CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208751Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	21 Sep 2017
From	Lisa Yanoff, M.D.
Subject	Cross-Discipline Team Leader Review of Class 2 Resubmission for insulin aspart
NDA/BLA #	208751
Applicant	Novo Nordisk
Date of Resubmission	29 Mar 2017
PDUFA Goal Date	29 Sep 2017
Proprietary Name / Established (USAN) names	FIASP/insulin aspart
Dosage forms / Strength	100 units/mL in 10 mL vials and 3 mL FlexTouch device
Proposed Indication(s)	to improve glycemic control in adults with diabetes mellitus
Recommended:	Approval

Cross Discipline Team Leader Review

1. Introduction

This document contains the summary review for the Class 2 resubmission of New Drug Application 208751, received 29 Mar 2017, and submitted under the 505(b)(1) regulatory pathway for marketing approval of insulin aspart (FIASP[1]) to improve glycemic control in adults with diabetes mellitus. The reader is referred to the multiple discipline reviews for a more detailed discussion of the issues.

The first cycle NDA for FIASP was issued a Complete Response on 7 Oct 2016 for deficiencies pertaining to Clinical Pharmacology (pharmacokinetics assessments) and Immunogenicity (assays were insufficient).

This memo relies upon or references the following documents:

Subject	Author	Date
Clinical Efficacy and Safety review	Dr. Hyon Kwon	22 Sep 2017
Nonclinical review	Dr. Arulasanam Thilagar	12 Jul 2017
Office of Clinical Pharmacology (OCP) review	Dr. Shalini Wickramaratne Senarath Yapa	6 Sep 2017
Office of Biotechnology Products (OBP) review	Dr. Bruce Huang	6 Sep 2017
Division of Medication Error Prevention and Analysis (DMEPA) labeling review	Dr. Ariane Conrad	7 Aug 2017; 23 Aug 2017
Proprietary Name review	Dr. Todd Bridges	6 Jun 2017
Office of Prescription Drug Promotion (OPDP) labeling review	Dr. Ankur Kalola	20 Sep 2017
OPDP and Division of Medical Policy Programs (DMPP) Patient Labeling review	Aman Sarai	20 Sep 2017
End of Review Meeting Minutes		12 Jan 2017
Complete Response Letter		7 Oct 2016

[1] Under the first cycle review the proposed proprietary name that was used in reviews was (b) (4) Fiasp is the revised proposed proprietary name, i.e., (b) (4) and Fiasp are the same product.

2. Background

Insulin aspart is an analog of human insulin indicated to improve glycemic control in patients with diabetes mellitus in which the amino acid proline has been replaced with aspartic acid in position B28 to increase the rate of absorption as compared to regular human insulin. As a 'rapid-acting insulin analog', insulin aspart is typically administered at mealtime to reduce postprandial hyperglycemia, i.e. increase in blood glucose related to carbohydrate ingestion. It is usually administered in conjunction with a basal insulin product, although in patients with type 2 diabetes it can be used without basal insulin. Rapid-acting insulin analogs are also used in continuous subcutaneous insulin infusion therapy (i.e. insulin pumps) for both basal and bolus coverage in type 1 diabetes patients. The currently marketed insulin aspart product is approved in the U.S. under the tradename NovoLog, and is one of the several rapid-acting insulin analogs[2] currently marketed in the U.S. NovoLog was approved for treatment of adult patients with diabetes mellitus on June 7, 2000.

The product under review in this NDA (proposed tradename FIASP) is a new formulation of insulin aspart that contains 2 additional excipients intended to change the pharmacokinetic/pharmacodynamic (PD/PD) profile of the drug to make the onset of action faster than NovoLog. However, NovoLog and FIASP still have the same active ingredient. In FIASP, nicotinamide (also known as niacinamide or vitamin B3) was added to increase the absorption of insulin aspart after administration by increasing the proportion of monomers of insulin, and L-arginine was added to stabilize the formulation. Insulin products with a faster onset of action than those currently available are in theory desirable because the earlier onset of action would allow for dosing closer to mealtime or even after the meal with resultant better matching to carbohydrate intake. This altered (or 'left-shifted') PK profile was the rationale for development of FIASP.

The first cycle NDA for FIASP was issued a Complete Response (CR) on 7 Oct 2016 for deficiencies pertaining to Clinical Pharmacology and Immunogenicity. The bioanalytical method used to (b) (4) (for the purpose of the primary pharmacokinetic analyses) was deemed unreliable. As a result, the reliability of the pharmacokinetic data for all clinical pharmacology studies that used this method was called into question. In addition, the CR letter cited multiple deficiencies regarding the validation of the radioimmunoprecipitation assay (RIA) for the detection of insulin aspart-specific and cross-reactive anti-human insulin anti-drug antibodies. The specific details of both CR issues can be found in the CR letter and Appendix A of this summary memo.

There were also several 'Additional Comments' that were not approvability issues including a request to provide data to address the safety of longer-term infusion and higher doses of FIASP that are likely to occur in the clinical setting[3], specifically with regards to the excipients,

[2] Other approved rapid-acting insulin analogs administered parenterally include Humalog (insulin lispro, NDA 020563) and Apidra (insulin glulisine, NDA 021629). Additionally, Afrezza (human insulin, NDA 022472) is a rapid-acting insulin product administered by oral inhalation.

[3] In support of intravenous (IV) administration, you have submitted stability data of FIASP when diluted in two types of intravenous infusion fluids (0.9% NaCl and 5% glucose) at concentrations of 0.5 U/mL and 1.0 U/mL

nicotinamide and arginine, a request to provide analyses that could distinguish treatment-boosted vs. treatment-emergent anti-drug antibody responses[4], and a comment related to a potential outstanding device issue regarding (b) (4).

An End of Review meeting was held on 15 Dec 2016 between the Agency and the sponsor. Agreements were made regarding the bioanalytical method that would be used to address the Clinical Pharmacology deficiencies, i.e. that it was acceptable to use a total insulin aspart assay to characterize the pharmacokinetics (PK) of FIASP, acceptability of reanalysis of stored samples from previously conducted studies, acceptability of providing PK data from an ongoing Clinical Pharmacology study (3922), and the plans for immunogenicity testing. Agreement was also reached that the resubmission would (b) (4)

(Section 1 of Module 3.2.P.8.3). FIASP is stable for 24 hours at room temperature post dilution. We also acknowledge that clinical pharmacology study NN1218-3949 investigated the PK and PD of FIASP following IV administration of a relatively low dose of FIASP (0.02 U/kg). We do not expect any difference in the PD of FIASP vs. NovoLog following IV administration since the active ingredient is insulin aspart. However, there are no data establishing the safety of the drug product (including excipients) for longer-term IV infusion and at higher doses that are likely to be used in the clinical setting. With regard to nonclinical data, the single-dose rabbit local tolerance study (#212147), which was the only study that included IV dosing, was adequate to assess toxicity of accidental exposure or very short-term exposure, but was not adequate to support long term repeated IV exposure. The nonclinical study that you conducted to support clinical studies with SC dosing was a 4 week local tolerance study (#212251) in rats. You should clarify how you plan to address the safety of longer-term infusion and higher doses of FIASP that are likely to occur in the clinical setting, specifically with regards to the excipients, nicotinamide and arginine.

[4] See Appendix A

(b) (4)

3. CMC / Device

The recommendation from the Office of Pharmaceutical Quality (OPQ) (including the manufacturing inspection recommendation) was approval on the first cycle.

There is no new CMC/Device information in the resubmission.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology reviewer recommended approval of this NDA on the first cycle. See her review dated August 29, 2016.

For the resubmission, the only nonclinical information reviewed related to intravenous use of FIASP. The original review noted that with regard to nonclinical data, the single-dose rabbit local tolerance study (#212147), which was the only study that included IV dosing, was adequate to assess toxicity of accidental exposure or very short-term exposure, but was not adequate, in and of itself, to support long term repeated IV exposure. The nonclinical reviewers determined that longer-term IV use of FIASP is supported by several considerations including the mechanism of action for absorption enhancement properties of nicotinamide [the effect of nicotinamide on insulin is related to enhancement of insulin monomer formation, rather than an effect secondary to increased local blood flow (e.g., vasodilation) proximal to the SC injection site] and additional information provided by the sponsor showing that the excipients are contained in several FDA-approved parenteral multi-vitamin drugs as a co-API (active pharmaceutical ingredient).

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewer Dr. Shalini Wickramaratne Senarath Yapa (from the Office of Clinical Pharmacology [OCP]) recommends Approval after reviewing the new Clinical Pharmacology information in the resubmission.

The data package in the resubmission was agreed upon at the End of Review meeting (discussed above) and was intended to address the Clinical Pharmacology deficiencies listed in the CR letter. Specifically, the bioanalytical method used [redacted] (b) (4) (for the purpose of primary pharmacokinetic analyses) was deemed unreliable. Refer to Appendix A of this memo for the entire description of the Clinical Pharmacology deficiencies. The sponsor's approach to address the deficiencies was to base their submission on a total insulin aspart bioanalytical method [redacted] (b) (4). (Of note, the sponsor had measured total insulin aspart concentrations in some studies but reported these as exploratory endpoints.) As such the data package in the resubmission consists of 1) retrospective reanalysis of total aspart concentrations from previous studies, 2) reanalysis of samples from one study using a *total* insulin aspart bioanalytical method and 3) a new meal challenge study (3922) assessing total insulin aspart concentrations.

The bioanalytical method for total insulin aspart was concluded to be appropriately validated by the Clinical Pharmacology reviewers. Refer to 3.2.8 Summary of Bioanalytical Method Validation in the Clinical Pharmacology review for details.

Clinical Pharmacology Studies Relevant to the Submission	
3887	Euglycemic clamp –T1DM
3889	Standardized meal test – T1DM
3891*	Euglycemic clamp –T1DM
3918	PK/PD in Japanese subjects – T1DM
3921	PK/PD of postmeal FIASP vs. premeal Novolog – T1DM
3922	**Meal challenge study**
3978*	Euglycemic clamp –T1DM
3949	PK in healthy volunteers

Bolded: New study conducted after the first review cycle and included in resubmission
*Samples from these studies were used in PK reanalysis

Key Clinical Pharmacological Characteristics of FIASP

Below is a summary of the major PK/PD parameters for FIASP. Similar to the Clinical Pharmacology review, reference to 'aspart concentrations' in the following subsections refers to total aspart concentration unless otherwise specified.

Pharmacokinetics

Single dose PK

Absorption

- Following SC administration of 0.2 unit/kg single dose of FIASP in patients with T1DM, the mean onset of appearance was ~2.5 minutes post-dose and mean time to maximum insulin aspart concentration was achieved ~63 minutes post-dose
- Following SC administration of single doses ranging from 0.06 to 0.28 unit/kg in patients with T1DM, a proportional increase in total insulin aspart exposure and maximum concentrations of insulin aspart was observed with an increase in FIASP dose
- The absolute SC bioavailability of insulin aspart in healthy subjects following administration of a 0.2 unit/kg FIASP dose in the abdomen, deltoid, and thigh was 85%, 76%, and 75%, respectively

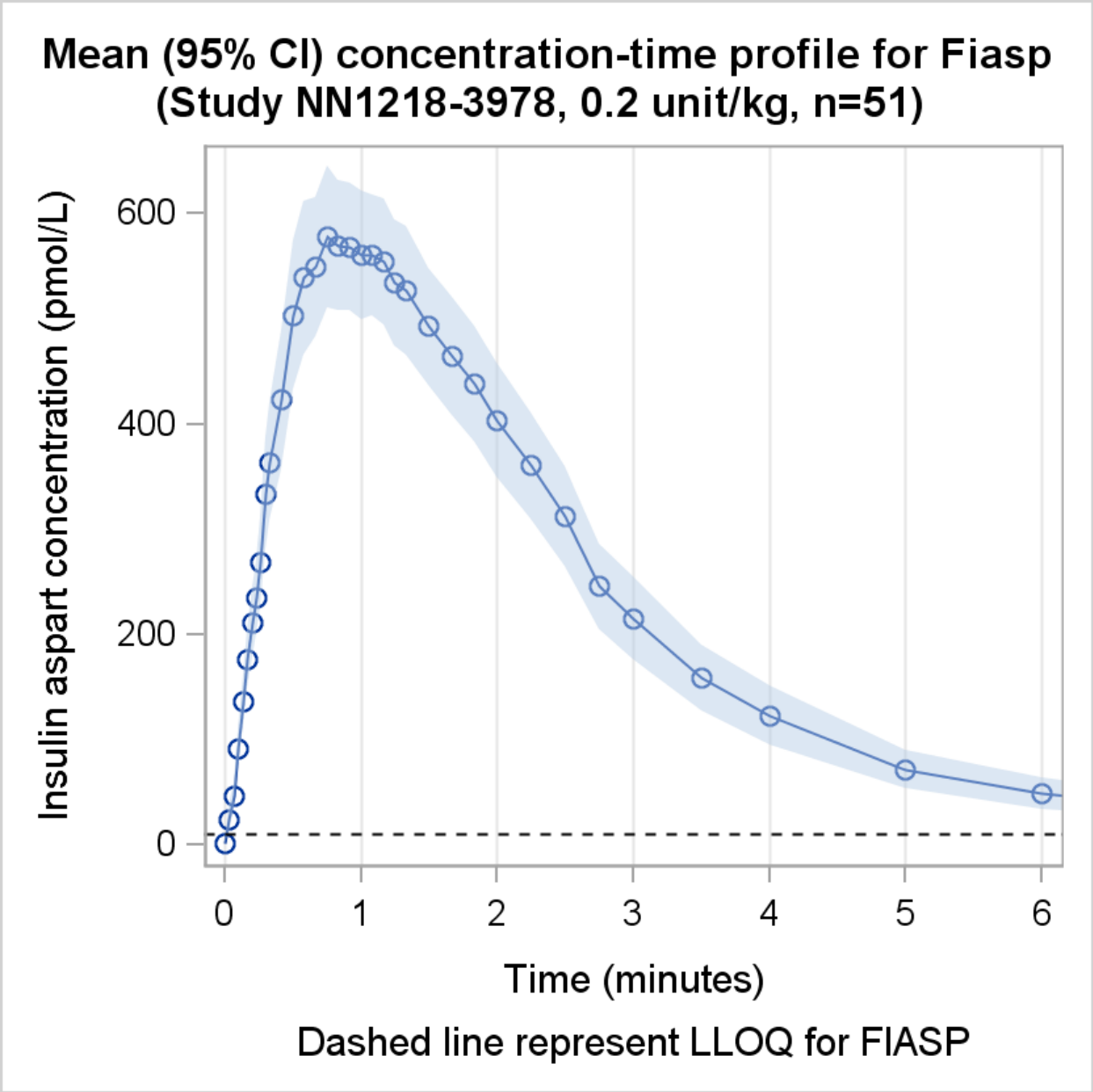
Distribution

- Following IV administration of 0.02 unit/kg FIASP in healthy subjects, the geometric mean volume of distribution for insulin aspart was 0.15 L/kg
- Insulin aspart has a low binding affinity to plasma proteins (<10%), similar to that seen with regular human insulin

Elimination

- Following SC administration of 0.2 unit/kg single dose of FIASP in patients with T1DM, the geometric mean terminal half-life for FIASP was 68.1 minutes (median: 65.5 minutes)

 Following IV administration of 0.02 unit/kg FIASP in healthy subjects, the geometric mean clearance and elimination half-life was 0.90 (L/hr)/kg, and 7.2 minutes, respectively



Special populations
In patients with T1DM, the total exposure and maximum concentrations of insulin aspart following administration of FIASP was comparable between different age groups (younger adult and geriatric patients) and between genders (male and females). The total exposure of insulin aspart was comparable between different body mass index (BMI) categories, however maximum concentrations of insulin aspart increased with decreasing BMI category. Renal impairment and race/ethnicity overall showed no clinically meaningful impact on the PK of FIASP. A trend for an increase in total insulin aspart exposure with an increase in the level of total anti-insulin aspart

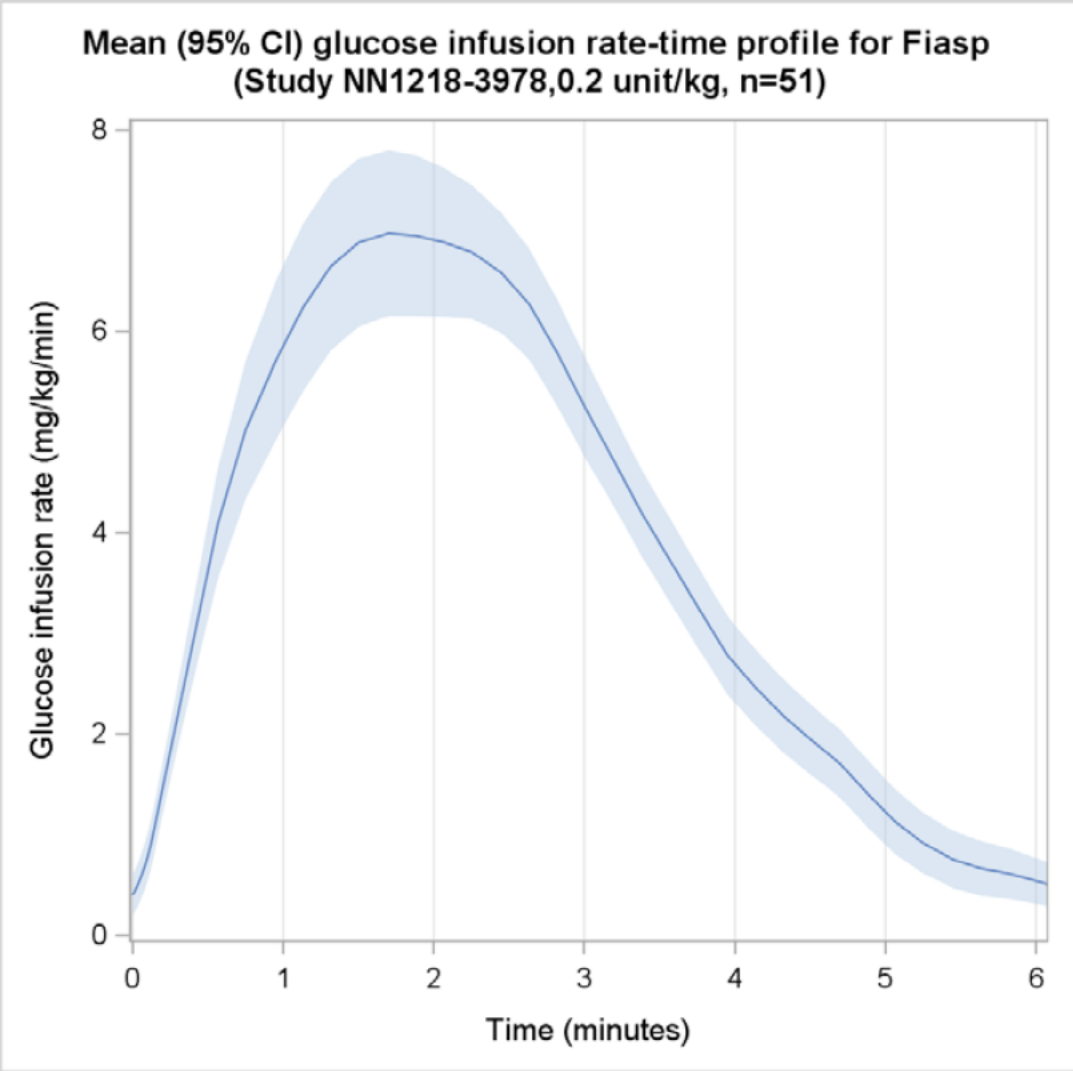
antibodies was observed following administration of FIASP. However, this did not translate into any differences in PD (see below).

Pharmacodynamics

Euglycemic clamp studies

Glucose lowering effect

- In 3 euglycemic clamp studies, following SC administration of 0.2 unit/kg single dose of FIASP in patients with T1DM, the geometric mean onset of action was 11 to 17 minutes (range) and time to maximum glucose lowering effect was 109 to 119 minutes (range). The geometric mean duration of action was 342 to 476 minutes (range) for FIASP
- The total glucose lowering effect and maximum glucose lowering effect increased in slightly less than linear manner within increasing dose of FIASP (0.1, 0.2, 0.4 unit/kg)
- Following SC administration of 0.2 unit/kg FIASP, the within-subject variability for total glucose lowering effect and maximum glucose lowering effect was 18.3% and 19.3%, respectively
- There was no correlation between anti-insulin antibodies and glucose lowering effect in a pooled analysis of studies 3987, 3887, and 3891



Clinical interpretation of Clinical Pharmacology data

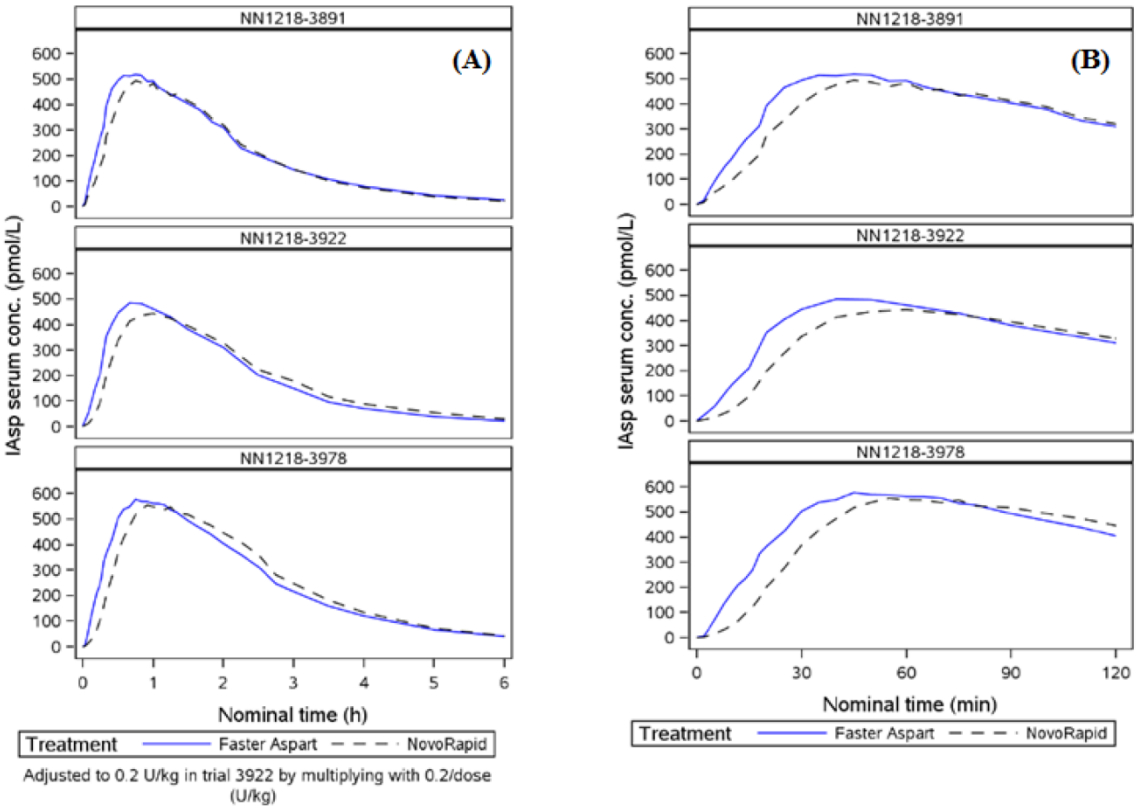
In addition to confirming the PK/PD characteristics of FIASP using a valid bioanalytical method, the Clinical Pharmacology review extensively discusses the clinical relevance of the comparative PK/PD data for FIASP vs. NovoLog in light of the stated rationale for its development (b) (4) [redacted].

In all 3 studies examined, the total exposure of insulin aspart (AUC0-tlast) and Cmax was comparable between FIASP and NovoLog.

With regard to differences between the two, overall the onset of appearance of FIASP was faster, time to 50% Cmax and tmax occurred earlier, and early insulin aspart exposure was greater for FIASP when compared to NovoLog following SC administration. Comparative PK concentration-time profiles are shown below with comparative data following (Curves generated by the Sponsor; figures from Dr. Wickramaratne Senarath Yapa's review. The Clinical

Pharmacology reviewers concur with the Sponsor that in all studies, a slight left shift in the PK profile of FIASP compared to NovoLog was observed.

Mean insulin aspart serum concentration-time profile for FIASP and NovoLog stratified by study (A) 0-6 hrs and (B) 0-2 hrs[6]



A faster mean onset of appearance was observed for FIASP when compared to NovoLog, with the mean onset of appearance for FIASP (2.53 min) appearing to be twice as fast compared to NovoLog (5.24 min) in Study 3978 (estimated mean treatment difference of -2.71 min [-3.26; -2.16][7]). The mean time to 50% Cmax and mean time to tmax was earlier for FIASP compared to NovoLog in the 3 studies. In Study 3978, the mean treatment difference for mean time to 50% Cmax and time to tmax for FIASP when compared to NovoLog was statistically significant (-9.41 min [- 11.54; -7.29] and -10.42 min [-18.52; -2.31], respectively). In all studies, the largest difference in insulin aspart exposure for FIASP compared to NovoLog was observed in the initial 15 mins post-dose, with the estimated mean treatment ratio ranging from 1.93 to 3.55. 'Late insulin aspart exposure' data also supported the left shifted concentration-time profile of FIASP. For example, in Study 3922, the mean estimated time to late 50% Cmax was shorter (22.9 min) for FIASP when compared to NovoLog; (see Clinical Pharmacology review for details).

[6] In Studies 3978 and 3891 a 0.2 unit/kg dose was administered; in Study 3922 the administered actual dose ranged from 0.06-0.28 unit/kg (for this study, serum concentrations are adjusted to a dose of 0.2 unit/kg). NovoRapid is the EU-approved insulin aspart product representing NovoLog in these studies.

[7] 95% Confidence Interval in this section unless otherwise specified

With regard to Pharmacodynamics, as expected the total and maximum glucose lowering effects were comparable between FIASP and NovoLog in euglycemic clamp studies. PD data from euglycemic clamp studies in patients with T1DM also showed an earlier onset of action, time to 50% GIRmax (glucose infusion rate) and GIRmax, and a greater early glucose lowering effect for FIASP compared to NovoLog. For example, the primary objective of Study 3978 was to compare the early PD response, defined by area under the GIR profile from 0-2 hrs (AUCGIR,0-2hr), for FIASP and NovoLog. The estimated treatment ratio (FIASP/NovoLog) for AUCGIR,0-2hr was 1.10 [1.00; 1.22] (p=0.058), which suggests an approximately 10% greater early glucose lowering effect of FIASP when compared to NovoLog.

While differences in PK/PD were observed in the highly controlled glucose clamp setting in type 1 DM (i.e., a sensitive method to measure small differences in these parameters), postprandial glucose (PPG) excursion data from meal challenge studies showed that the PPG of pre-meal FIASP was comparable to pre-meal NovoLog. Further, following post-meal dosing of FIASP (20 min after start of intake of a standardized meal), PPG was on average higher than pre-meal NovoLog. The Clinical Pharmacology reviewers state that meal challenge studies are the more clinically relevant paradigm to investigate the clinical meaningfulness of the observed PK differences, and they believe that even though euglycemic clamp studies showed PD differences that also suggest a left shift for FIASP, that these differences would not be expected to translate into a clinically meaningful difference in the clinical setting given the results observed on the meal challenge studies. I note that in several analyses there were trends favoring FIASP in terms of supporting that there may be a left shifted time action profile in the postmeal setting; however, the results are not statistically significant and no conclusions should be drawn that there are any important clinical differences between FIASP and NovoLog with regard to time action profile after a meal challenge. (b) (4) .

The Clinical Pharmacology reviewer concludes that that *magnitude* of differences evident in the PK/PD profile from clamp studies is not large enough to translate to significant impact on PPG as anticipated when FIASP and NovoLog are administered in identical manner. Hypothetically, I believe it remains possible that in patients that are very insulin sensitive (i.e., pediatric patients) a difference in PPG lowering could be shown.

Postmeal FIASP

In meal study 3921 (reviewed during the first cycle), plasma glucose profiles after a single SC dose of FIASP administered 20 minutes after the start of the standardized meal were higher than those for NovoLog administered immediately before the meal. Specifically, the primary endpoint of the study, mean plasma glucose concentrations from 0-6 hr after the start of intake of a standardized meal (PGav, 0-6hr), was 13% higher for post-meal FIASP when compared to pre-meal NovoLog (estimated treatment ratio of 1.13 [1.06; 1.21] 90%CI, p=0.002). This would be expected to translate into a smaller glucose lowering effect for FIASP administered 20 minutes after the start of a meal when compared to NovoLog at the start of the meal. Further, these data are consistent with the findings of the Phase 3 trial in T1DM which showed non-inferior (based

on a margin of 0.4%) but numerically worse HbA1c lowering from FIASP administered 20 minutes after the start of a meal vs. NovoLog at the start of the meal.

The Clinical Pharmacology reviewer states that "the post-meal PD data does point to some extent that differences in PK/PD profile of FIASP from NovoLog are close but not optimal for post-meal use as the time of administration, as it comes at a cost of lesser control on PPG excursion for post-meal FIASP when compared to pre-meal NovoLog and even pre-meal FIASP." It is unknown how FIASP given, for example, 10 minutes after the meal vs. NovoLog at the start of the meal would have compared. In other words, the study did not identify the 'ideal' time for administration of FIASP with respect to meals, but rather identified a window of timing with respect to meals that was predictive of clinically safe and effective glucose lowering to proceed with into Phase 3.

6. Clinical Microbiology

See Section 3: CMC

7. Clinical/Statistical- Efficacy

Efficacy was established during the first review cycle and there were no new efficacy studies in the resubmission. Drs. Kwon (Clinical) and Cambon (Biostatistics) reviewed the original studies in detail; please see their reviews and please refer to my original CDTL memo for a summary of efficacy. Efficacy is also discussed in the benefit risk assessment of this memo.

8. Safety

Safety data in the FIASP NDA were reviewed during the first cycle and no deficiencies specifically related to observed safety concerns were identified. Refer to Dr. Kwon's original Clinical Safety review and my CDTL memo for details. Further, there are no new safety findings in the resubmission that change the benefit risk assessment of FIASP. See Dr. Kwon's second cycle Clinical Safety review.

However, as noted above there were multiple deficiencies regarding the validation of the radioimmunoprecipitation assay (RIA) for the detection of insulin aspart-specific and cross-reactive anti-human insulin anti-drug antibodies that led to the Complete Response. As with all therapeutic protein products, immunogenicity is a potential safety concern, and the potential for immunogenicity should be adequately addressed in an NDA submission for a protein product.

The Office of Biotechnology Products (OBP) reviewer, Dr. Bruce Huang, conducted the immunogenicity review of FIASP for the second cycle resubmission. It was concluded that the sponsor has adequately responded to the immunogenicity-related deficiencies in the CR letter and that the NDA is approvable from an immunogenicity perspective. An itemized list of the

deficiencies and the sponsor's responses (which were all deemed acceptable) may be found in the OBP memorandum.

The sponsor also provide a response to the additional comment regarding distinguishing between treatment emergent and treatment boosted antibody responses in clinical trial 3852. The OBP reviewers found the methodology acceptable and noted that there were no meaningful differences between treatment arms with regard to either treatment emergent or treatment boosted antibody responses; this was true for anti-insulin antibodies that can detect both endogenous and exogenous insulin and insulin analogs, i.e. 'cross-reacting anti insulin antibodies' as well as drug specific antibodies, i.e. antibodies specific to insulin aspart. OBP states that "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."

Although clinical investigations of the impact of antibodies on clinical outcomes, such as correlating antibody response with HbA1c lowering and risk of hypoglycemia, did not show any obvious impact, these are relatively insensitive methods of evaluating the impact of immunogenicity. A statement that (b) (4)

The following is recommended for product labeling:

In a 26-week study in adult subjects with type 1 diabetes (Study A *[see Clinical Studies (14)]*), among the 763 subjects who received FIASP, 97.2% were positive for cross-reacting anti-insulin antibodies (AIA) at least once during the study, including 90.3% that were positive at baseline. A total of 24.8% of patients who received FIASP were positive for anti-drug (insulin aspart) antibodies (ADA) at least once during the study, including 17.3% that were positive at baseline.

9. Advisory Committee Meeting

No issue rose to the level of needing to convene an advisory committee meeting for this NDA.

10. Pediatrics

This application triggers the Pediatric Research Equity Act (PREA) because of the change in dosing regimen, and therefore, pediatric studies under PREA are recommended. The initial pediatric study plan (iPSP) was agreed on August 28, 2015. The PSP was discussed at the PeRC meeting on August 24, 2016, and the PeRC agreed with the sponsor's plan for a partial waiver in patients 0 to <1 years of age with T1DM and patients 0 to <10 years of age with T2DM because the studies are impossible or highly impractical and to the deferral in patients 1 to <18 years of age with T1DM and patients 10 to <18 years of age with T2DM. A Phase 3 efficacy and safety study in children and adolescents with T1DM is recommended as postmarketing requirement.

11. Other Relevant Regulatory Issues

The proprietary names FIASP and FIASP FlexTouch were conditionally approved on June 2, 2017.

12. Labeling

Labeling negotiations are ongoing at the time of this review. Notable issues include:

Dosing and administration: Trial 3852 demonstrated that dosing FIASP up to 20 minutes after a meal results in a reduction in HbA1c that is not unacceptably worse than NovoLog administered at mealtime[8]. It is acceptable to allow for dosing up to 20 minutes after a meal in the Dosing and Administration section of labeling. Further, although only the T1DM trial had a postmeal treatment arm, it is acceptable to allow for postmeal use in T2DM because T2DM is the less insulin sensitive population and any adverse efficacy or safety findings would be more apparent in the T1DM population.

(b) (4)

In his review of the original NDA, the statistics reviewer Dr. Cambon noted that the MMRM primary analysis does not adequately address missing data and should not be the analysis used for labeling purposes, and that the sensitivity analysis which most closely addresses missing data should be the one put in the label; however, upon review of both analyses he considered them to be similar enough to use the primary analysis results in labeling.

Recommendations for labeling of immunogenicity data are discussed above.

Approved labeling will conform to the Pregnancy and Lactation Labeling Rule (PLLR). Refer to the consult from the Division of Pediatric and Maternal Health review (DPMH) conducted during the first review cycle.

OPDP has provided labeling review and has concurred that the current version of the proposed labeling minimizes (b) (4) to the degree possible. LDT, DMPP and DMEPA have also reviewed and provided comments on the proposed labeling.

13. Recommendations/Risk Benefit Assessment

[8] In presubmission meetings before the original NDA was submitted FDA agreed that a study demonstrating non-inferiority of Fiasp given postmeal as compared to NovoLog given at mealtime on change in HbA1c could support a 'postmeal' dosing regimen for Fiasp.

- Recommended Regulatory Action

Approval

Approval is recommended because the Applicant has satisfied deficiencies related to the reliability of the bioanalytical method used to assess PK samples in the Clinical Pharmacology program and deficiencies related to the anti-insulin antibody assay validation as identified by the Office of Biotechnology Products review, and the application has otherwise met the regulatory standards for approval.

- Risk Benefit Assessment

The applicant has demonstrated in three adequate and well-controlled trials the glycemic efficacy of FIASP in patients with type 1 and type 2 diabetes administered as bolus insulin either premeal/mealtime (0-2 minutes before meals) or post-meal (20 minutes after the meal). The tables below summarize the trials and the corresponding efficacy findings in the FIASP phase 3 program.

Phase 3 Efficacy and Safety Studies in FIASP Clinical Development Program	
3852 – T1DM 26 weeks + 26 week extension Noninferiority study	FIASP premeal vs. NovoLog premeal, both on basal insulin (blinded) FIASP postmeal vs. NovoLog premeal, both on basal insulin Levemir (open-label)
3853 – T2DM 26 weeks Noninferiority study	FIASP premeal vs. NovoLog premeal, both on basal insulin glargine and metformin (blinded)
4049 – T2DM 18 weeks Superiority study	FIASP premeal + basal insulin + metformin vs. basal insulin + metformin (open-label)

Treatment Group	N	Baseline Mean	End of Trial Mean	LS Mean Change from Baseline	Treatment Diff versus NovoLog (95% CI)
Type 1 Diabetes Mellitus					
Trial 3852: *26-week basal-bolus in combination with insulin detemir*					
Mealtime FIASP	381	7.62	7.31	-0.32	-0.15 (-0.23, -0.07)
Postmeal FIASP	382	7.63	7.51	-0.13	0.04 (-0.04, 0.12)
Mealtime NovoLog	380	7.58	7.42	-0.17	
Type 2 Diabetes Mellitus					
Trial 3853: *26-week basal-bolus in combination with insulin glargine and metformin*					
Mealtime FIASP	345	7.96	6.63	-1.38	-0.02 (-0.15, 0.10)
Mealtime NovoLog	344	7.89	6.59	-1.36	
Trial 4049: *18-week basal-bolus versus basal in combination with metformin*					
Mealtime FIASP +basal	116	7.93	6.78	-1.16	-0.94 (-1.17, -0.72)*
Basal	120	7.92	7.70	-0.22	

*Treatment difference versus basal insulin

Active-control Trials 3852 and 3853 met the primary endpoints and demonstrated the non-inferiority of FIASP vs. NovoLog both given at mealtime (pre-specified non-inferiority margin of 0.4% for HbA1c). Superiority of FIASP plus basal insulin was superior to basal insulin alone

in the T2DM population in trial 4049. Sensitivity analyses did not change the overall conclusions.

In Trial 3852, HbA1c lowering in the mealtime FIASP arm was nominally superior to mealtime NovoLog. However, a superiority claim vs. NovoLog for the primary endpoint for Study 3852 is not warranted since this finding was not replicated across both studies 3852 and 3853. Further, the study was designed with non-inferiority vs. NovoLog as the primary hypothesis test and a test for superiority was not included in the testing hierarchy to control for type 1 error.

Treatment with mealtime FIASP in patients with T1DM led to statistically larger decrease in 2-hour PPG increment (key secondary endpoint) compared to NovoLog (treatment difference of -12.01 mg/dL [95% CI: -23.33, -0.70]), but sensitivity analyses to address the impact of missing data did not confirm this statistical significance. The 2-hour PPG increment was numerically increased with postmeal FIASP compared to NovoLog with treatment difference of 5.32 mg/dL (95% CI: -6.05, 16.68). The larger decrease in 2-hr PPG increment for FIASP compared to NovoLog may be driving the better HbA1c reduction, although this cannot be known for certain. It is also notable that there was less of a reduction in PPG with postmeal FIASP than with mealtime NovoLog. While not a prespecified comparison it is evident from the data that mealtime FIASP results in more PPG reduction than is afforded by postmeal FIASP at 1 and 2 hrs. At 3 hours the difference is small.

Numerically there was a larger decrease in the 2-hour PPG increment in the FIASP group compared to NovoLog group in patients with T2DM (trial 3853), but this decrease was not statistically significant (treatment difference of -6.57 mg/dL [95% CI: -14.54, 1.41]). The estimated treatment difference in change from baseline in 1-hour PPG increment after 26 weeks reached statistical significance favoring FIASP group, with treatment difference between FIASP versus NovoLog of -10.63 mg/dL (95% CI: -19.56, -1.69). There were no statistically significant differences between treatment for change from baseline in 3 hour and 4 hour PPG increments.

These data as well as exploratory analyses conducted by the Applicant of composite endpoints combining glycemic control and hypoglycemia risk, and the supporting PPG data derived from standardized meal test studies conducted as part of the phase 3 pivotal trial in T1DM seem to suggest that the small increase in early absorption for FIASP as compared to NovoLog may prove to be beneficial for patients with good insulin sensitivity such as T1DM patients by allowing for administration of the bolus insulin closer to mealtime. Whether HbA1c reduction can also be meaningfully improved with FIASP as compared to NovoLog remains uncertain. In the T2DM trial there was no apparent difference between premeal FIASP and premeal NovoLog, perhaps because insulin sensitivity is lower in these patients. Of additional relevance here is the conclusion of the Clinical Pharmacology reviewers that it may be the magnitude of differences in PK/PD parameters that is not large enough to translate into a meaningful benefit. It is also interesting that (b) (4) . The Applicant has agreed to (b) (4)

[redacted] (b) (4)

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The safety profile of FIASP is similar to NovoLog and there are no additional safety concerns beyond what is known with rapid acting insulin products. Hypoglycemia related to the bolus injection given at mealtime may occur earlier for FIASP administered with the meal than with NovoLog administered with the meal. This finding likely reflects the specific time action profile of the two insulin products and does not affect the overall/risk benefit consideration.

Overall, I conclude that the NDA for FIASP has met the regulatory requirements for approval. However, it is not clear from the data submitted that FIASP offers patients any meaningful therapeutic advantage over existing therapies.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

This application triggers the Pediatric Research Equity Act (PREA) because of its new dosing regimen.

Appendix A – Deficiencies Listed in Complete Response Letter from First Cycle

CLINICAL PHARMACOLOGY

The bioanalytical method used (b) (4) (for the purpose of primary pharmacokinetic analyses) is deemed unreliable because of the issues listed below. As a result, the reliability of the pharmacokinetic data for all clinical pharmacology studies that used this method is called into question.

(b) (4)

(b) (4)

Our recommendations are as follows:

6. Develop and validate a new analytical method where (b) (4) . We recommend you use the validation acceptance criteria outlined in the draft "Guidance for Industry - Bioanalytical Method Validation," September 2013. If the analytical method meets the validation acceptance criteria, we recommend that (b) (4) (b) (4) (b) (4) reported in this NDA, we recommend that you submit this information to the Investigational New Drug Application (IND) to facilitate further discussion, before you resubmit this NDA.

(b) (4)

9. If quantification of total insulin aspart concentrations were to be planned, then this needs to be done for the key clinical pharmacology studies data intended to inform sections of labeling. For this approach, assurance of stability data of the retained test samples needs to be provided in the NDA. Utilizing total insulin aspart concentrations from only 3 studies (NN1218-3978, NN1218-3891, NN1218-3852), as you proposed in your email correspondence dated September 12, 2016, is not an acceptable approach. An extensive clinical program was carried out for this

NDA to establish different aspects of the PK/PD profile of FIASP including pharmacokinetic/pharmacodynamic (PK/PD) difference from NovoLog, dose-response relationship, injection site variation, (b) (4)

Therefore, proposing to quantify total insulin aspart concentrations from 3 studies has a number of limitations (listed below) which limits a comprehensive understanding of the PK/PD of FIASP and restricts the information that can be included in relevant sections of the proposed label. The limitations of quantifying total insulin aspart concentration from 3 studies are:

a. The data from select studies where total insulin is characterized for PK as a secondary measurement limits the comprehensive review of the clinical pharmacology data.

b. No data pertaining to the total insulin aspart concentrations from the meal challenge studies (mealtime, postmeal) will be assessed. We consider these studies as an integral part of comprehensive assessment of the PK/PD of FIASP.

c. (b) (4)

IMMUNOGENICITY

There are multiple deficiencies regarding the validation of the radioimmunoprecipitation assay (RIA) for the detection of insulin aspart-specific and cross-reactive anti-human insulin anti-drug antibodies as listed below.

10. Validation Report 215373 describes the QC3 suitability control as a guinea pig polyclonal anti-human insulin (GP□□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.

11. 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.

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 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.

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.

14. 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.

15. 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. For guidance refer to the draft "Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products," April 2016.

16. 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.

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.

18. 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 2.7.1 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 testing of clinical samples.

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.

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

/s/

LISA B YANOFF
09/27/2017

JEAN-MARC P GUETTIER
09/27/2017

I agree that the deficiencies identified in the first cycle of review have been adequately addressed in this resubmission. I concur with the recommendation to approve the application. My Benefit-Risk Summary and Assessment for the product is unchanged and can be found in the Division Director Summary Review in DARRTS under NDA208751 reference ID number 3996719. See this document for details.