child was counted. The fetal outcome was categorized as: Live birth without congenital anomalies (LB without CA), Live birth with CA (LB with CA), Fetal loss (includes spontaneous abortion (SAB), ectopic pregnancy and stillbirth) and Termination (TAB). The majority of the cases (76%) with birth type available were reported as full-term delivery. The table below displays the information:

Table 2: Pregnancy cases with fetal outcome available

		Source			
Fetal outcome	**Total N (%)**	**Clinical trials** N (%)	**Solicited** N (%)	**Literature** N (%)	**Spontaneous** N (%)
Total	2,304 (100%)	228 (100%)	1214 (100%)	39 (100%)	823 (100%)
Live birth without CA	1,972 (86%)	169 (74%)	1049 (86%)	28 (72%)	726 (88%)
Live birth with CA	128 (5.6%)	24 (10%)	65 (5%)	9 (23%)	30 (4%)
Fetal loss[a]	150 (6.5%)	26 (11%)	73 (6%)	0	51 (6%)
with fetal defects	*2*	*0*	*1*	*0*	*1*
Termination	54 (2.3%)	9 (4%)	27 (2%)	2 (5%)	16 (2%)
with fetal defects	*13*	*1*	*8*	*0*	*4*

[a] Fetal loss includes still birth, spontaneous abortion, and ectopic pregnancy. N: number of cases; CA: congenital anomalies

Source: Applicant's Response to IR dated March 3, 2016

Summary

The following statement, derived from the currently available literature and composed by DPMH, has been added to recent labels for products to treat DM in pregnancy:

> *The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as*

20-25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

In the Novo Nordisk safety database, the outcome of pregnancy with all sources combined in 86% of cases was LB without CA. The overall rate of LB with CA at 5.8% is at the low end of the range quoted above for women with pre-gestational diabetes. The rate of fetal loss in the Novo Nordisk safety database for all sources combined is 6.5%, well below the quoted rate above. There does not appear to be a signal of concern regarding the use of insulin aspart during pregnancy with regard to fetal outcomes. However, there are limitations inherent in data derived from a pharmacovigilance database that preclude the ability to draw definitive conclusions.

Lactation

Literature Review

The applicant did not identify any articles on insulin aspart and lactation or breastfeeding in their literature search. DPMH also conducted a review of PubMed, Embase, ReproTox, Shepard's and TERIS for published literature regarding insulin aspart and use in lactation. DPMH findings were similar to those of the applicant with the exception of one article in Bulgarian discussing insulin aspart and lactation which included a discussion of general principles of treatment for women with diabetes in pregnancy and lactation and one article discussed below by Whitmore in 2012 (see below discussion).

There are published studies regarding endogenous insulin and lactation. Both the presence of insulin and good metabolic control support the onset of lactogenesis. Insulin in conjunction with other hormones has a role in the differentiation of myoepithelial cells in the breast tissue, enhances the uptake of glucose by mammary cells, and stimulates formation of triglycerides. The formation of milk protein and mammary enzymes is induced by prolactin and promoted by insulin and cortisol[14].

In a study by Shehadeh et al, the investigators analyzed insulin content in human milk of 90 healthy mothers. Insulin was present in the milk of all study subjects. The insulin concentration was not significantly influenced by gestational age at delivery[15].

In 2002, Shulman et al. evaluated the effects of enteral administration of insulin on eight preterm infants[16]. The authors conducted a case-control study to evaluate the association between administration of insulin (Humulin) to preterm infants and effects on gastrointestinal (GI) development and reduction of feeding intolerance. The study matched eight insulin treated

[14] Lipscomb K, Novy MJ. The Normal Puerperium, Lactation Physiology. In: DeCherney AH, Nathan L, Goodwin TM et al. eds. *Current Diagnosis and Treatment-Obstetrics & Gynecology*. 10th Ed. New York, NY: McGraw-Hill, 2007. http://online.statref.com/document.aspx?fxid=30&docid=185.Accessed Dec 22, 2010.
[15]Shehadeh, N, Khaesh-Goldberg E, Shamir R, et al. Insulin in human milk: postpartum changes and effect of gestational age. Arch Dis Child Neonatal Ed. 2003; 88:214-216.
[16] Shulman RJ. Effect of enteral administration of insulin on intestinal development and feeding tolerance in preterm infants: a pilot study. Arch Dis Child Fetal Neonatal Ed. 2002;86:131-133.

infants born at 26 to 30 weeks gestation with 80 infants from a prospective feeding trial conducted from 1992-1997. Clinical characteristics were well matched in both groups. The infants received 1U/kg Humulin every six hours via nasogastric tube followed by their usual feed. They initially started parenteral and enteral feeds until they were able to tolerate full enteral feeding. They received human milk or formula as needed, and management of the feeding regimens for both the Humulin treated and the control infants was per the nursery protocol and neonatology staff. The serum glucose concentration was measured 0, 30, 90 minute intervals after the first, second and fifth doses of Humulin. The glucose concentrations noted were baseline of 8.9 (3.2) mmol/l, 9.7(3.1) mmol/l at 30min, and 9.6(2.9)mmol/l at 90min (mean SD for 1st dose). No hypoglycemia events were noted, and therefore, the infants did not appear to experience significant fluctuation in serum glucose levels after enteral administration of Humulin. The authors noted that one study limitation was the use of controls obtained in a retrospective fashion, although the infants were managed in the same nursery with the same protocols.

In a study by Shehadeh, insulin levels in milk were 60 milliunits/L (range 6.5 to 306 milliunits /L) in 42 mothers without diabetes who had full term infants between 3 and 30 days postpartum[17]. The same author later reported that insulin levels averaged 59 milliunits/L on day 3 postpartum and 40 milliunits/L on day 7 postpartum in 24 mothers without diabetes who had full term infants. Mothers of preterm infants had non-significant changes in milk insulin levels[18].

In a study by Whitmore, published in 2012[19], milk was analyzed from five mothers without diabetes, 4 mothers with type 1 diabetes (who were treated with insulin replacement therapy-insulin aspart and lantis), and 5 mothers with type 2 diabetes (who were being treated with a combination of diet, exercise and metformin) who collected milk samples over a 24-hour period. Samples were analyzed for total and endogenous insulin content. All mothers in the three groups were breast feeding at the time and were within 4 months postpartum. All of the insulin present in the milk of type 1 mothers was exogenous.

According to the LactMed website,[20]

> Mothers with diabetes using insulin may nurse their infants[15]. Exogenous insulin is excreted into breast milk, including newer biosynthetic insulins (i.e., aspart, detemir, glargine glulisine, lispro). Insulin is a normal component of breast milk and may decrease the risk of type 1 diabetes in breastfed infants[21,22,23].

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[17] Shehadeh N et al. Importance of insulin content in infant diet: suggestion for a new infant formula. Acta Paediatr. 2001; 90:93-5.

[18] Shehadeh N, Khaesh-Goldberg E, Shamir R et al. Insulin in human milk: postpartum changes and effect of gestational age. Arch Dis Child Fetal Neonatal Ed. 2003; 88:F214-6.

[19] Whitmore TJ et al. Analysis of Insulin in Human Breast Milk in Mothers with Type 1 and Type 2 Diabetes Mellitus. International Journal of Endocrinology Volume 2012, Article ID 296368, 9 pages.

[20] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[21]Shehadeh N et al. Importance of insulin content in infant diet: suggestion for a new infant formula. Acta Paediatr. 2001; 90:93-5.

> Pasteurization of milk by the Holder method reduces the concentration of insulin in milk by about half[24]… Lactation onset occurs later in patients with type 1 diabetes than in women without diabetes, with a greater delay in mothers with poor glucose control[25, 26].

Hale[27] reports that "no data" is available regarding how much insulin is present in breast milk but states that insulin use is "compatible with breast-feeding".

Summary of the Applicant's Pharmacovigilance Database

Seventy-two (72) cases of the 5,219 cases reported to the Novo Nordisk safety database with the PT 'exposure during breastfeeding' were identified for insulin aspart. No safety concerns were identified from these case reports.

Summary

I was able to find one study that assessed the presence of insulin aspart in human milk, but no studies on the drug's effects on the breastfed child or effects on milk production/excretion. Endogenous insulin is present in human milk and exogenous insulin, including insulin aspart, is excreted into breast milk. No adverse reactions have been associated with infant exposure to insulin through the consumption of human milk. Both LactMed and Hale state that insulin use is compatible with breast feeding. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for insulin, any potential adverse effects on the breastfed child from insulin aspart or from the underlying maternal condition.

During discussions with the division clinical team we were advised that only information regarding the "insulin aspart" molecule would be included in labeling. Therefore, much of the above information regarding levels of endogenous insulin found in breast milk will not be discussed in labeling.

Females and Males of Reproductive Potential

In addition to the applicant's search of published literature for information regarding insulin aspart and fertility, DPMH also conducted a review of published literature in PubMed and Embase to evaluate the use of insulin aspart and its effects on fertility. No relevant publications were found in either search.

---

[22] Shehadeh N et al. Insulin in human milk and the prevention of type 1 diabetes. Pediatr Diabetes. 2001; 2(4):175-7.
[23] Tiittanen M et al. Dietary insulin as an immunogen and tolerogen. Pediatr Allergy Immunol. 2006; 17:538-43.
[24] Ley SH et al. Effects of pasteurization on adiponectin and insulin concentrations in donor human milk. Pediatr Res. 2011; 70:278-81.
[25] Stanley K, Fraser R, Bruce C. Physiological changes in insulin resistance in human pregnancy: longitudinal study with the hyper-insulinaemic euglycemic clamp technique. Br J Obstet Gynaecol. 1998; 105:756-9.
[26] Neubauer SH et al. Delayed lactogenesis in women with insulin-dependent diabetes mellitus. Am J Clin Nutr. 1993; 58(1):54-60.
[27] Hale, T. Medications and Mother's Milk. Hale Publishing, 2012.

As was discussed in the nonclinical section, in fertility studies in male and female rats, at subcutaneous doses up to 200 units/kg/day (approximately 32 times the human subcutaneous dose, based on units/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed.

Summary

There is no information available on the effect of insulin aspart on fertility in males or females of reproductive potential (b) (4)..

CONCLUSIONS

The Fiasp label has been updated to comply with the PLLR. Available information from randomized controlled trials in 441 pregnant women with diabetes mellitus treated during the latter part of pregnancy that have been reported in the published literature on insulin aspart, the active ingredient of FIASP, did not identify a drug-associated risk with use during pregnancy. DPMH has the following recommendations for labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" subsections[28].
- **Lactation, Section 8.2**
  - The "Lactation" subsection of labeling was formatted in the PLLR format to include: the "Risk Summary".[29]

(b) (4)

RECOMMENDATIONS

DPMH revised sections 8.1, 8.2, and 8.3 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

[28] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

[29] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1-Risk Summary.

[30] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, C-8.3 Females and Males of Reproductive Potential.

DPMH Proposed Fiasp Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no (b) (4) available with FIASP use in pregnant women. (b) (4) available information from published randomized controlled trials (b) (4) with insulin aspart (b) (4) [see Data]. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [*see Clinical Considerations*].

In animal reproduction studies (b) (4) administration of subcutaneous insulin aspart to non-diabetic pregnant rats and rabbits during the period of organogenesis did not cause adverse developmental effects at exposures 8 times and equal to the human subcutaneous dose of 1.0 unit/kg/day, respectively. Pre- and post-implantation losses and visceral/skeletal abnormalities were seen at higher exposures; however, and are considered secondary to maternal hypoglycemia [*see Data*].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk
Poorly controlled diabetes increases the fetal risk for (b) (4) still birth, macrosomia related morbidity (b) (4)

Data
Human Data
(b) (4) published randomized controlled trials of 441 pregnant women with diabetes mellitus treated with insulin aspart starting during the late 2nd trimester of pregnancy did not identify (b) (4) association of insulin aspart with major birth defects or adverse maternal or fetal outcomes. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including a variable duration of treatment and relatively small size of the majority of the trials.

(b) (4)

Animal Data

[redacted]

Fertility, embryo-fetal and pre-and postnatal development studies have been performed with [redacted] insulin aspart [redacted] and regular human insulin in [redacted] rats and rabbits. In a fertility and embryo-fetal development study, insulin aspart was administered [redacted] before mating, during mating, and throughout pregnancy. Further, in a pre- and postnatal development study insulin aspart was given throughout pregnancy and during lactation to rats. In an embryo-fetal development study insulin aspart was given to female rabbits during organogenesis. The effects of insulin aspart did not differ from those observed with subcutaneous regular human insulin. Insulin aspart, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 units/kg/day (approximately 32 times the human subcutaneous dose of 1.0 unit/kg/day, based on human exposure equivalents) and in rabbits at a dose of 10 units/kg/day (approximately three times the human subcutaneous dose of 1.0 unit/kg/day, based on human exposure equivalents). No significant effects were observed in rats at a dose of 50 units/kg/day and in rabbits at a dose of 3 units/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 unit/kg/day for rats and equal to the human subcutaneous dose of 1.0 unit/kg/day for rabbits, based on human exposure equivalents. The effects are considered secondary to maternal hypoglycemia.

8.2 Lactation

Risk Summary

One small published study reported that exogenous insulin, including insulin aspart, was present in human milk. [redacted] effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for insulin, any potential adverse effects on the breastfed child from insulin aspart or from the underlying maternal condition.

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

/s/

JANE E LIEDTKA
05/06/2016

TAMARA N JOHNSON
05/06/2016

LYNNE P YAO
05/09/2016

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, Ophthalmic Device Branch (REGO)

Date: April 18, 2016

To: Anika Lalmansingh, CDER/OMPT/CDER/OPQ/DRBPMII
Anika.lalmansingh@fda.hhs.gov

Song Kim (Sonni), CDER/OMPT/CDER/OPQ/DRBPMII
Song.Kim@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Anika Lalmansingh

Through: Viky Verna, Combination Product Lead, REGO, DMQ, OC, CDRH

Viky Verna -S
Digitally signed by Viky Verna -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Viky Verna -S, 0.9.2342.19200300.100.1.1=2000495623
Date: 2016.04.26 09:26:10 -04'00'

From: Crystal Lewis, REGO, DMQ, OC, CDRH

Applicant: Novo Nordisk
PO Box 846
Plainsboro, New Jersey 08536
FEI#

Application # NDA 208751

Consult # ICC#1500677

Product Name: Fiasp PDS290 Faster Aspart pen-injector

Pre-Approval Inspection: No

Documentation Review: No Additional Information Required

Final Recommendation: **APPROVAL**

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 NDA 208751.

PRODUCT DESCRIPTION

The Fiasp insulin drug product is a faster-acting insulin aspart that is intended for subcutaneous injection, (b) (4) or intravenous infusion for the treatment of diabetes mellitus. The combination product consists of a drug product inside a cartridge and a pen-injector. It is identified as a pre-filled disposable PDS290 Faster Aspart pen-injector (see figures 1 and 2).

Figure 1 PDS290 Faster Aspart pen-injector (arbitrary label design)

Figure 2 PDS290 Faster Aspart pen-injector without cap (arbitrary label design)

REGULATORY HISTORY

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

1. Novo Nordisk A/S
   Novo Alle 1
   Bagsvaerd, Denmark DK-2880
   FEI # 3000151819

Responsibility – the firm is responsible for formulation, filling and inspection of the 3 ml cartridge and 10 ml vials. The firm is responsible for quality control of the 3 ml cartridge and 10 ml vial: chemical, physical and microbiological – sterility testing and Bacterial endotoxin testing. The firm is also responsible for stability testing and batch release.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted on 3/31/2016 to 4/8/2016. The inspection covered drugs and was classified NAI.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

Inspection Recommendation:
An inspection is not required because:

- A recent inspection of the firm was acceptable.

2. Novo Nordisk A/S
   Brennum Park
   Hilleroed, Denmark DK-3400
   FEI# 3003131673

Responsibility – the firm is responsible for: developing, maintaining design history, manufacturing of components, pre- and final assembly, labeling and packaging of the PDS290 Faster Aspart pen-injector. The firm is also responsible for quality control of the 3 ml cartridge, PDS290 Faster Aspart pen-injector and 10 ml vial: chemical, physical and stability testing except for sterility testing.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted on 1/11/2016 to 1/22/2016. The inspection covered drugs and was classified VAI.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

Inspection Recommendation:

- A recent inspection of the firm was acceptable.

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

(b) (4)

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

(b) (4)

Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review.

RECOMMENDATION

The application for Fiasp PDS290 Faster Aspart pen-injector, NDA 28751 is approvable from the perspective of the applicable Quality System Requirements.

(1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

(2) There were no facility inspections for compliance with applicable Quality System Requirements needed for approvability determination.

DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=PIV, serialNumber=D72A10D821086C4471A26DA1685901084990C04D872A8243E7
Date: 2016.04.26 08:57:42 -04'00'

Crystal Lewis

Prepared: Clewis: 4/18/2016
Reviewed: VVerna: 4/25/2016

CTS No.: ICC1500677
NDA 208751

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

Inspectional Guidance

Firm to be inspected:

1. Novo Nordisk A/S
   Novo Alle 1
   Bagsvaerd, Denmark DK-2880
   FEI # 3000151819

2. Novo Nordisk A/S
   Brennum Park
   Hilleroed, Denmark DK-3400
   FEI# 3003131673

CDRH recommends the inspection under the applicable Medical Device Regulations of Novo Nordisk A/S, located in Bagsvaerd, Denmark (FEI #3000151819) and Novo Nordisk A/S, located in Hilleroed, Denmark (FEI #3003131673)

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)

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 3452
Phone: 301-796-6116

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Viky Verna
Combination Product Branch Lead,
REGO,
DMQ
Office of Compliance, WO66 RM 3435
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

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

/s/

ANIKA A LALMANSINGH
04/27/2016
Uploading on behalf of Crystal Lewis, REGO, DMQ, OC, CDRH.

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

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

Application: NDA 208751

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Fiasp (fst-insulin aspart) injection (all pending)

Applicant: Novo Nordisk

Receipt Date: December 8, 2015

Goal Date: October 8, 2016

1. Regulatory History and Applicant's Main Proposals

This is a 505(b)(1) application. This product is a reformulation of an already approved product, insulin aspart (NDA 20986).

The sponsor is proposing the following indication: To improve glycemic control in adults with diabetes mellitus.

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 of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies will be corrected prior to approval.

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4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-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

Selected Requirements of Prescribing Information

See Appendix for a sample tool illustrating Highlights format.

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: *Length of the highlights section is slightly over 1/2 page.*

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 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 for HL format.

Comment:

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. Headings in HL must be presented in the following order:

Heading	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 five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

YES 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:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval 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 title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title 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 must be placed immediately beneath the BW title, and should be centered 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 title 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 five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the 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) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

YES 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES

22. 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 (or will have)** 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

NO 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment: *A place holder is included in this version of the label, however, this will need to be updated with the actual date.*

Contents: Table of Contents (TOC)

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

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. 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 26. The same title 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 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. 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 (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. 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 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**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:

YES 32. 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)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "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 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), 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:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

NO 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *Current PI says "see FDA- approved….". We will revise to "Advise the patient ot read the FDA-approved…"*

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) 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: Highlights and Table of Contents Format

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

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

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

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

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
02/02/2016

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 # 208751	NDA Supplement #: N/A	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Fiasp (pending) Established/Proper Name: fst-insulin aspart (pending) Dosage Form: injection Strengths: 100 units/mL		
Applicant: Novo Nordisk Agent for Applicant (if applicable): N/A		
Date of Application: December 8, 2015 Date of Receipt: December 8, 2015 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: October 8, 2016	Action Goal Date (if different): October 7, 2016	
Filing Date: February 6, 2016	Date of Filing Meeting: January 27, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☒ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): To improve glycemic control in adults with diabetes mellitus		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
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 (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☒ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ 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 (FDCA Section 505B) ☐ 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): 106878	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA 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.***	☒	☐		
Are the 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.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
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***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

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 *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ 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
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☒		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• 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 bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same 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 another listed drug product containing the same active moiety, 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 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but 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***	☐	☒		
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***	☐	☐	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☒	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
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 the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

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).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
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:	☒	☐		

[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 (3397/3792), 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)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
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)?	☒	☐	☐	
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.*	☒	☐		
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				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both 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 FD&C Act 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.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: 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:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☒	☐		

[2]

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), 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.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
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."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
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?	☒	☐		

http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

If no, request applicant to submit SPL before the filing date.				
Is the PI submitted in PLR format?[4]	☒	☐		
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.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5] Has a review of the available pregnancy and lactation data been included?	☒ ☒	☐ ☐	☐ ☐	 We are requesting the sources of clinical information (literature review, postmarketing cases), summary of clinical information and justification for their proposed labeling in the 74 day letter.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

	☐ 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.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
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:***	☒	☐	☐	CDRH
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** March 2, 2011 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** June 22, 2015 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐			Two clinical SPA requests submitted on 12/1/2014, but did not qualify. Both requests denied on 12/19/2014.

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 27, 2016

BACKGROUND: This is a 505(b)(1) application. This product is a reformulation of an already approved product, insulin aspart (NDA 20986).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Callie Cappel-Lynch	Y
	CPMS/TL:	Julie Van der Waag	Y
Cross-Discipline Team Leader (CDTL)	Lisa Yanoff		Y
Division Director/Deputy	Jean-Marc Guettier		Y
Office Director/Deputy	Curtis Rosebraugh		N
Clinical	Reviewer:	KC Kwon	Y
	TL:	Lisa Yanoff	Y
Social Scientist Review (*for OTC products*)	Reviewer:	NN	
	TL:	NN	
OTC Labeling Review (*for OTC products*)	Reviewer:	NN	
	TL:	NN	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	NN	
	TL:	NN	
Clinical Pharmacology	Reviewer:	Shalini Wickramaratne Senarath Yapa	Y
	TL:	Manoj Khurana	Y
• Genomics	Reviewer:	NN	
• Pharmacometrics	Reviewer:	NN	
Biostatistics	Reviewer:	Alex Cambon	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Miyun Tsai Turton	Y
	TL:	Lee Elmore	Y
Statistics (carcinogenicity)	Reviewer:	NN	
	TL:	NN	
Product Quality (CMC) Review Team:	ATL:	Muthu Ramaswamy	Y
	RBPM:	Anika Lalmansingh	Y
• Drug Substance	Reviewer:	N/A	N
• Drug Product	Reviewer:	Muthu Ramaswamy	N
• Process	Reviewer:	Erin Kim	N
• Microbiology	Reviewer:	Koushik Paul	N
• Facility	Reviewer:	Juandria Williams	N
• Biopharmaceutics	Reviewer:	N/A	N
• Immunogenicity	Reviewer:	TBD	N
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Aman Sarai	N
	TL:	Marcia Britt Williams	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Ankur Kalola	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Ariane Conrad	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	Naomi Redd	N
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Cynthia Kleppinger	Y
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	NN	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	NN	
	TL:		
Other reviewers/disciplines			
• CDRH	Reviewer:	Carolyn Cochenour	Y
	TL:	Alan Stevens	N
Other attendees	Bindi Nikhar (OCP)		Y
	Janice Weiner (ORP)		Y
	Patrick Raulerson (ORP)		Y
	Monika Houstoun (ADL)		Y

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

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 NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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:
• 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
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ 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
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CDRH</u> **Comments**:	☒ FILE ☒ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Jean-Marc Guettier (division director) **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): N/A **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Filing Date: February 6, 2016** **Day 74 Letter Date: February 19, 2016** **Next Team Meeting: March 16, 2016 2:00-3:00pm** **Mid-Cycle Meeting: May 11, 2016 1:00-2:00pm** **Review Completion Goal Date according to GRMP: September 2, 2016** **Send Labeling/ PMR/ PMC to applicant : September 9, 2016** **PDUFA Goal Date: October 8, 2016**

	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. Review Classification: ☒ Standard Review ☐ Priority Review

	ACTION ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	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.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter

☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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
02/01/2016