CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209196Orig1s000

OTHER REVIEW(S)

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:	November 1, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209196
Product Name and Strength:	Admelog, insulin lispro, injection, 100 units/mL, 1000 units per 10 mL vial Admelog SoloStar, insulin lispro, injection, 100 units/mL, 300 units per 3 mL pen
Applicant/Sponsor Name:	Sanofi-Aventis
Submission Date:	October 25, 2017
OSE RCM #:	2016-2516-3
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 resubmitted carton and container labeling for Admelog (Appendix A) to determine if they are acceptable from a medication error perspective. DMEP requested this review as part of their evaluation of the 505(b)(2) NDA Class I resubmission for Admelog. We found the carton labeling and container labels acceptable in our previous label and labeling review.[a]

1.1 REGULATION HISTORY

Sanofi-Aventis submitted NDA 209196 (Admelog, insulin lispro) on November 1, 2016. The NDA received a Tentative Approval letter on September 1, 2017 due to patent protection of the reference listed drug (Humalog, NDA 020563) upon which this application relies. Sanofi-Aventis resubmitted the NDA as a Class 1 resubmission on October 11, 2017.

[a]Conrad A. Review of Revised Label and Labeling for Admelog (NDA 209196). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Aug 29. RCM No.: 2016-2516-2.

2 CONCLUSION

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

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/s/

ARIANE O CONRAD
11/01/2017

HINA S MEHTA
11/01/2017

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 29, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209196
Product Name and Strength:	Admelog, insulin lispro, injection, 100 units/mL, 1000 units per 10 mL vial Admelog SoloStar, insulin lispro, injection, 100 units/mL, 300 units per 3 mL pen
Applicant/Sponsor Name:	Sanofi-Aventis
Submission Date:	August 24, 2017 and August 28, 2017
OSE RCM #:	2016-2516-2
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 Admelog (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 Admelog are acceptable from a medication error perspective. We have no further recommendations at this time.

[a]Conrad A. Review of Revised Label and Labeling for Admelog (NDA 209196). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Aug 21. RCM No.: 2016-2516-1.

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/s/

ARIANE O CONRAD
08/29/2017

HINA S MEHTA
08/30/2017

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
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Maternal Health Labeling Review

Date: August 24, 2017 **Date consulted:** April 5, 2017

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

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

To: Division of Metabolic and Endocrine Products (DMEP)

Drug: insulin lispro

NDA: 209196

Applicant: Sanofi

Subject: Pregnancy and Lactation Labeling

Indication: To improve glycemic control in adults and children with diabetes mellitus.

Materials Reviewed:

- Applicant's submission, dated November 1, 2016
  - Proposed annotated label
  - Clinical Overview Addendum, module 2.5
  - Summary of Clinical Safety, module 2.7.4
  - Response to filing issues identified, submitted February 3, 2017
  - 120-day safety update, submitted March 1, 2017
- Prior Division of Pediatric and Maternal Health Labeling Reviews for insulin analogs,
  - Insulin glargine, NDA 208722, by C. Ceresa, February 22, 2017 (DARRTS Reference ID: 4059586)

- Insulin degludec and insulin aspart, NDA 203313, and insulin degludec, NDA 203314, by J. Liedtka, November 10, 2016 (DARRTS Reference ID: 4012685)
- Insulin aspart, NDA 208751, by J. Liedtka, May 6, 2016 (DARRTS Reference ID: 3928027)

Consult Question: DGIEP requests input regarding proposed PLLR labeling

INTRODUCTION

On November 1, 2016, the applicant (Sanofi) submitted a 505(b)(2) NDA for insulin lispro injection, relying on the safety and efficacy findings for Humalog (insulin lispro)(NDA 020563), the reference listed product (RLD). The Division of Metabolic and Endocrine Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input regarding compliance of the proposed labeling with the Pregnancy and Lactation Labeling Rule (PLLR) [1].

BACKGROUND

Regulatory History

- This 505(b)(2) NDA is a human insulin analog seeking the same indication as the RLD, Humalog, and has the same routes of administration (subcutaneous and intravenous) and dosing regimen. This 505(b)(2) product is the first follow-on product to the RLD in the US, and considered a biosimilar in the EU. The 505(b)(2) product is being developed for global marketing; however, at the time of the 120-day safety update, it has not been marketed in any country.
- Humalog was approved in the U.S. in 1996 and is indicated "to improve glycemic control in adults and children with diabetes mellitus."

Current Humalog Labeling

The current labeling for Humalog was last approved June 6, 2017, and is in the Physician Labeling Rule format, but does not yet comply with PLLR format. The Pregnancy subsection carries a Pregnancy Category B classification. The Nursing Mothers subsection recommends that "caution should be exercised when HUMALOG is administered to a nursing woman". Neither subsection communicated a specific safety concern. Humalog does not affect hormonal oral contraceptive levels. There are no specific recommendations directed to females and males of reproductive potential. Excerpts of the labeling are provided in the Appendix.

Diabetes and Pregnancy

- 90% of all pregnant diabetic women have gestational diabetes mellitus whereas 10%.have type 1 (insulin-dependent diabetes) and type 2 (non-insulin dependent diabetes).[2]

[1] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[2] Reece, EA, Hobbins, JC: Clinical Obstetrics, Third Edition, Chapter 38: Diabetes Mellitus in Pregnancy, pp: 292-305, Jan 14, 2008

- Uncontrolled pre-gestational diabetes during pregnancy is associated with adverse maternal and fetal outcomes pregnancy such as diabetic ketoacidosis, preeclampsia, spontaneous abortions (SAB), preterm delivery, polyhydramnios, stillbirth and cesarean section due to fetal macrosomia.
- Poorly controlled pre-gestational diabetes 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.

For more information on the background risk of adverse outcomes for the pregnant women with diabetes and her developing fetus, the reader is referred to previous DPMH Maternal Health Labeling Reviews on insulin analogs.[1,2,3]

REVIEW

Pregnancy

Nonclinical

The applicant relied on the nonclinical data from the RLD. Insulin lispro is not genotoxic or clastogenic. No adverse developmental effects were observed in nonclinical embryofetal development studies in rats or rabbits, except for fetal growth retardation when pregnant rats were administered a subcutaneous dose approximately 3 times the human dose based on body surface area comparisons. No effects on weight were observed with rabbits.

Applicant's Pharmacovigilance Database Review

The applicant searched their pharmacovigilance database for cases of patients who received either the 505(b)2 insulin lispro product or the RLD during pregnancy or lactation, or pregnancy of partner. A total of 6 cases were retrieved from the 12 month safety study EFC12619. Only one case of pregnancy relates to the 505(b)2 product. The information is not adequate to contribute to any conclusions about safe use of insulin lispro during pregnancy. The cases are summarized below in Table 1.

[1] Insulin glargine, NDA 208722, by C. Ceresa, February 22, 2017 (DARRTS Reference ID: 4059586)
[2] Insulin degludec and insulin aspart, NDA 203313, and insulin degludec, NDA 203314, by J. Liedtka, November 10, 2016 (DARRTS Reference ID: 4012685)
[3] Insulin aspart, NDA 208751, by J. Liedtka, May 6, 2016 (DARRTS Reference ID: 3928027)

Table 1: Cases of Pregnancy Reported in the Applicant's Pharmacovigilance Database*

Study/ Patient ID	Age/Relationship to patient	Country	Drug	Exposure	Outcome
Study EFC12619 / 392-006-009	(b) (6)	(b) (6)	SAR342434	(b) (6)	(b) (6)
Study EFC12619 /643-003-00		(b) (6)	RLD		
Study EFC12619 /616-004-00			RLD		
Study EFC12619 /643-002-00			RLD	n/a	
Study EFC12619 / 276-007-001			RLD	n/a	
Study EFC12619 / 840-029-004			RLD	n/a	

*From Applicant's Response to filing issues identified, submitted February 3, 2017
† 505(b)2 product

Applicant's Literature Review

The applicant reviewed the available published literature for insulin lispro exposure during pregnancy using Embase and Medline. The search parameters used were: ('insulin lispro'/exp/mj OR (insulin* NEAR/2 (lispro* OR lyspro*)):ab,ti) AND ('pregnancy'/exp/mj OR 'pregnant woman'/exp/mj OR 'primigravida'/exp/mj OR 'lactation'/exp/mj OR 'breast feeding'/exp/mj OR 'labor'/exp/mj OR pregnan*:ab,ti OR gestation*:ab,ti OR gravid*:ab,ti OR childbear*:ab,ti OR (child* NEAR/1 bear*):ab,ti OR primigravid*:ab,ti OR lactat*:ab,ti OR ((breast* OR lactic* OR

mammar* OR milk*) NEAR/2 (secret* OR excret* OR releas* OR feed*)):ab,ti OR breastfeed*:ab,ti) AND ([humans]/lim OR human*:ab,ti OR 'patient'/exp OR patient*:ab,ti). The applicant found 45 publications with relevant information; of which 38 describe insulin lispro as a treatment option with gestational diabetes. The applicant provided summaries of five publications that assess for adverse outcomes during pregnancy (see Table 1), four that state insulin lispro does not cross the placenta, and two that describe insulin lispro does not adversely impact progression of diabetic retinopathy during pregnancy.

The five publications that assess for adverse outcomes during pregnancy are comprised of two retrospective studies, two meta-analyses, and a letter in response to one meta-analysis. The publications (including the large, multinational, multicenter study by Wyatt JW *et al.* 2005) did not demonstrate an increased association of insulin lispro with congenital anomalies when compared to the background rate in patients with diabetes, or any association of insulin lispro with neonatal hypoglycemia, congenital malformation, NICU admission, cesarean section rate, respiratory distress syndrome, macrosomia, preterm delivery, miscarriage or stillbirth. In the meta-analyses, three small studies raised concern about an increased incidence of large for gestational age (LGA; birthweight greater than 90th percentile for gestational age) infants among patients with pre-gestational diabetes; however, there are limitations of the meta-analysis as adjustment for risk factors for LGA (e.g., maternal weight) was not conducted.[1, 2] A summary of the two retrospective studies and the two meta-analyses are in Table 2 below.

The applicant has not conducted and is not aware of an insulin lispro pregnancy registry.

DPMH Literature Review

DPMH reviewed PubMed for published literature on use of insulin lispro in both pregnant women with pre-gestational and gestational diabetes. No additional safety issues were identified. Briggs and Freeman[3] also reviewed the published in vitro studies regarding whether insulin lispro crosses of the human placenta. The studies demonstrate that insulin lispro could cross the placenta at very high concentrations; however, it was not clear that insulin lispro crosses at clinically relevant doses. Briggs and Freeman describe published case reports where insulin lispro was used during the first trimester. Outcomes were as follows:

- Pregnant women with type 1 diabetes, lispro started before conception, termination at 20 weeks gestation due to intrauterine growth restriction and severe fetal embryopathy (multiple cardiac abnormalities, polysplenia, and abdominal situs inversus) with normal karyotype; unknown cause of defects, authors believe suboptimal glycemic control contributed to outcome

[1] E. Edson-Heredia, R.D. Rohwer, M. Wong, P. Wang, A. Vambergue, and V. Koivisto. Studies Assessing Risk of Treatments for Diabetes Mellitus and Adverse Pregnancy Outcomes Should Control for Known Risk Factors Diabetes Technology & Therapeutics. December 2012, 14(12): 1183-1184.
[2] González C, and Corcoy R. Response to "studies assessing risk of treatments for diabetes mellitus and adverse pregnancy outcomes should control for known risk factors". Diabetes Technology and Therapeutics. 2012; 14(12):1185-6.
[3] Briggs GG, Freeman RK. (2015). Drugs in Pregnancy and Lactation. Tenth edition. Philadelphia. Wolters Kluwer Health.

- Pregnant women with type 1 diabetes, lispro started third week of gestation, delivered 2.82 kg male at 37 weeks by Caesarean section; sudden infant death at 3 weeks of age, autopsy revealed congenital diaphragmatic hernia – stomach and intestine into the chest cavity – and bilateral undescended testes; unknown cause of defects, authors believe suboptimal glycemic control contributed to outcome
- Cases noted from the manufacturer: 19 women in insulin lispro clinical trials became pregnant and gave birth to live infants; one with right dysplastic kidney

Briggs and Freeman further reviewed eight published studies that described outcomes of 836 pregnancies (n=735 pre-gestational, n=101 gestational) with use of insulin lispro. No adverse developmental outcomes were reported in 303 pregnancies from seven of the studies. The remaining 533 pregnancies were reported from the multinational, multicenter study (Wyatt JW *et al.* 2005, described in Table 2 below).

Reproductive databases (TERIS, ReproTox) have no reviews for use of insulin lispro during pregnancy; however, Shepard's database describes the outcomes of the Wyatt JW *et al.* 2005 study.

Summary

With over 20 years of the RLD insulin lispro use in the US, the published data do not support a clear association with insulin lispro and major birth defects, miscarriage, or adverse maternal or fetal outcomes. In addition, any assessment of potential drug effects encounters considerable confounding due to the higher incidence of adverse developmental outcomes from the underlying disease (especially pre-gestational diabetes). DPMH recommends a revised Section 8.1 Pregnancy to include a brief summary of the available published data and the below class labeling language:

> Risk Summary
>
> All pregnancies have a background risk of birth defect, loss or other adverse outcomes. 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 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
>
> Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Table 2: Published Observational Studies for Insulin Lispro Exposure During Pregnancy, cited by Applicant

Author /Date	Study Design	Drug/ Comparator	Study population; n per group	Country/Notable demographics	Pregnancy/Infant outcomes	Comments/Limitations
Wyatt JW et al. 2005[1]	Retrospective medical record review	Humalog, no comparator	496 women with pre-gestational diabetes on drug at least 1 month prior to conception and during the first trimester; 96% continued on drug in second and third trimesters; 533 pregnancies with 542 offspring	52 centers located in Brazil, Canada, Finland, Israel, Italy, Poland, South Africa and the United States: 85.6% were Caucasian, 0.4% African descent, and 97.2% had Type 1 diabetes mellitus	-500 live births, 31 spontaneous abortions, 7 elective abortions, 4 stillbirths; -5.4% (27 of 496, adjusted for mothers and pregnancy) [95% CI (3.45%, 7.44%)] with major congenital anomalies: cardiovascular (ventricular septal defect *n* = 6, patent ductus arteriosus *n* = 2, congenital heart defect NOS *n* = 2, double outlet right ventricle *n* = 2, secundum atrial septal defect *n* = 1), skeletal (*n* = 5; pre-axial polydactyly, limb reduction defect, hypoplastic arm, clubfoot and scoliosis), genitourinary (*n* = 4; hypospadias with hydronephrosis, micropenis, renal cysts and hydroceles), central nervous system (*n*= 2; hydrocephalus and anencephaly);) and craniofacial (*n*= 2; cleft lip and cleft palate) -0.4% (2 of 496) with minor congenital anomalies	Eli Lilly sponsored study; no internal comparator group; Author cited published rates of major congenital anomalies 2.1-10.9% in infants born to mothers with diabetes
Aydin Y et al. 2008[2]	Retrospective medical record review	Insulin lispro/regular human insulin	86 women with pre-gestational or gestational diabetes: 27 insulin lispro, 59 regular insulin	Turkey	No statistical difference between groups for gestational age, mode of delivery, type of diabetes, number of liveborn, stillbirth and miscarriages; 9 congenital anomalies reported in regular insulin group, none in insulin lispro; 1 stillbirth in each treatment group; no statistical difference in incidence of congenital anomalies between treatment groups	

[1] Wyatt JW, Frias JL, Hoymet HE, Jovanovic L, Kaaja R, Brown F, Garg S, Lee-Parritz A, Seely EW, Kerr L, Mattoo V, Tan M, and the IONS Study Group. Congenital anomaly rate in offspring of mothers with diabetes treated with insulin lispro during pregnancy. Diabet Med 2005;22:803–7.

[2] Aydin Y, Berker D, Direktör N, Ustün I, et al. Is insulin lispro safe in pregnant women: Does it cause any adverse outcomes on infants or mothers? Diabetes Research and Clinical Practice. 2008; 80(3):444-8.

Author /Date	Study Design	Drug/ Comparator	Study population; n per group	Country/Notable demographics	Pregnancy/Infant outcomes	Comments/Limitations
Lv S et al. 2015[1]	Meta-analysis	Insulin analogs: aspart, lispro, glargine, determir	24 studies met the eligibility criteria; for lispro, 1 review article and 8 observational studies with 1561 women with pre-gestational or gestational diabetes; 452 insulin lispro, 1089 regular insulin	Turkey, Italy, US (Ohio), Spain, Netherlands, Poland, United Kingdom	Lispro use associated with slightly higher birth weight and an increased incidence of large for gestational age births (RR = 1.42) compared with regular insulin; lispro was not related to higher rates of neonatal hypoglycemia, congenital malformation, NICU admission, cesarean section rate, respiratory distress syndrome, macrosomia, preterm delivery, or stillbirth	Includes Aydin Y et al. 2008; Authors state LGA findings cannot be mediated by metabolic control and may be related to lispro itself; lispro homology with insulin-like growth factor-1 raises the possibility of increased growth in fetuses; Insufficient data prohibited statistical adjustments based on SES factors or maternal weight gain; more studies to confirm results
Gonzalez-Blanco C et al. 2010[2]	Systematic review and meta-analysis	Insulin lispro/regular human insulin	4 observational studies with women with type 1 diabetes mellitus treated with lispro versus regular insulin prior to conception	Netherlands, Finland, Poland, Italy	The rate of large-for-gestational age newborns was higher in the lispro group (relative risk 1.38; 95% CI 1.14–1.68). No differences between groups gestational age at birth, birth weight, and rate of diabetic ketoacidosis, pregnancy-induced hypertension, pre-eclampsia, spontaneous miscarriages, interruptions, total abortions, cesarean section, preterm birth, macrosomia, small-for gestational-age newborns, stillbirth, neonatal and perinatal mortality, neonatal hypoglycemia, and major malformations.	3 of the 4 studies included in Lv S et al. 2015; the same 3 studies were used in analysis of LGA; authors did not perform either a meta-analysis of individual data or adjustment for known risk factors of LGA

[1] Lv S, Wang J, and Xu Y. Safety of insulin analogs during pregnancy: A meta-analysis. Archives of Gynecology and Obstetrics. 2015; 292(4):749-56.
[2] González-Blanco C, Chico A, Gich I, and Corcoy R. Glycaemic control and pregnancy outcomes in women with type 1 diabetes: A systematic review and meta-analysis comparison between lispro and regular insulin. Diabetologia. 2010; 53(1):S433-4.

Lactation
Both the applicant and DPMH reviewed the published literature and found no human data available to inform a safety concern with use of insulin lispro during lactation.

Reproductive databases (TERIS, ReproTox), Hale's book[1], and LactMed[2] provided no information on insulin lispro use during lactation. However, the LactMed database described that endogenous insulin is normally present in breastmilk and is likely actively transported into breastmilk. Insulin is thought to contribute to the breastfed infant's intestinal maturation and to decrease the risk of development of type 1 diabetes. It is expected that exogenous insulin (such as insulin lispro and other insulin analogs) would also be present in breastmilk.

Summary
Despite over 20 years of the RLD insulin lispro use in the US, there are no data on the use of insulin lispro during lactation to warrant description of any safety concern in the labeling. In addition, insulin analogs are expected to be present in the breastmilk, similar to endogenous insulin. Per the PLLR, DPMH recommends that the benefit risk statement regarding breastfeeding appear in labeling subsection 8.2 Lactation.

Females and Males of Reproductive Potential
DPMH review of the published literature found no animal or human data regarding effects of insulin lispro on fertility. Reproductive databases provided no additional information.

Summary
Because there are no data regarding effects of insulin lispro on human fertility, and no concerns of fetal harm to warrant labeling recommendations for contraception use or pregnancy testing, DPMH recommends that subsection 8.3 Females and Males of Reproductive Potential be omitted from the labeling.

CONCLUSIONS
The Pregnancy and Lactation, subsections of this 505(b)(2) insulin lispro labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of labeling was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" sections.
- **Lactation, Section 8.2**
  - The "Lactation" section of labeling was formatted in the PLLR format to include: the "Risk Summary."
- **Patient Counseling Information, Section 17**

[1] Hale T (2014). Medications and Mothers' Milk, 16th edition. Plano, TX. Hale Publishing, L.P.
[2] The LactMed database provides information for FDA-approved drugs when available on maternal levels in breastmilk, 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.

LABELING RECOMMENDATIONS
DPMH made revisions to subsections 8.1 and 8.2 of the labeling for compliance with the PLLR. DPMH labeling recommendations are below with changes tracked, and reflect the July 12, 2017 labeling meeting discussions with the DMEP review team. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

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FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary

The limited available data with TRADENAME in pregnant women are insufficient to determine a drug associated risk of adverse developmental outcomes. Published studies with another insulin lispro product used during pregnancy have not reported an association with insulin lispro and major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*. In animal reproduction studies, pregnant rats and rabbits were administered insulin lispro subcutaneously during the period of organogenesis. Fetal growth retardation was observed in offspring of rats exposed to insulin lispro at a dose approximately 3 times the human subcutaneous dose of 1.0 unit/kg/day. No adverse effects on embryo/fetal development were observed in offspring of rabbits exposed to insulin lispro at doses approximately up to 0.24 times the human subcutaneous dose of 1.0 unit/kg/day *(see Data)*.

(b) (4) The estimated background risk of major birth defects is 6%-10% in women with pre-gestational diabetes with an 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 in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Human Data

Published data from retrospective studies and meta-analyses do not report an association with another insulin lispro and major birth defects, miscarriage, or adverse maternal or fetal outcomes when insulin lispro is used during pregnancy. However, these studies cannot definitely establish or exclude the absence of any risk because of methodological limitations including small sample size, selection bias, confounding by unmeasured factors, and some lacking comparator groups.

Animal Data

In a combined fertility and embryo-fetal development study, female rats were given another subcutaneous insulin lispro injections of 5 and 20 units/kg/day (0.8 and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) from 2 weeks prior to cohabitation through Gestation Day 19. There were no adverse effects on female fertility, implantation, or fetal viability and morphology. However, fetal growth retardation was produced at the 20 units/kg/day-dose as indicated by decreased fetal weight and an increased incidence of fetal runts/litter.

In an embryo-fetal development study in pregnant rabbits, insulin lispro doses of 0.1, 0.25, and 0.75 unit/kg/day (0.03, 0.08, and 0.24 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) were injected subcutaneously on Gestation days 7 through 19. There were no adverse effects on fetal viability, weight, and morphology at any dose.

8.2 Lactation

Risk Summary

There is no information regarding the presence of insulin lispro in human milk, the effects on the breastfed infant, or the effects on milk production. Endogenous insulin is present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed child from TRADENAME or from the underlying maternal condition.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise females of reproductive potential to inform their health care professional if they are pregnant or are contemplating pregnancy.

APPENDIX:
Labeling of the Humalog (RLD; last approved June 6, 2017)

8

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking HUMALOG.

Although there are limited clinical studies of the use of HUMALOG in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome.

In a combined fertility and embryo-fetal development study, female rats were given subcutaneous insulin lispro injections of 5 and 20 units/kg/day (0.8 and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) from 2 weeks prior to cohabitation through Gestation Day 19. There were no adverse effects on female fertility, implantation, or fetal viability and morphology. However, fetal growth retardation was produced at the 20 units/kg/day-dose as indicated by decreased fetal weight and an increased incidence of fetal runts/litter.

In an embryo-fetal development study in pregnant rabbits, insulin lispro doses of 0.1, 0.25, and 0.75 unit/kg/day (0.03, 0.08, and 0.24 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) were injected subcutaneously on Gestation days 7 through 19. There were no adverse effects on fetal viability, weight, and morphology at any dose.

8.3 Nursing Mothers

It is unknown whether insulin lispro is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HUMALOG is administered to a nursing woman. Use of HUMALOG is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

17.6 Women of Reproductive Potential

Advise females of reproductive potential with diabetes to inform their doctor if they are pregnant or are contemplating pregnancy *[see Use in Specific Populations (8.1)]*

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/s/

TAMARA N JOHNSON
08/24/2017

LYNNE P YAO
08/25/2017

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 21, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209196
Product Name and Strength:	Admelog, insulin lispro, injection, 100 units/mL, 1000 units per 10 mL vial Admelog SoloStar, insulin lispro, injection, 100 units/mL, 300 units per 3 mL pen
Applicant/Sponsor Name:	Sanofi-Aventis
Submission Date:	August 18, 2017
OSE RCM #:	2016-2516-1
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 Admelog (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 Admelog are not acceptable from a medication error perspective. This review identified a deficiency with the NDC numbers on the container label and carton label for the pen device and we provide one recommendation in Section 3.

[a]Conrad A. Label and Labeling and Human Factors Results Review for Admelog (NDA 209196). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Apr 19. RCM No.: 2016-2516 and 2017-210.

3 RECOMMENDATIONS FOR SANOFI-AVENTIS

(b) (4)

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/s/

ARIANE O CONRAD
08/21/2017

HINA S MEHTA
08/21/2017

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

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

Memorandum

Date: **August 14, 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)

Subject: OPDP Labeling Consult Request

NDA 209196 ADMELOG (insulin lispro injection), for subcutaneous or intravenous use

On November 3, 2016 OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI), Patient Information (PPI), Instructions for Use (IFU), and Carton and Container labeling for ADMELOG. OPDP's comments on the proposed draft PI and Carton and Container labeling are based on the versions sent via email by Callie Cappel-Lynch on August 10, 2017.

OPDP's comments on the proposed draft PI are provided directly on the marked version below. We have no comments on the Carton and Container labeling at this time.

Additionally, OPDP will work collaboratively with DMPP to provide comments on th PPI and IFU under separate cover.

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
08/14/2017

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:	August 14, 2017
To:	Jean-Marc Guettier, M.D. 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)**
From:	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	ADMELOG (insulin lispro injection)
Dosage Form and Route:	for subcutaneous or intravenous use
Application Type/Number:	NDA 209176
Applicant:	sanofi-aventis U.S. LLC, A SANOFI COMPANY

1 INTRODUCTION

On November 1, 2016, sanofi-aventis U.S. LLC, A SANOFI COMPANY submitted for the Agency's review a new drug application (NDA) for ADMELOG (insulin lispro injection) for subcutaneous or intravenous use. ADMELOG (insulin lispro injection) for subcutaneous or intravenous use is a rapid-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

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 November 3, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and IFUs for ADMELOG (insulin lispro injection) for subcutaneous or intravenous use.

2 MATERIAL REVIEWED

- Draft ADMELOG (insulin lispro injection) for subcutaneous or intravenous use PPI and IFUs received on November 1, 2016, and received by DMPP and OPDP on August 10, 2017.
- Draft ADMELOG (insulin lispro injection) for subcutaneous or intravenous use Prescribing Information (PI) received on November 1, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 10, 2017.
- Approved HUMALOG (insulin lispro injection), for subcutaneous or intravenous use comparator labeling dated June 6, 2017.
- Approved LANTUS (insulin glargine injection) solution for subcutaneous injection comparator labeling dated July 17, 2015.
- Approved TOUJEO (insulin glargine injection) U-300, for subcutaneous comparator labeling dated February 25, 2015.

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.

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.

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)
- 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)
- ensured that the PPI and IFUs are consistent with the approved comparator labelings where applicable.

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
08/14/2017

MARCIA B WILLIAMS
08/14/2017

ANKUR S KALOLA
08/14/2017

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

MEMORANDUM OF REVIEW – IMMUNOGENICITY ASSAY CONSULT

NDA number:	209196
Subject:	Review of antibody detection assay (consult) for DMEP
Start Date:	April 11th, 2017
Finish Date:	July 22nd, 2017
Revision Date:	July 26th, 2017
From:	Brian Roelofs, Ph.D., Product Quality Reviewer, CDER/OPQ/OBP/DBRR II
Through:	Juhong Liu, Ph.D., Acting Review Chief, CDER/OPQ/OBP/DBRR II
Product:	SAR342434 (Insulin Lispro)
Indication:	Diabetes mellitus
Route of Administration:	Injection
Sponsor:	Sanofi-Aventis US, LLC
Clinical Division:	CDER/ODEII/DMEP
RPM:	Callie Campbell-Lynch (OND/ODEII/DMEP)

I. SUMMARY AND RECOMMENDATION:

a. Summary

The sponsor submitted a validation report of the immunogenicity assays used to evaluate the presence of anti-insulin antibodies (AIA) in patients treated with SAR342434 in two clinical trials included in this NDA. The assays are based on radio-immunoprecipitation (RIPA) principles for the detection, confirmation, and titer determination of anti-SAR342434 antibodies. The sponsor used a 5% false positive rate in testing 100 normal human plasma samples to determine the cut point for positive samples in initial screening. A 1% false positive rate was applied to determine the cut point for the confirmatory assay, and the sponsor verified the precision, specificity, sensitivity, effect of sample matrix, drug tolerance, and stability of samples prior to assay performance under a range of conditions. The data indicate the assays conform to the requirement specified in FDA guidance on immunogenicity assays and they are appropriate to evaluate AIA in clinical samples.

b. Recommendations:

The immunogenicity assays are appropriate to detect anti-SAR342434 antibodies.

II. REVIEW

*Figures and tables excerpted from submission unless otherwise indicated.

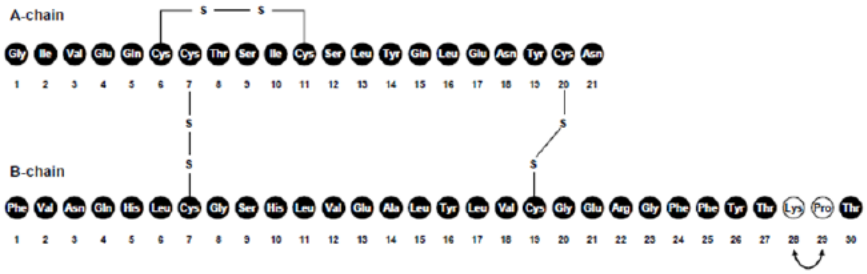
Table of Contents

1. Overview
2. Radioimmunoprecipitation (RIPA) method for anti-drug antibodies (ADA) detection
3. Normalization factor determination for floating cut point calculation
4. Low positive control calculation and system suitability
5. Validation - Precision

A. Inter-assay and Intra-assay
B. Confirmatory assay
6. Validation – Specificity of confirmatory assay
7. Validation – Sensitivity
8. Validation – Method (matrix) selectivity
9. Validation – Drug tolerance
10. Validation – Stability
A. Bench-Top
B. Refrigerator
C. Freeze/Thaw
D. Long Term Storage

1. Overview

The sponsor submitted SAR342434 as a Section 505(b)(2) New Drug Application (NDA) as a follow-on product to Humalog (NDA, 020563). SAR342434 is a two-chain peptide consisting of 51 amino acids. The A-chain is composed of 21 amino acids, the B-chain of 30 amino acids. It is identical to human insulin, except at positions 28 and 29 of the B-chain, where an L-proline and L-lysine have been swapped. The following figure depicts the location of the amino acid changes and the location of three disulfide bonds (the same as human insulin):



SAR342434 is produced via recombinant DNA technology with *E. coli* (b) (4) strain as the host for the expression plasmid. (b) (4)

(b) (4)

SAR342434 drug product is intended for distribution as solution for injection at a concentration of 100 U/mL in 3 mL cartridges assembled into disposable injectors and as solution for injection at a concentration of 100 U/mL in 10 mL vials. Excipients include metacresol (b) (4) glycerol (b) (4) dibasic sodium phosphate, zinc oxide, sodium hydroxide, hydrochloric acid, water for injection, (b) (4) none of which are anticipated to induce an immunogenic response.

2. RIPA method for ADA detection

The sponsor enlisted (b) (4) to design and validate a RIPA-based method for the detection of ADA. The method serves as the foundation for the screening, confirmation, and

titration assays. All three assays operate on a similar experimental paradigm, summarized as follows:

(b) (4)

[redacted]

Reviewer Comment:

While RIPA-based approaches are not as common as others for immunogenicity assays, RIPA is a sensitive and powerful in vitro technique

(b) (4)

(b) (4)

[redacted]

(b) (4)

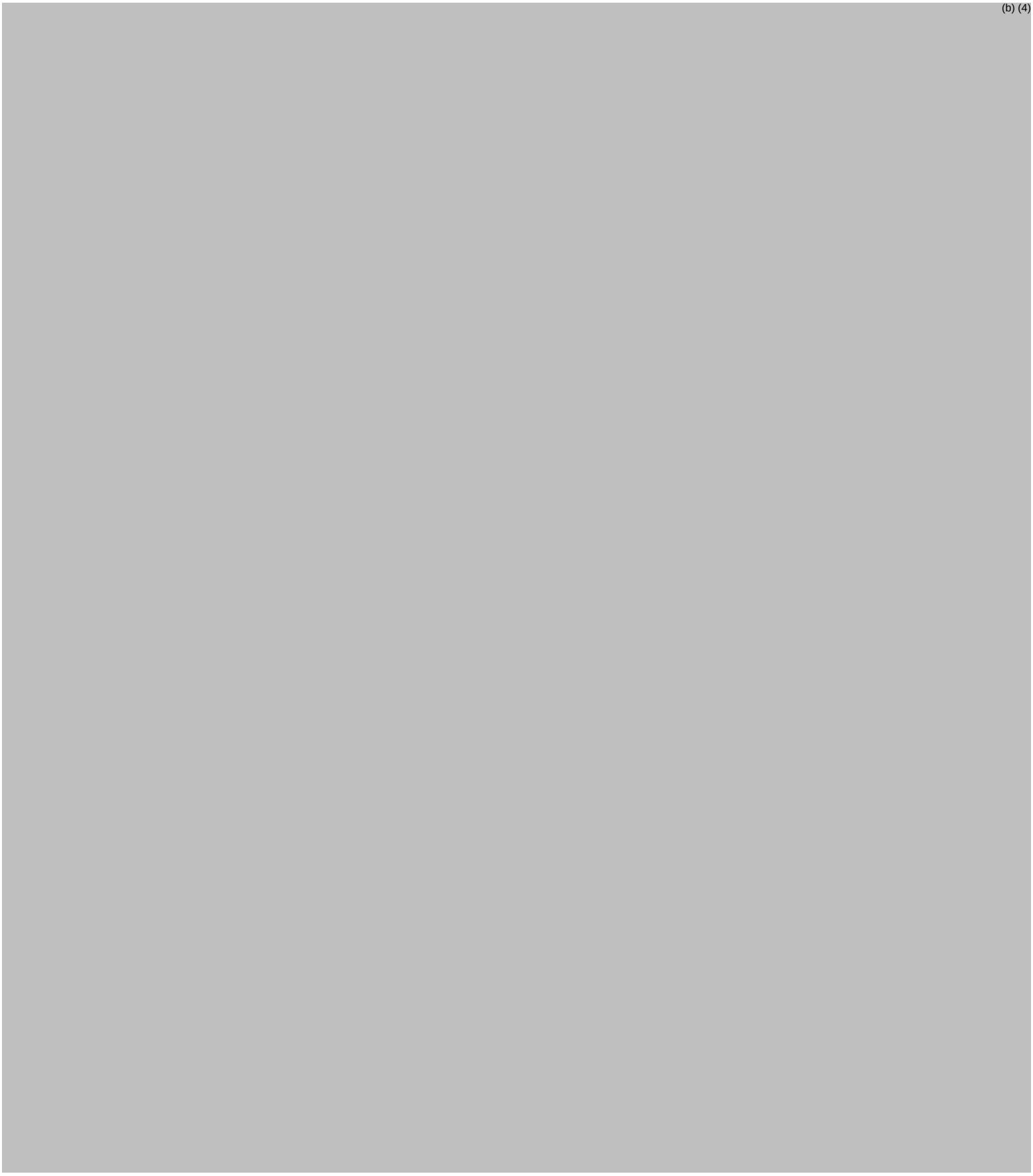
3. Normalization factor determination of cut points

The sponsor chose to use a floating cut point approach with a normalization factor (NF) for each immunogenicity assay. (b) (4)

(b) (4)

(b) (4)

(b) (4)



(b) (4)

(b) (4)

Reviewer Comment:

(b) (4)

The suitability test demonstrated a consistent performance of the assay across a suitable range of positive control antibody concentrations.

5. Validation - Precision

A. Inter-assay and Intra-assay

The sponsor assessed inter- and intra-assay specificity by spiking human plasma with high PC, mid PC, low PC-1, low PC-2, and NC in 6 runs (inter) of triplicate (intra) samples by two different analysts. The following table summarizes the mean, standard deviation, and coefficient of variation (CV) values obtained for inter- and intra-assay precision:

	Inter-assay			Intra-assay				
	Mean (%)	Std. Dev.	CV (%)	Range of Means (%)	Range of Std. Dev.	Range of CV (%)	ANOVA Std. Dev.	ANOVA CV (%)
High	76.8	4.8	6.2	70.4-80.7	0.7-5.6	0.9-7.9	3.4	4.4
Mid	27.9	3.6	12.7	23.4-30.7	0.1-4.8*	0.3-20.3**	2.0	7.2
Low-1	9.7	0.6	6.4	8.8-10.2	0.1-0.6	0.6-7.1	0.4	4.6
Low-2	8.9	0.6	6.8	8.1-9.4	0.1-0.7	1.1-7.4	0.4	4.4
Negative	4.9	0.4	8.3	4.6-5.5	0.2-0.5	3.6-10.0	0.3	6.4

* - The third replicate of mid PC test from assay Val-041 returned a result signifiantly lower than all other tests of that concentration, leading to a high standard deviation (4.8, range of all others was 0.1-0.9) and %CV (20.3, all others were 0.3-3.0).
†-Table prepared by reviewer

The standard by which inter- and intra-assay precision was assessed was the CV, with a target of <25%. All assays passed this acceptance criterion, and (b) (4) judged them to be acceptable.

Reviewer Comment:
While the standard used to assess acceptability of the precision (b) (4) was high, all of the concentrations analyzed were significantly lower than this target. Sufficient inter- and intra-assay precision were demonstrated over a suitable number of tests.

B. Confirmatory assay

(b) (4) performed confirmatory precision assays for each of the following drugs: SAR342434, Humalog EU, Humalog US, human insulin, insulin glargine, and insulin glargine M1. (b) (4) (b) (4)

(b) (4)

The target criterion for confirmatory precision was CV < (b) (4) The following table summarizes the CV obtained from each assay:

(b) (4)

Reviewer Comment:

(b) (4)

(b) (4)

(b) (4) *The precision of the confirmatory assay is acceptable.*

6. Validation – Specificity of confirmatory assay

(b) (4) assessed the specificity of the confirmatory assays by analyzing the reduction in the mean response %B/T in normal plasma samples with anti-insulin at the high PC (b) (4) and low PC-2 (b) (4) concentrations after addition of (b) (4) of SAR342434, Humalog EU, Humalog US, human insulin, insulin glargine, and insulin glargine M1. In all cases, the addition of (b) (4) of drug reduced the signal of high and low PC to below confirmatory assay cut point levels.

Reviewer Comment:

If the assay is specific, the addition of each insulin drug should compete the PC antibody away from I^{125}-SAR342434, preventing the precipitation of the tracer and reducing the counts. The specificity of the confirmatory assay is validated by this assay, and the use of PC antibody at both the high and low concentrations imparts confidence in the ability of the confirmatory assay to function in the presence of a range of endogenous patient ADAs.

Specificity was further confirmed in the drug tolerance tests, reviewed below.

7. Validation - Sensitivity

(b) (4) determined the titer and assay sensitivity by (b) (4)

(b) (4)

Reviewer Comment:

(b) (4)

(b) (4)

8. Validation – Method (matrix) selectivity

To assess method selectivity, the sponsor evaluated individual human and diabetic plasma samples with or without low (40 ng/mL) or high (1000 ng/mL) positive control antibody. The following tables show the %B/T obtained with normal and diabetic human plasma samples:

Normal Plasma Samples:

		Unspiked	High Spike	Low Spike
Conc.(ng/mL)		0.000	1000.000	40.000
Sample	Lot #	Mean Response (%B/T)		
1	BRH719870	**7.5**	75.9	10.3
2	BRH719871	6.5	79.8	10.7
3	BRH719872	6.4	79.6	11.1
4	BRH719873	6.8	73.0	9.9
5	BRH719874	7.4	75.5	10.2
6	BRH719920	6.7	76.2	9.5
7	BRH719921	6.5	72.8	9.0
8	BRH719922	6.5	79.4	9.9
9	BRH719923	7.0	78.3	9.9
10	BRH719924	7.0	82.5	12.4
Pool	2013-070-1A	6.3	80.3	11.1

Diabetic Plasma Samples:

		Unspiked	High Spike	Low Spike
Conc. (ng/mL)		0.000	1000.000	40.000
Sample	Lot #	Mean Response (%B/T)		
1	BRH711077	**8.6**	70.3	12.1
2	BRH711078	**14.2**	71.3	17.7
3	BRH711079	7.2	74.9	11.2
4	BRH711080	**7.9**	57.4	10.8
5	BRH711081	**32.6**	72.7	35.4
6	BRH711082	**9.3**	71.5	11.4
7	BRH711083	7.1	69.5	10.2
8	BRH692875	**15.0**	50.2	17.6
9	BRH692877	7.4	48.4	8.9
10	BRH692878	6.8	69.8	10.4

The cut point was 7.5 for this analysis. The bold font indicates samples that were above the plate-specific cut point. These samples did not meet acceptance criteria, and were not used in analysis. The sponsor provided documentation that 8 of the 10 samples were provided from patients in treatment for diabetes; therefore it is likely that they may have developed antibodies prior to this testing.

Reviewer Comment:

All spiked samples in both matrix types displayed an increase in mean %B/T, supporting matrix selectivity. The finding that 6/10 diabetic samples registered %B/T values above the cut point prior to PC antibody spike is consistent with data from clinical trials for Type I diabetes patients, in which (b) (4) *display ADA prior at baseline analysis. In support of the assay's effectiveness, mean %B/T increased even in these samples in the presence of antibody spike. The data and analysis provided indicate the assay is selective in the presence of normal and diabetic plasma matrices.*

9. Validation – Drug tolerance

The sponsor tested concentrations of SAR342434, Humalog EU, Humalog US, human insulin, insulin glargine, and insulin glargine M1 ranging from 0-200 ng/mL against 40 ng/mL (the low PC) of anti-human insulin antibody to assess drug tolerance. The following chart summarizes the results obtained across 6 different assay runs:

Range of Test Drug (ng/mL)	ng/mL PC	SAR342434	Humalog EU	Humalog US	Human Insulin	Insulin Glargine	Insulin Glargine M1
0-200	0	0	0	0	0	0	0
	40	5	10	5	3	15	0
0-8	0	0	0	0	-	-	0*
	40	0	4	0	-	-	6*
0-10	0	0	0	0	-	-	-
	40	6	8	5 (8,10)**	-	-	-
0-10	0	0	0	0	-	-	-
	40	2	6	5	-	-	-
0-2	0	0	0	0	-	-	-
	40	2	2	2	-	-	-
0-6	0	-	-	-	-	-	0
	40	-	-	-	-	-	6/6/4

* - This assay was performed with 0-6 ng/mL of Insulin Glargine M1, all tested concentrations were above cut point

** - In this assay, all concentrations were above the cut point except 6 ng/mL, so the drug tolerance was recorded as 5 ng/mL (first concentration below the lowest below cut point value) but 8 and 10 ng/mL were also noted because they was above the cut point too

†-Table prepared by reviewer

(b) (4) performed multiple runs with different concentration ranges to test drug tolerance. (b) (4)

(b) (4)

Reviewer Comment:

The provided data support low tolerance levels of (b) (4) ng/mL of insulin lispro products with this assay. This presents an (b) (4) ratio of insulin lispro:ADA before the drug tolerance is exceeded and the assay returns a %B/T value that is less than the cut point.

This result supports the sensitivity of the assay, as (b) (4) ng/mL is a low concentration of drug to be sufficient to compete out the I^{125}-SAR342434 tracer. As stated above, the sample collection time is at least (b) (4) hours after treatment, at a point when drug concentrations are expected to be approximately (b) (4)-fold lower than the range observed in the drug tolerance assay. Therefore, there are no concerns posed by the low drug tolerance level, and the strong sensitivity is preferred in the assay.

10. Stability

A. Bench-Top

To test bench-top stability, (b) (4)

(b) (4)

B. Refrigerator

(b) (4)

C. Freeze/Thaw

(b) (4)

(b) (4)

D. Long Term Storage

To test long term storage stability, (b) (4)

(b) (4)

Reviewer Comment:

The standard deviation and %CV were both acceptably low for bench-top and refrigerator stability tests, indicating sufficient stability for the samples and the subsequent performance of the immunogenicity assay. While no trends in sample performance were observed over (b) (4) *months storage of the samples at* (b) (4) *freeze-thaw cycles demonstrate a trend of negative effect on the ability of high PC to return a %B/T value similar to baseline numbers. This is not surprising, and the sponsor should incorporate this knowledge in the performance of the assay,* (b) (4)

II. FUTURE INSPECTION ITEMS:

None

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/s/

BRIAN A ROELOFS
07/26/2017

JUHONG LIU
07/26/2017

Clinical Inspection Summary

Date	7/25/2017
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Sonia Doi, Clinical Analyst William Chong, M.D., Team Leader Callie Cappel-Lynch, Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA/BLA #	NDA 209196
Applicant	Sanofi-Aventis U.S. LLC
Drug	insulin lispro [rDNA origin] (biosimilar)
NME (Yes/No)	No
Therapeutic Classification	Antidiabetic
Proposed Indication(s)	Treatment of diabetes mellitus
Consultation Request Date	12/22/2016
Summary Goal Date	7/28/2017
Action Goal Date	9/1/2017
PDUFA Date	9/1/2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

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

In general, based on the inspections of the six clinical sites, the inspectional findings support validity of data as reported by the Sponsor under this NDA.

The classification for Drs. Gromniak and Maheshwari 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. Bhargava, Jedynasty, Késmárki and Selam is No Action Indicated (NAI). Data from these sites 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.

II. BACKGROUND

Sanofi-aventis U.S. LLC has submitted a new drug application for SAR342434 (insulin lispro [rDNA origin], 100 Units/mL) solution for injection. SAR342434 is developed as a follow-on product to Humalog (100 units/mL, NDA 020563, (b) (4)), and is intended to have the same indications, dosage form, route of administrations and dosing regimen. While a follow-on product in the US, SAR342434 is considered as a biosimilar in the EU.

Inspections were requested for the following two studies:

- **EFC12619** Six-month, Randomized, Open-label, Parallel-group Comparison of SAR342434 to Humalog® in Adult Patients With Type 1 Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period

Study EFC12619 began (b) (6) and completed (b) (6). There were 83 active sites in eight countries that screened 668 subjects and randomized 507 subjects. Overall, 461 patients completed the 12-month treatment period. The primary efficacy endpoint was change in HbA1c from baseline to Week 26.

- **EFC13403** Six-month, Randomized, Open-label, Parallel-group Comparison of the Insulin Analog SAR342434 to Humalog® in Adult Patients With Type 2 Diabetes Mellitus also Using Insulin Glargine

Study EFC13403 began (b) (6) and completed (b) (6). There were 103 active sites in 12 countries that screened 707 subjects and randomized 505 subjects. Overall, 458 patients completed the 26-week treatment. The primary endpoint was change in HbA1c from baseline to Week 26.

III. RESULTS (by Site):

Name of CI/ Address Site#	**Protocol # and # of Subjects Randomized**	**Inspection Date**	**Classification**
Anuj Bhargava 411 Laurel Street Suite 3262 Des Moines, IA 50314* Site 840004 Site 840230 **New address effective 04/24/12 1031 Office Park Road, Suite 2* *W. Des Moines, IA 50265*	EFC12619 Site 840004 10 subjects EFC13403 Site 840230 15 subjects	04/03 – 04/07/2017	No Action Indicated (NAI)*
Elwira Gromniak ul. Teofila Starzynskiego 2 Indywidualna Specjalistyczna Praktyka Leharska 70-506 Szczecin Poland Site 616003	EFC12619 10 subjects	03/27 – 03/29/2017	Voluntary Action Indicated (VAI)*
Krustyna Jedynasty Centralny Szpital Klinicsny MSW Endokrynologii i Diabetologii ul.Woloska 137 Warszawa, Mazowieckie 02-507 Poland Site 616002	EFC12619 16 subjects	04/03 – 04/04/2017	No Action Indicated (NAI)*
Nora Késmárki Általános Belgyógyászat - Nefrológia Szekeres Jozsef u. 2-8. Nagykanizsa, NA 8800 Hungary Site 348210	EFC13403 10 subjects	04/24 – 04/28/2017	No Action Indicated (NAI)*
Hiralal Maheshwari 380 N. Terra Cotta Road Suite A Crystal Lake, IL 60012 Site 840012	EFC12619 14 subjects	05/01 – 05/16/2017	Voluntary Action Indicated (VAI)*
Jean Louis Selam 2492 Walnut Ave Suite 130 Tustin, CA 92780 Site 840259	EFC13403 11 subjects	03/27 – 03/28/2017	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. Anuj Bhargava/ Site 840004 EFC12619 and Site 840230 EFC13403

For Study EFC12619, there were 13 subjects screened and 10 subjects enrolled into the study; 10 subjects completed the study. All subject records were reviewed. The first subject for Study EFC12619 was screened on (b) (6) The (b) (6) (b) (6) was the IRB for this study.

For Study EFC13403, there were 17 subjects screened and 15 subjects enrolled into the study; 14 subjects completed the study. All subject records were reviewed. The first subject for Study EFC13403 was screened on (b) (6). The (b) (6) was the IRB for this study.

Dr. Bhargava is the founder and President of Iowa Diabetes and Endocrinology Research Center (IDERC). Dr. Bhargava routinely conducts clinical trials at this location. Subjects were either recruited from IRB approved ads or other referral sources (physicians, participants in former studies, word of mouth, etc.). All subjects signed and dated the IRB approved informed consent forms before participating in the studies.

(b) (6)

All study records were organized and legible. There was no under-reporting of adverse events. The primary endpoint was verifiable. There were no concerns regarding discrepancies comparing the source documents to the data line listings submitted by the sponsor.

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.

2. Elwira Gromniak/ Site 616003 EFC12619

There were 10 subjects screened and 10 subjects enrolled into the study; 10 subjects completed the study. There were 10 subject records reviewed.

Dr. Gromniak stated that most of her study subjects come from her private clinic patients, and a few are referred to her from other physicians. She spends approximately 75% of her time conducting clinical research in endocrinology and diabetes.

Both a central Ethics Committee (EC) and the [redacted] (b) (6) are required to review and approve study protocols, amendments, and consent forms. The EC used by Dr. Gromniak is [redacted] (b) (6)
Polish law requires all medical records be maintained for a minimum of 20 years.

A contract interpreter assisted with review of the content of the files. All study records were organized and legible. There was no under-reporting of adverse events. The primary endpoint was verifiable. All deviations and adverse events were appropriately reported to the study sponsor and the Ethics Committee (EC). There were no discrepancies between the data at the site and the data line listings submitted to the FDA by the study sponsor.

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

- Failure to adhere to the investigational plan. Specifically, Dr. Gromniak reported that Subjects [redacted] (b) (6) and [redacted] (b) (6) had prior exposure to Humalog, when in fact they did not. This resulted in incorrect stratification by the IVRS/IWRS randomization assignment.

The sponsor sent a memo to the study sites regarding previous Humalog use, dated 3/25/2016, reminding them that, "In case the question is answered incorrectly in IVRS, it leads to a stratification error which is a major Protocol deviation. ***In case Prior Humalog question in IVRS is incorrectly answered at randomization, the data cannot be changed within the IVRS (Perceptive database) and the discrepancy will lead to the patient being randomized to the incorrect strata. Perceptive will track the discrepancy with an abnormality code 'Stratification error'".

Dr. Gromniak recorded "Yes" for the two subjects for "Previous Humalog Experience", and then made corrections to the records when the error was discovered and also informed data management.

<u>OSI Reviewer Comment</u>: Protocol Number EFC12619 stated that randomized subjects were to be stratified by HbA1c obtained at screening (<8.0% versus > 8.0%), prior use of Humalog (Y/N) and geographical region (Non-Japan; Japan). Randomization ratio is 1:1. The treatment was still assigned randomly, even if the Investigator answered incorrectly. Subject [redacted] (b) (6) *was assigned to the SAR product and Subject* [redacted] (b) (6) *was assigned to Humalog. This is not a serious deviation that would impact the validity or reliability of the submitted data. Both of these protocol deviations were reported to FDA with the NDA submission.*

Dr. Gromniak sent a written response on April 17, 2017 and acknowledged the errors in the randomization. She stated that she will verify patient source data twice before entering it into the IVRS for all future studies.

3. Krustyna Jedynasty/ Site 616002 EFC12619

There were 19 subjects screened and 16 subjects enrolled into the study; 16 subjects completed the study. There were 16 subject records reviewed.

Professor Edward Franek, MD, a Sub-Investigator for the study under review, was present for the inspection. (b) (6) Dr. Franek and Dr. Jedynasty are the Principal Investigators for the studies conducted in the hospital's outpatient diabetes clinic. They take turns acting as the Principal Investigator or a Sub-Investigator for new studies. Potential subjects for the study were obtained from the hospital clinic patients. No advertising was done for subject recruitment.

Both a central Ethics Committee (EC) and the (b) (6) are required to review and approve study protocols, amendments, and consent forms. The EC used by Dr. Jedynasty is (b) (6)

A contract interpreter assisted with review of the content of the files. All study records were organized and legible. There was no under-reporting of adverse events. The primary endpoint was verifiable. All deviations and adverse events were appropriately reported to the study sponsor and the Ethics Committee (EC), as required. There were no discrepancies between the data at the site and the data line listings submitted to the FDA by the study sponsor.

One of the 16 subjects was incorrectly randomized. Subject # (b) (6) had prior exposure to Humalog from (b) (6) through (b) (6) The case report form asks "Has this subject used Humalog previously?" The question should have asked if the subject used Humalog within the last 6 months prior to screening, as stated in the protocol. The sponsor provided a memo, dated (b) (6) that notes, "The 'previous Humalog use' question during IVRS randomization refers to Humalog intake (exposure) in the last 6 months prior to screening visit." This resulted in incorrect stratification by the IVRS/IWRS randomization assignment.

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.

4. Nora Késmárki/ Site 348210 EFC13403

There were 10 subjects screened and 10 subjects enrolled into the study; 10 subjects completed the study. There were 10 subject records reviewed. The first subject was consented (b) (6). All of the study subjects were recruited from Dr. Késmárki's and the sub-investigator's patient population.

All study documents were submitted to the independent Central Ethics Committee for (b) (6) Study documents were then approved by the local Ethics Committee (EC) (b) (6)

The approved protocol was in English. (b) (6) Annual Reports and Progress Reports are not required to be submitted to the national or the local EC.

(b) (6)

Study documents were well organized and complete. All study documents were hard copies and available for review, but they were in Hungarian. (b) (6) assisted in translating some of the documents during the inspection. The approved Hungarian version of the informed consent form was translated from Hungarian to English by a certified translator in preparation for the inspection.

For all 10 study subjects, an incorrect date-of-birth (DOB) was used on the interactive voice response system/interactive web response system (IVRS) forms, laboratory forms, and laboratory results. The subject's year of birth was correct on the forms, but the day and month were not correct. During the inspection, Dr. Késmárki and (b) (6) stated that the subject's DOBs were "masked" to protect patient privacy and to comply with Hungarian law. Dr. Késmárki and (b) (6) also provided statements that included sections of the Hungarian law that applied to "masking" patient data. Furthermore, the central EC will not approve any clinical studies in Hungary that allows subject's initials and their exact date of birth to be included on study documents. Study staff had written the subject numbers on all of the subject's progress notes and medical documents. There was also a Subject Log in the Regulatory Binder that included the subject's numbers and their correct dates of birth.

All of the subject's study diaries were complete and appeared to have been completed by each subject in their own handwriting. It also appeared that the investigator or one of the sub-investigators had reviewed each diary with each subject. Study Subject (b) (6) had used white-out in their diary for Visits 3 and 4. Study Subject (b) (6) had used white-out in their diary for Visits 3, 4, 5, 6, and 7. (b) (6) explained that both she and her sub-investigators had addressed the use of white-out with the subjects each time that the subject's had used the white-out in their diaries, but the subjects continued to use the white-out.

Subject (b) (6) was assigned to the wrong stratum during randomization. The question as to whether the patient had received Humalog during the last 6 months was answered "yes" but it should have been answered "no".

There was no under-reporting of adverse events seen. The primary endpoint was verifiable. There were no concerns regarding discrepancies comparing the source documents to the data line listings submitted by the sponsor.

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.

5. Hiralal Maheshwari/ Site 840012 EFC12619

There were 17 subjects screened and 14 subjects enrolled into the study; 12 subjects completed the study. Two subjects withdrew consent and did not complete the study. All subject records were reviewed. All subjects were recruited from Dr. Maheshwari's private practice. The IRB of record was (b) (6)

The regulatory binder and study record were organized and legible. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable. There were no concerns regarding source documents and comparison to the data line listings.

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. Specifically, laboratory specimens for C-peptide and/or albumin/ creatinine ratio were not collected for two subjects (b) (6) at Visit 3 (Day 1, baseline).
2. Investigational drug disposition records are not adequate with respect to dates. Specifically, the site did not accurately document the date received for one shipment of 46 kits of investigational product.

It was also discussed with Dr. Maheshwari that two adverse events were not reported to the sponsor in a timely manner (over 50 days as noted previously by the monitor) and that destroyed investigational product was placed in bio-hazard waste boxes in an unlocked area, which was accessible to all employees at the firm.

OSI Reviewer Comment: Dr. Maheshwari submitted a response to the 483 items May 25, 2017. His response regarding corrective and preventive actions was determined to be acceptable.

6. Jean Louis Selam/ Site 840259 EFC13403

There were 12 subjects screened and 11 subjects enrolled into the study; nine subjects completed the study. There were 10 subject records reviewed. The IRB of record was (b) (6)

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable. There were no concerns regarding source documents and their comparison to the data line listings.

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.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm./ NDA 209196
DMEP/Division Director/ Jean-Marc Guettier
DMEP /Deputy Director/Jim P. Smith
DMEP/Team Lead/William Chong
DMEP/Clinical Reviewer/ Sonia Doi
DMEP /Regulatory Project Manager/Callie Cappel-Lynch
OSI/DCCE/Division Director/Ni Aye Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Janice Pohlman
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Joseph Peacock/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/s/

CYNTHIA F KLEPPINGER
07/25/2017

JANICE K POHLMAN
07/25/2017

KASSA AYALEW
07/25/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)

Date:	July 12, 2017
To:	Muthukumar Ramaswamy, CDER/ONDP/DNDPII/NDPBVI, E-mail: Muthukumar.Ramaswamy@fda.hhs.gov CDER/OPQ/OPF: Juandria.Williams@fda.hhs.gov
From:	Jamie Kamon-Brancazio, REGO/DMQ/OC, CDRH, WO 66, Rm 3427, E-mail: Jamie.Kamon-Brancazio@fda.hhs.gov

Jamie Kamon-brancazio -A

Digitally signed by Jamie Kamon-brancazio -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001568505, cn=Jamie Kamon-brancazio -A
Date: 2017.07.13 11:05:39 -04'00'

Applicant/Licensure:	Sanofi-Aventis U.S. LLC
Submission (Type & Number):	NDA 209196
Combination Product Name:	Insulin Lispro (rDNA origin) injection
Combination Product Intended Use:	Diabetes Mellitus
ICCR Number:	ICCR
ICCR Instruction (ICCR Form):	Consultative Review
Pre-Approval Inspection:	No
Documentation Review (Status):	Complete Adequate
CDRH/OC Recommendation:	Approvable

The Office of Compliance at CDRH received a consult request from CDER to evaluate NDA 209196, to review the results of the device constituent manufacturing inspection and to review the 21 CFR 820 requirements of the combination product.

Site inspection evaluation

A drug inspection was performed at the Sanofi-Aventis Deutschland GmbH manufacturing facility in Frankfurt Main, Germany. (b) (4)

(b) (4)

The inspection covered the following systems:

- Quality
- Facilities and Equipment
- Materials Management
- Production
- Laboratory Systems

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application NDA 209196 and has the following recommendations:

CDRH recommends approval for NDA 209196 based on the status of the recent inspection at Sanofi-Aventis Deutschland GmbH, Frankfurt Main, Germany. This inspection was classified VAI.

The desk review of the responses provide for compliance with the Medical Device Regulations showed no deficiencies, CDRH would recommend a review of the final validation data collected on the final combination product post-approval.

Crystal Lewis -S

Digitally signed by Crystal Lewis -S
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Date: 2017.07.12 12:22:42 -04'00'

Crystal Lewis

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/s/

ANIKA A LALMANSINGH
07/18/2017
Uploaded on behalf of Crystal Lewis

CONSULTING REVIEW MEMORANDUM- Amendment

DATE: **August 18, 2017**

TO: **Callie CappelLynch**
CDER/OND/ODEII/DMEP

FROM: **Stayce Beck, Ph.D., M.P.H.**
Chief, Diabetes Diagnostic Devices Branch
CDRH/OIR/DCTD/DDDB

Stayce Beck -S
2017.08.29 14:21:41 -04'00'

APPLICANT NAME: **Sanofi Group**

SUBJECT: **NDA 209196**
SAR342434, Insulin Lispro (ADMELOG)

Recommendation: **Appropriate for use in pump systems**

Review Team:
Joshua Balsam – Lead Consulting Reviewer
Jisun Yi – Clinical Consult
Stayce Beck – Diabetes Division Branch Chief

Consult Description:
The NDA Lead Reviewer requested a consult from CDRH to assess two studies provided by Sanofi: 1) a clinical safety study conducted by Sanofi to support the safe use of their insulin in two currently marketed insulin pumps, and 2) a bench study to demonstrate insulin stability in two currently marketed insulin pumps.

On July 5, 2017, the OIR consult sent the following conclusion to CDER regarding the use of SAR342434 (ADMELOG) in insulin pumps:
"Based on the information currently available, Sanofi has an outstanding device issue because there is not currently a legally marketed insulin pump in the US which lists their insulin product as being compatible. However, CDRH is willing to work with CDER and Sanofi in order to resolve this outstanding issue."

The review team met on July 26, 2017, August 9, 2017 and August 16, 2017 to discuss the outstanding device issue. OIR believes that the sponsor has provided data to demonstrate the safe use of SAR342434 (ADMELOG) in the Animas Vibe insulin pump and the Medtronic Paradigm Insulin Pumps. However, Animas and Medtronic have not submitted premarket submissions to update their labeling to include this novel insulin product. The current labels for these devices and our thoughts regarding the appropriateness for being used with SAR 342434 (ADMELOG) are listed below:

Medtronic Insulin Pumps:

The insulin pump labels state the following regarding the use of insulins with the specific Medtronic pumps:

1. Medtronic 630G and 530G Pumps:

The pump is intended for use with U100 insulin. The following insulins have been tested by Medtronic Diabetes and found to be safe for use in MiniMed 530G insulin pumps:

- *Humalog*
- *Novolog*

Before using different insulin with this pump, check the insulin label to make sure the insulin can be used with the pump.

This label was updated in 2016 to include: "*DO NOT use any other insulin with your pump other than the above specified rapid-acting U-100 insulins (Humalog, NovoLog). Use of the incorrect insulin, or insulin with a greater or lesser concentration, may result in over delivery or under delivery of insulin. This could lead to very low or very high blood glucose levels. Very high BG levels may lead to Diabetic Ketoacidosis and very low glucose levels may lead to coma and death. If you are unsure about whether you can use a specific insulin with this pump, please consult with your healthcare provider.*"

2. Medtronic Paradigm Insulin Pumps (without the Threshold Suspend):

The Paradigm pump is intended for use with U100 insulin. The following insulins have been tested by Medtronic Minimed and found to be safe for use with the Paradigm REAL-Time insulin pumps (MMT-523, MMT-723, MMT-523K, and MMT-723K)

- *Humalog*
- *Novolog*

Before using a different insulin with this pump, check the insulin label to make sure the insulin can be used with this pump.

OIR Comment: The insulin pump materials for the Medtronic pumps are the same and therefore even though the Sponsor only tested the 530G pumps, the testing indicates that it is safe to use SAR 342434 (ADMELOG) in the Medtronic pumps. However, they did not test the Threshold Suspend feature of the 530 and 630G pumps. Therefore, they would need to do this to use SAR 342434 (ADMELOG) in these pumps. Further, the label for the

530 and 630G pumps are rather narrow and state that you should not use any other insulin with your pump other than the above specified rapid-acting U-100 insulins (Humalog, NovoLog). It has been noted by the CDER review team that the label for the 530G pump posted online does not state: *"DO NOT use any other insulin with your pump other than the above specified rapid-acting U-100 insulins (Humalog, NovoLog). Use of the incorrect insulin, or insulin with a greater or lesser concentration, may result in over delivery or under delivery of insulin. This could lead to very low or very high blood glucose levels. Very high BG levels may lead to Diabetic Ketoacidosis and very low glucose levels may lead to coma and death. If you are unsure about whether you can use a specific insulin with this pump, please consult with your healthcare provider."* However, Stayce Beck contacted Medtronic on August 24, 2017 and they stated that they have indeed updated the label for the 530G to include this statement even though the version on their website might not be the most up to date version. Therefore, it is not appropriate to use SAR 342434 (ADMELOG) in these pumps and they should not be listed in the SAR 342434 (ADMELOG) label.

However, the label for the Paradigm pumps is more permissive and does not state that a user should not use other insulins with the pump, and the studies conducted support the use of SAR 342434 (ADMELOG) in these pumps. Further, Stayce Beck also received clarification that the Medtronic Paradigm pumps are still being sold at this time. Therefore, we believe that it would be appropriate to list these pumps in the SAR 342434 (ADMELOG) label per CDER's recommendation.

Animas Insulin Pumps:

The insulin pump labels state the following regarding the use of insulins with the specific Animas pumps:

1. Animas Vibe (PMA):

Your Animas® Vibe™ Insulin Pump is designed and calibrated to deliver U100 rapid-acting insulin. The following rapid-acting insulin has been tested by Animas® and found to be safe for use in the System: Humalog® and NovoLog®. The use of any other insulin with your System has not been tested.

2. Animas One Touch Ping (510k):

Your pump is designed and calibrated to deliver U100 insulin. Use of any insulin with lesser or greater concentration can result in serious injury or death.

- *The following insulins have been tested by the pump manufacturer and found to be safe for use in the insulin cartridge of the pump: Humalog®, Novolog®,*

and Apidra®. Before using a different insulin with this pump, check the insulin drug label to make sure it can be used with the pump.

OIR Comment: The sponsor has provided data to support the use of SAR 342434 (ADMELOG) in the Animas Vibe insulin pump. They did not provide data to support the use of SAR 342434 (ADMELOG) in the Animas One Touch Ping pump. However, these pumps are very similar and the differences are not ones that would be expected to impact the safety of the use of SAR 342434(ADMELOG) in the pump. Therefore, we believe that the sponsor has provided data to support the use of SAR 342434 (ADMELOG) in both Animas pumps. While there are a few statements in the Animas pump labels that are more restrictive than the general statements indicating the pump is safe for use with *Humalog® and Novolog®,* **we believe that the general comments in the pump labels are permissively broad enough to imply that other rapid acting U100 insulins might be appropriate for use in these pumps. Therefore, we believe that it would be appropriate to list these pumps in the SAR 342434 (ADMELOG) label per CDER's recommendation.**

Conclusion:

OIR believes it is appropriate to label SAR 342434 (ADMELOG) for use with insulin pumps. We understand that there are no insulin pump labels that specifically state that SAR 342434 (ADMELOG) is for use in the pumps; however, we believe that the insulin drug label could have a section stating that data was provided to support the use of SAR 342434 (ADMELOG) with Medtronic Paradigm pumps, and the Animas Vibe and One Touch Ping Pumps. At this time, the SAR 342434 (ADMELOG) label states: "Use ADMELOG in accordance with the insulin infusion pump systems instructions for use. See the insulin infusion pump system labeling to determine if ADMELOG can be used with the pump system." While we recommend that the insulin label include a statement saying that data was provided to support the use of SAR 342434 (ADMELOG) with Medtronic Paradigm pumps, and the Animas Vibe and One Touch Ping Pumps, if CDER decides not to include this statement, then we believe the risk to patients is minimal because the insulin label says to refer to specific pump labeling for use with SAR 342434 (ADMELOG) and none of the pumps are labelled for use with SAR 342434 (ADMELOG), so not that many people will use it in those pumps. Although some pumps may have labeling that could be interpreted to permit the use of SAR 342434 (ADMELOG) with those pumps, of the pumps we are aware of that are still on the market, only the pumps for which data was provided to support the use of SAR 342434 (ADMELOG) with the pumps have such labeling. Therefore, OIR defers the decision regarding including the names of insulin pumps in the SAR 342434 (ADMELOG) labeling to CDER.

Please note that this amendment memo is authored by Stayce Beck since Joshua Balsam is out of the office.

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/s/

CALLIE C CAPPEL-LYNCH
08/29/2017
signing on behalf of Stayce Beck

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

GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM

Date: June 19, 2017

To: Anika Lalmansingh, Regulatory Project Manager
Division of Business Process Management I (DRBPMI),
Office of Program and Regulatory Operations (OPRO),
Office of Product Quality (OPQ),
Center for Drug Evaluation and Research (CDER) / Center for Biologics Evaluation and Research (CBER)

From: Sarah Mollo

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

Subject: Consult for NDA 209196, ICC1600768

Applicant	sanofi-aventis U.S. LLC
Indication for Use	diabetes-mellitus
Drug / Biologic Constituent	Insulin lispro injection
Device Constituent	multi-dose pen injector

Recommendation: Pen-Injector, Device Constituent Parts of the Combination Product are Approvable with PMR/PMC(s) – See Section III for Insulin Pump Clinical Review Summary and Section VIII for PMC(s)

Digital Signature Concurrence Table	
Reviewer	Sarah B. Mollo -A Digitally signed by Sarah B. Mollo -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sarah B. Mollo -A, 0.9.2342.19200300.100.1.1=2001712033 Date: 2017.06.19 17:41:04 -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: 2017.06.30 15:37:28 -04'00'

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I. Purpose / Background

Purpose of Review

- **CDER sharepoint consult request**: The drug product is packaged in vials and also as a combination product consisting of prefilled cartridges and pre-assembled disposable multi-dose pen injectors. A consult is requested for an evaluation of the device.

- SAR342434 solution for injection is developed as a follow-on product to Humalog (100 units/mL, NDA 020563, Product 001), and is intended to have the same indications, dosage form, route of administrations and dosing regimen. The drug substance SAR342434 has the identical amino acid sequence and structure as the Humalog insulin lispro. The drug product has the same formulation composition and strength as the listed drug product.

- Insulin lispro solution for injection 100 U/mL (SAR342434) is filled in two different primary container closure systems, a 3 mL cartridge and a 10 mL vial. The final drug product will be available in 2 presentations, a 10 mL vial and a 3 mL disposable pre-filled pen (3 mL cartridge irreversibly integrated in a disposable pen injector).

Indications for use of the combination product
SAR342434 solution for injection is developed as a follow-on product to Humalog (100 units/mL, NDA 020563, Product 001), and is intended to have the same indications, dosage form, route of administrations and dosing regimen.

Indications and Usage in Insulin Lispro labeling:
TRADENAME is a rapid-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus1.2

Dosage and Administration

- Subcutaneous injection: Administer TRADENAME by subcutaneous injection within 15 minutes before a meal or immediately after a meal.

- Continuous subcutaneous infusion (Insulin Pump): Administer TRADENAME by continuous subcutaneous infusion using an insulin pump.

- Intravenous Infusion: Administer TRADENAME by intravenous infusion ONLY after dilution and under medical supervision.

- The sponsor has generated data to support SAR342434's use in insulin pumps, which was discussed at the end of the pre-NDA meeting. Sanofi since had further discussions with CDER and CDRH, as summarized in the [Correspondence Regarding Meetings] in Module 1.6.3.

    - The pumps used in the study contain CGM and are reviewed in OIR under a PMA.

    - **CDRH/ODE is not reviewing a specific pump or pumps, but is reviewing the information provided to determine if the appropriate data to support the use of pumps in general has been included within the clinical study.**

clinical submission. See Section III. for the Insulin Pump Clinical Review Summary.

- There are no pumps labeled for use with this specific insulin. Multiple discussions have occurred surrounding the possible outstanding device issue with the sponsor, CDER and CDRH. The following two options have been discussed:

(b) (4)

[redacted]

This review covered the following review content for the **pen-injector constituent** of the combination product:
- Inspection of sponsor's design input activities
- Inspection of sponsor's design verification activities
- Confirmation of standards conformance, where relied upon
- Inspection of test methods and results of bench top testing completed
- Inspection of stability testing completed on the device constituent part

This review did not cover the following content:
- Review of drug product
- Review of primary container closure-drug product interaction, sterility, or toxicology
- Manufacturing of the drug product
- Manufacturing of the device constituent part of the combination product
- Design input, verification testing, or biocompatibility of the pumps that were used for the clinical trial

Product	Indications for Use
TRADENAME (insulin lispro for injection), for subcutaneous or intravenous use	TRADENAME is a rapid-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus. (1)

II. Administrative

Documents Reviewed:

Document Title	Document Number	Date -Version	Location
User Requirement Specification	LA-EP2006_PFS_in X100L_URS_2	01/01/2016 – Version C	GSR Sequence 0000 / Section 3.2.P.7.2

CONTAINER CLOSURE SYSTEM Disposable pen injector	(b) (4)	EN 2.0	GSR Sequence 0008 / Section 3.2.P.7.2
RESPONSE TO AGENCY REQUEST SAR342434 - insulin lispro INFORMATION REQUEST DATED 10-Mar-2017		17-Mar-2017	GSR Sequence 0009 / 1.11.2 Non-clinical information amendment
RESPONSE TO FDA REQUEST INFORMATION ON TOPICS RELATED TO THE PEN-INJECTOR DATED ON 23-Feb-2017		03-Mar-2017	GSR Sequence 0008 / 1.11.2 Non-clinical information amendment
SPECIFICATION(S) Pen injector: Specifications of assembled insulin lispro pen injector		June 2017	GSR Sequence 0017/ 3.2.P.5.1 Specifications
Insulin lispro 100 U/mL - Essential performance requirements (signed)	(b) (4)	02-Mar-2017	GSR Sequence 0008/ P.2.4 Pen injector
Human Factors Engineering / Usability Report	(b) (4)		GSR Sequence 0005/ 5.3.5.4
Comparison of Clinical Pen-injector versus Commercial Pen-injector	(b) (4)	EN 1.0 October 2016	GSR Sequence 0000/ 3.2.P.2
Biocompatibility Reports	(b) (4)	EN 1.0	GSR Sequence 0000/ 3.2.P.2
Pen-Injector Risk Management Summary		EN 1.0	GSR Sequence 0000/ 3.2.P.2
Container closure system - Overview of the results of risk management		EN 1.0	GSR Sequence 0000/ 3.2.P.2
Insulin Lispro- Original NDA- 10-Jan-2017 Response- ProposedPI-Feb 2017			GSR Sequence 0004/ 1.14.1.3 Draft Labeling Text

CDRH Review Team:

Team Member	Role	Deficiencies
Sarah Mollo (CDRH/ODE/GHDB)	Lead Reviewer	n/a
Patricia Beaston (CDRH/ODE/GHDB)	Consultant – Clinical	No deficiencies- See Section III. for review summary

III. Insulin Pump Clinical Review Summary

The sponsor has generated data to support SAR342434's use in insulin pumps, which was discussed at the end of the pre-NDA meeting. **CDRH/ODE is not reviewing a specific pump or pumps, but is reviewing the information provided to determine if the appropriate data to support the use of pumps in general has been included within this submission.** Patricia Beaston was consulted to evaluate the acceptability of the insulin pump data from the clinical study to support a 510(k) or PMA application.

Dr. Beaston provided the following summary of her review:

> The Sponsor has developed a "follow-on" insulin lispro (SAR342434) for the treatment of diabetes. The Sponsor has performed a randomized cross-over study (PDY13502) comparing the safety of delivery of SAR342434 to reference listed drug (RLD) insulin lispro (Humalog) by insulin infusion pumps. The primary evaluation was for indications of infusion set occlusion. Occlusion is the critical safety factor that limits the interval for infusion set changes because of the severity of conditions that result in the failure to deliver insulin; especially in patients with type 1 diabetes. The study demonstrated that the difference in suspected infusion set occlusion is not significantly different between the subject insulin and the RLD. Therefore, the Sponsor has provided sufficient data to support the safe use of SAR342434 for delivery by insulin infusion pump.
>
> The elements to support this finding are:
> - A clinical study enrolling patients who were identified to be proficient with the use of their insulin pump to facilitate identification and management of hyperglycemia. Additionally, these patients would be expected to have an individualized bolus dose calculation such that treatment of hyperglycemia would provide an expected response.
> - A primary evaluation that is testable and clinically relevant; a suspected occlusion was "*defined as failure to correct hyperglycemia (plasma glucose ≥ 16.7 mmol/L [300mg/dL]) by insulin bolus via the insulin pump*".
> - A subject insulin that is described to have the same PK/PD profile as the RLD insulin.
>
> However, there is currently no pump, either 510(k) or PMA, under review for labeling to claim use with SAR342434. Therefore there is an outstanding device issue.

(b) (4)

(b) (4)

Reviewer Comments
1. The labeling still includes the language, "*Continuous subcutaneous infusion (Insulin Pump): Administer TRADENAME by continuous subcutaneous infusion using an insulin pump*." This possible outstanding device issue is being worked out with CDRH (OIR AND ODE), CDER, and OCP.

(b) (4)

IV. Device Description and Performance Requirements

The design of the insulin lispro pen injector is based on the already marketed SoloStar® pen injector, which is combined with insulin glargine solution for injection 100 U/mL (Lantus®, NDA 21-081) and which has been modified for the application of the insulin lispro solution for injection. The modification comprises the colors of the body, cap, injection button and dose selector. In addition, the injection button of the insulin lispro pen injector possesses a raised ring (tactile element, see Figure 2).

The pen injector is designed to deliver multiple doses of variable volume after an initial priming step. This priming step is required before each injection.

(b) (4)

(b) (4)

Device Characteristic	Description / Specification
Injector Name	TRADENAME SoloStar prefilled pens
Injector Platform Name	SoloStar® pen injector
Priming Dose / Volume	2 units
Dose accuracy	ISO 11608-1 at standard atmospheric conditions (b) (4)
Injection Time	Not a specification, but directions instruct the user to hold pen in place for 10 seconds after dose dial hits "0"

Injection Site	subcutaneous tissue of the abdominal wall, thigh, upper arm, or buttocks
Injection tissue and depth of injection	-Subcutaneous -depth is based on needle- not included with device, user instructed to use compatible needle
Audible / visual feedback	-Doses can be dialed in 1 unit increments. Each unit of insulin lispro is accompanied by a 'click' which can be felt. Dialing a dose will result in changes to the numbers displayed in the dosage window at the back end of the pen injector body. -Dispensing a dose by pressing the injection button all the way back into the pen body will return the unit number in the dosage window back to "0". Further button travel is prevented by a tactile stop. -The number of units remaining as displayed on the cartridge holder dose scale will be reduced by the amount that has been dispensed.
Cap Removal Force	(b) (4)
Activation Force	Pen-injector- n/a; however, essential performance requirements include: • maximum dispense force of (b) (4) N
Visibility of medication container	The cartridge holder is made of transparent plastic material, facilitating full visibility of the drug product cartridge
Last Dose Specifications and Safety Features	-Cartridge has a scale printed onto it, which is intended to aid the user in determining the number of units remaining within the device -Once the labeled volume has been dispensed from the cartridge, the 'last dose stop' is engaged and no further doses can be set -Once the labeled volume has been dispensed from the cartridge, the 'last dose stop' engages if the user attempts to set an additional dose. Thus, it is not possible to set a dose larger than the volume remaining in the device.
Needle Specifications • Length(s) • Gauge(s) • Connection type o ISO 11608-2:2012 o Prestaked	• Length(s)- not specified • Gauge(s)- not specified • Connection type- o ISO 11608-2:2012 IFU contains the following guidance for choosing compatible needles: *Always use needles* that are compatible for use with TRADENAME SoloStar, e.g. needles from BD (such as BD Ultra-Fine®), Ypsomed (such as Clickfine®), Owen Mumford (such as Unifine® Pentips®) or Artsana (such as Insupen®).* "Dose accuracy of the insulin lispro pen injector was

	determined according to the dose accuracy method of ISO 11608-1 using BD Micro-Fine™ Ultra needles (0.25 mm (31G) x 8 mm)."
Type of Use (e.g. single use, disposable, reusable, other)	disposable
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	self-injection by the patients
Injection mechanism (e.g., manual piston, spring, gas, etc.)	manual
Method of actuation	A dose is dispensed by pushing the injection button fully back toward the pen body and subsequently maintaining pressure (with the needle in place within the patient) on the button for 10 seconds without retrieving the needle
Automated Functions	none
Residual Medication	Extractable volume is (b) 3.0 mL; Once the labeled volume has been dispensed from the cartridge, the 'last dose stop' engages if the user attempts to set an additional dose. Thus, it is not possible to set a dose larger than the volume remaining in the device
Delivered Volume (for single dose or selectable volume range for multidose pens)	-1 to 80 Units -3 mL cartridge (300 units of insulin total)
Drug Container Type	cartridge consists of a glass tube, sealed at both ends with rubber components
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	Units
Environments of use	-The device is intended for a domestic in-house use in a non-sterile environment. -The device will typically be used by patients in their home and will be self-administered. -It could be administered to a patient whilst in an institutionalized care environment.
Storage conditions and expiry	3 years at 5°C±3°C
Graduation marks / fill lines	Cartridge has a scale printed onto it, which is intended to aid the user in determining the number of units remaining within the device
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	-Step 1: Check your pen • Take a new pen out of the refrigerator at least 1 hour before you inject. Cold insulin is more painful to inject. • 1A Check the name and expiration date on the label of your pen. • 1B Pull off the pen cap. • 1C Check that the insulin is clear. • 1D Wipe the rubber seal with an alcohol swab.

clothing, etc.) • Changing / disposing needles • Etc.	- Step 2: Attach a new needle • 2A Take a new needle and peel off the protective seal. • 2B Keep the needle straight and screw it onto the pen until fixed. Do not over-tighten. • 2C Pull off the outer needle cap. Keep this for later. • 2D Pull off the inner needle cap and throw away. -Step 3: Do a safety test • 3A Select 2 units by turning the dose selector until the dose pointer is at the 2 mark. • 3B Press the injection button all the way in. When insulin comes out of the needle tip, your pen is working correctly. - Step 4: Select the dose • 4A Make sure a needle is attached and the dose is set to '0'. • 4B Turn the dose selector until the dose pointer lines up with your dose. - Step 5: Inject your dose • 5A Choose a place to inject as shown in the picture above. • 5B Push the needle into your skin as shown by your healthcare provider. o Do not touch the injection button yet. • 5C Place your thumb on the injection button. Then press all the way in and hold. • 5D Keep the injection button held in and when you see "0" in the dose window, slowly count to 10. • 5E After holding and slowly counting to 10, release the injection button. Then remove the needle from your skin. -Step 6: Remove the needle • 6A Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap. Then push firmly on. • 6B Grip and squeeze the widest part of the outer needle cap. Turn your pen several times with your other hand to remove the needle. • 6C Throw away the used needle in a puncture-resistant container (see "Throwing your pen away" at the end of this Instructions for Use). • 6D Put your pen cap back on. o Do not put the pen back in the refrigerator. o Only use your pen for up to 28 days

	after its first use. -After first use • Keep your pen at room temperature below 86°F (30°C). • Keep your pen away from heat or light. • Do not put your pen back in the refrigerator. • Do not store your pen with the needle attached. • Store your pen with the pen cap on. • Keep out of the reach of children.
Safety Features • Needle safety	For the safety and convenience of the user, as well as for the protection of the cartridge, a pen cap is incorporated as part of the pen system.
Electronics / Data transmission • Display • Control functions • Data transmission technology • Data being transferred	n/a
Material composition of injector	The following materials are used in the insulin lispro pen injector: (b) (4) (b) (4) (b) (4) for the standard 3 mL cartridge

An IR was sent to the sponsor on February 23, 2017, requesting a separate signed and dated document for the essential performance requirements, the sponsor provided the document, Pharmaceutical development – Container closure system – Essential performance and safety requirements of the pen injector", (b) (4) on March 6, 2017 under 3.2.P.2.4 with the following table:

Table 1 - Essential performance and safety requirements of the insulin lispro pen injector

Essential performance and safety requirement	Specification
Cap removal force	The cap removal force shall be within a range of (b) (4)
Needle compatibility	The pen injector shall be compatible with standard disposable needles that meet the requirements of the screw on/off test defined in EN ISO 11608-2, ie the screw-on torque is (b) (4) Nm and the screw-off torque is (b) (4) Nm
Dial torque	The torque for dialing a dose and back-dialing shall be (b) (4) Nmm (mean peak) and (b) (4) Nmm (break-loose/end peak), respectively
Dose number visibility	The dose numbers and marking lines shall be visible and legible at environmental lighting conditions of (b) (4) from a reading distance of (b) (4) cm (requirement for visual inspection of ISO 11608-1)
Dose Accuracy	The quantity of medication injected must correspond to the dialed amount and shall match the dose accuracy requirements of ISO 11608-1 in standard atmospheric conditions (b) (4) (b) (4)
Dispense force	The maximum dispense force shall be (b) (4) N
Cap attachment force	The cap attachment force shall be (b) (4) N

LSL = lower specification limit
USL = upper specification limit

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
Buquoy, Bernadette	CMC Approval	02-Mar-2017 16:21 GMT+0100

V. Design Control Review

A. Design Review Summary

{INSERT SUMMARY OF THE COMPLETE DESIGN REVIEW INCLUDING ANY OUTSTANDING REVIEW ISSUES}

B. Design Control Documentation Check

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		3.2.P.2.4 "Pharmaceutical development – Container closure system – Essential performance and safety requirements of the pen injector" (b) (4)
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	x		3.2.P.2.4 Pen injector performance test (ISO 11608-1) (b) (4) Version 2.0 3.2.P.2.4 Pen injector performance test (ISO 11608-1) - Appendix (b) (4) Version 2.0 3.2.P.2.4 "Pharmaceutical development – Container closure system – Design control process – Appendix" (b) (4)
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	x		3.2.P.2 Pharmaceutical Development Pen-injector Risk Management Summary (b) (4) (b) (4) Pen-injector Overview of the results of risk management (b) (4)
Validation Data • Human factors • Clinical data	x		Sponsor provided a comparison of the user interface elements and user interactions between the Lantus SoloStar and Insulin Lispro Pen Injector (see validation section of memo). The only differences were tasks related to differentiation. The HF report assessing differentiation can be found in: "Human Factors Engineering / Usability Report" (b) (4) (b) (4) SN #0005; 5.3.5.4 Comparison of Clinical Pen-injector versus Commercial Pen-injector" under 3.2.P.2 SN #0000 Tabular Listing of Clinical Studies
Traceability Documentation	x		

***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.**

An IR was sent to the sponsor on February 23, 2017 requesting a trace matrix for the essential performance requirements. The sponsor provided the following on March 6, 2017:

Table 3 - Trace matrix for essential performance and safety requirements

Essential performance and safety requirement	Specification	Verification data	Accelerated aging / simulated shipping[a] (Yes/No)	Batch release testing[b] (Yes/No)
Cap removal force	The cap removal force shall be within a range of (b) (4)	**Summative information:** Section 3.2.1 of (b) (4) **Verification report extracts:** Figure 1 and Figure 2 of (b) (4)	Yes	No
Needle compatibility	The pen injector shall be compatible with standard disposable needles that meet the requirements of the screw on/off test defined in EN ISO 11608-2, ie the screw-on torque is (b) (4) Nm and the screw-off torque is (b) (4)	**Summative information:** Section 3.2.2 of (b) (4) **Verification report extract:** Figure 3 of (b) (4)	Yes	No
Dial torque	(b) (4) The torque for dialing a dose and back-dialing shall be (b) (4) Nmm (mean peak) and (b) (4) Nmm (break-loose/end peak), respectively.	**Summative information:** Section 3.2.3 of (b) (4) **Verification report extracts:** Figure 4 and Figure 5 of (b) (4)	Yes	No
Dose number visibility	The dose numbers and marking lines shall be visible and legible at environmental lighting conditions of (b) (4) from a reading distance of (b) (4) requirement for visual inspection - ISO 11608-1).	Verification has been performed as part of the dose accuracy tests according to ISO 11608-1 (see below)	Yes	No
Dose Accuracy	The quantity of medication injected must correspond to the dialed amount and shall match the dose accuracy requirements of ISO 11608-1:2014 at standard atmospheric conditions (b) (4) See (b) (4) for dose accuracy specification limits.	**Summative information:** (b) (4) **Verification report extracts:** Table 5 to Table 12 of (b) (4) **Statistical analysis of dose accuracy data:** Section 2 of (b) (4)	Yes	Yes

Essential performance and safety requirement	Specification	Verification data	Accelerated aging / simulated shipping[a] (Yes/No)	Batch release testing[b] (Yes/No)
Dispense force	The maximum dispense force shall be (b) (4)	**Summative information:** Section 3.2.6 of (b) (4) **Verification report extracts:** Figure 6 and Figure 7 of (b) (4)	Yes	No
Cap attachment force	The cap attachment force shall be (b) (4)	**Summative information:** Section 3.2.1 of (b) (4) **Verification report extracts:** Figure 1 and Figure 2 of (b) (4)	Yes	No

(b) (4)

The response also included the following information:

> *The design of the pen injector in its entirety has been validated in several formative and summative Human Factors validation studies. This renders the separate validation of individual aspects of the essential performance and safety requirements unnecessary. Therefore, Table 3 does not contain separate references to validation data. The results of successful design validation are shown in the "Human Factors Engineering / Usability Report" (b) (4), which has been submitted in Module 5 of NDA 209196.*

(b) (4)

Essential performance requirements

The following table outlining the essential performance and safety requirements is located under 3.2.P.2., document Pen-injector- (b) (4)

The essential performance and safety requirements of the disposable insulin lispro pen injector including the specifications for these requirements are shown in Table 1.

Table 1 - Essential performance and safety requirements of the insulin lispro pen injector

Essential performance and safety requirement	Specification
Cap removal force	The cap removal force shall be within a range of (b) (4)
Needle compatibility	The pen injector shall be compatible with standard disposable needles that meet the requirements of the screw on/off test defined in EN ISO 11608-2, ie the screw-on torque is (b) (4) Nm and the screw-off torque is (b) (4)
Dial torque	The torque for dialing a dose and back-dialing shall be (b) (4) mean peak) and (b) (4) break-loose/end peak), respectively
Dose number visibility	The dose numbers and marking lines shall be visible and legible at environmental lighting conditions of (b) (4) from a reading distance of (b) (4) (requirement for visual inspection of ISO 11608-1)
Dose Accuracy	The quantity of medication injected must correspond to the dialed amount and shall match the dose accuracy requirements of ISO 11608-1 in standard atmospheric conditions (b) (4) (b) (4)
Dispense force	The maximum dispense force shall be (b) (4)
Cap attachment force	The cap attachment force shall be (b) (4)

LSL = lower specification limit
USL = upper specification limit

Reviewer Comment
IR sent on Februrary 23, 2017 asking for a separate signed and dated essential performance requirements document. IR also asked for dose accuracy specifications as the original table stated that the dose accuracy testing was performed according to the 11608-1 standard, but did not give the actual values. The above table was included in the signed and dated document that the sponsor sent on March 6, 2017.

C. Design Verification and Validation Review

Summary of Design V&V Attributes:

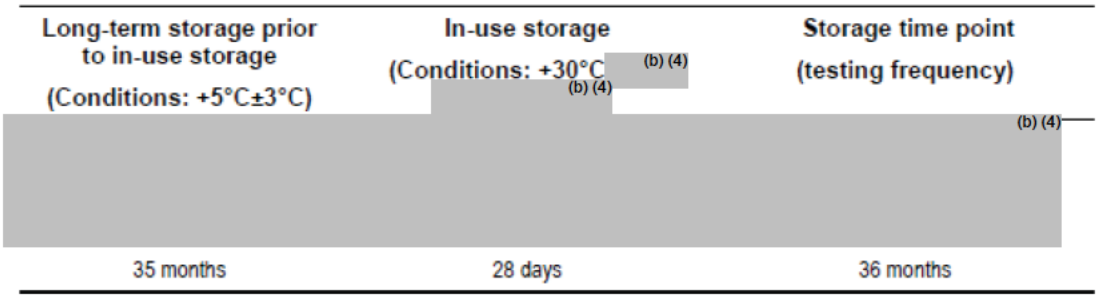
Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	x		
To-be-marketed device was used in the pivotal clinical trial?		X (but comparison provided-changes	

			would not impact device performance in clinical trial)	
Selectable dose range on device matches the labeled dose range for the medication?		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		
Conformance to applicable standards demonstrated	ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods	x		
	ISO 11608-2:2012 – Needles			x
	ISO 11068-4:2006 – Electronic and Electromechanical Pen Injectors			x
	ISO 11608-5:2012 – Automated Functions			x
Adherence to FDA Guidance: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products		x		
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry		x		
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility	x		
	Sterility			n/a
	Software / Cybersecurity			n/a
	Electrical Safety / EMC			n/a
	Human Factors	x		

Stability Studies

One batch of assembled insulin lispro pen injectors has been placed on long-term stability including in-use.

Table 2 - Storage conditions and testing frequency



After the in-use time period dose accuracy testing of the insulin lispro pen injectors is conducted according to ISO 11608-1.

The pen injectors are prepared according to the instructions for use. Dose accuracy is tested under defined test conditions:

- Temperature: 23°C±5°C;
- Relative humidity: 50%±25% RH

The following results are located under 3.2.P.8.3. Stability Data document: Dose accuracy of the pen injector (b) (4)

(b) (4)

Table 4 - Pen injector essential performance and safety requirements, and acceptance criteria

Essential performance requirement	No. of tested samples	Acceptance criteria
Cap attachment and removal force	(b) (4)	The cap removal force has to be in the range of (b) (4) at ambient conditions. The cap attachment force has to be (b) (4) at ambient conditions.
Needle compatibility		The pen injector must be compatible with needles that meet the requirements of the screw on/off test defined in ISO 11608-2, ie, the screw-on torque is (b) (4) and the screw-off torque is (b) (4)
Dose number visibility[a]		Dose numbers have to be readable at environmental lightning conditions of (b) (4) from a reading distance of (b) (4)
Dial torque[b]		The torque required to dial or back dial a dose shall be (b) (4) and (b) (4)
Dose accuracy		Complies with dose accuracy requirements in standard atmosphere according to ISO 11608-1.
Dispense force		The dispense force has to be (b) (4) (b) (4)

Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase III Study utilized the to-be-marketed device		X (see comparison of clinical and to-be marketed devices below	
Bioequivalence Study utilized to-be-marketed device		X	
Simulated Actual Use Study utilized to-be-marketed device		X	

Clinical Studies

This is a "follow-on" insulin product; therefore, CDER asks that the sponsor demonstrate that the manufacturing differences do not introduce risks to patient (e.g. patients should not exhibit increased formation of antibodies to insulin or an increased immune response to insulin as a result of the antibodies formed). The sponsor is asked to evaluate follow-on in a clinical study at least one year (ideally for both Type 1 and Type 2 patients in separate studies). The following two studies (one for Type 1 and one for Type 2) were performed using a similar pen injector- the similarities and differences of the to-be marketed pen and pen used in the clinical studies are discussed in the "Comparison of Clinical pen injector and to-be-marketed pen injector" section of this memo (below the summary of the clinical studies).

SAR342434-EFC13403 - insulin lispro

Title of the study: Six-month, Randomized, Open-label, Parallel-group Comparison of the Insulin Analog SAR342434 to Humalog® in Adult Patients With Type 2 Diabetes Mellitus also Using Insulin Glargine (EFC13403;SORELLA 2)

Phase of development: Phase 3

Objectives: The primary objective of this study was to demonstrate non-inferiority of SAR342434 versus Humalog in terms of changes in HbA1c from baseline to Week 26 in patients with type 2 diabetes mellitus (T2DM) also using Lantus

Devices: SAR342434 was supplied as 100 U/mL solution for subcutaneous (SC) injection in the SAR342434 SoloSTAR® disposable pen. Humalog was supplied as 100 U/mL solution for SC injection in the Humalog

KwikPen™ (EU- or US-approved Humalog comparator were used at sites depending on the countries, and were clearly identified.)

SAR342434-EFC12619 - insulin lispro
Title of the study: Six-month, Randomized, Open-label, Parallel-group Comparison of SAR342434 to Humalog® in Adult Patients With Type 1 Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period (EFC12619; SORELLA 1)-6 month
Phase of development: Phase 3
Objectives: The primary objective was to demonstrate non-inferiority of SAR342434 versus Humalog in terms of change in hemoglobin A1c (HbA1c) from baseline to Week 26 in patients with type 1 diabetes mellitus (T1DM) also using Lantus
Devices: SAR342434 was supplied as a 100U/mL solution in pre-filled SAR342434 SoloSTAR disposable pen Humalog was supplied as a 100U/mL solution in pre-filled Humalog KwikPen® disposable pen

Comparison of Clinical pen injector and to-be-marketed pen injector

For the application of insulin lispro solution for injection 100 U/mL, a disposable pen (insulin lispro pen injector) has been developed for commercial use (Figure 1). The design of this pen injector is based on the already marketed SoloStar® pen injector, which is combined with insulin glargine solution for injection 100 U/mL (Lantus®, NDA 21-081, Figure 2) and which was modified for the application of insulin lispro solution for injection. The insulin lispro pen injector is intended for commercial distribution, thus it is also referred to as the insulin lispro commercial pen injector in this application.

In phase 3 clinical trials, insulin lispro solution for injection 100 U/mL was administered by using another pen injector, named insulin lispro clinical pen injector (Figure 3). The design of this device is also based on the SoloStar. The insulin lispro clinical pen injector was used in studies EFC12619 and EFC13403 and will be referred to as the clinical pen injector hereafter. The phase 3 clinical studies began in 2014 (EFC12619) and 2015 (EFC13403), respectively and ended in 2016.

As both the clinical and commercial variant of the insulin lispro pen injector are based on the design of the already marketed SoloStar pen injector, information is provided hereafter that compares the pen injectors with each other and with marketed Lantus SoloStar in order to support the safe and effective use of the insulin lispro commercial pen injector.

Figure 1 - Insulin lispro pen injector, intended for commercial use

Table 1 - Comparison of main characteristics of clinical and commercial insulin lispro pen injectors and Lantus SoloStar

	Insulin lispro clinical pen injector	Insulin lispro commercial pen injector	Lantus SoloStar
Drug concentration	100 U/mL insulin lispro	100 U/mL insulin lispro	100 U/mL insulin glargine
Cartridge volume	3 mL	3 mL	3 mL
Insulin content per pen (cartridge)	300 U	300 U	300 U
Dose setting interval (units/volume per click)	1 U / 10 µL	1 U / 10 µL	1 U / 10 µL
Min single dose per injection	1 U	1 U	1 U
Max single dose per injection	80 U	80 U	80 U
Color pen cap/pen body	(b) (4)	light yellow	grey
Color cartridge holder		transparent	transparent
Color dosage selector		burgundy	dark grey
Color of injection button		burgundy	lilac
Raised ring on injection button	(b) (4)	yes	no
Scale on number sleeve	0 to 80 U	0 to 80 U	0 to 80 U
Use of device	Clinical trials EFC12619 and EFC13403	Intended for commercial use	Commercial use
Disposable device	yes	yes	yes
Dose accuracy according to ISO 11608-1	yes	yes	yes
Biocompatible according to ISO 10993-1	yes	yes	yes

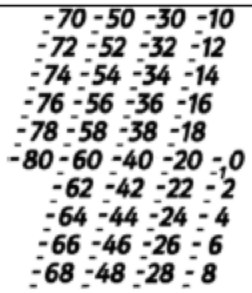
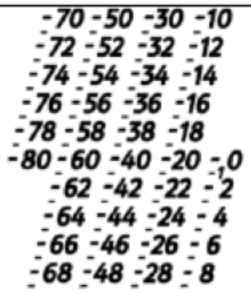
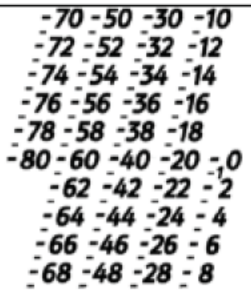
Mechanism subassembly

The mechanism subassembly is a high precision design component, representing the basis for accurate dose delivery. Pen injectors described here are based on the SoloStar design and share the same mechanism for setting and dispensing doses. By using the dosage selector, display of the dose in the dosage window and the injection button, the user can select and inject the desired dose. Before each injection, the user has to perform a priming step as described in the instructions for use.

Number sleeve

The number sleeves of the clinical and commercial insulin lispro pen injectors and the marketed Lantus SoloStar pen injector are identical, as can be seen in Figure 5. Each of the number sleeves contains marking lines, which indicate both even and odd unit increments, and dose numbers for every even unit value in the range from 0 to 80. In addition, the numeral '1' is printed on the number sleeves. Thus, users can set doses of 1 to 80 units of insulin using 1 unit increments (Table 1).

Figure 5 - Comparison of the number sleeves

Insulin lispro clinical pen injector	Insulin lispro commercial pen injector	Lantus SoloStar
		

Injection button
Clinical and commercial insulin lispro pen injectors feature the same shape of the injection button, which is also found on the Lantus SoloStar pen injector. However, the colors for the clinical and commercial insulin lispro pen injectors have been changed to support differentiation between the devices. (b) (4) *The injection buttons are presented in Figure 6.*

Figure 6 - Comparison of injection buttons

Insulin lispro clinical pen injector	Insulin lispro commercial pen injector	Lantus SoloStar
(b) (4)		
	Burgundy with added raised ring	Lilac without raised ring

DIFFERENCES BETWEEN THE DEVICES
Differences between the three pen injectors described here are only related to the colors of the pen components, the injection button and the drug content. The body, cap, dose selector and injection button are colored differently (Table 1). (b) (4) *In addition, the Lantus SoloStar contains insulin glargine solution for injection 100 U/mL, while insulin lispro clinical and commercial pen injectors contain insulin lispro solution for injection 100 U/mL (Table 1).*

Reviewer Comment

The following IR was sent on March 23, 2017:
You state that the "differences between the three pen injectors described here are only related to the colors of the pen components, the injection button and the drug content." Please confirm that there are no other differences between the design of the clinical and to-be marketed pen-injectors for insulin lispro.

Sponsor Response- March 6, 2017
Sanofi hereby confirms that there are no additional differences between the clinical and to-be marketed insulin lispro pen injectors.

3.1 PTC CASES OF THE INSULIN LISPRO CLINICAL PEN INJECTOR
A total of six complaints were reported during the clinical trials by patients using the insulin lispro clinical pen injector (Table 2). None of these PTC cases was linked to an adverse event (AE). Root cause analysis revealed that two of the PTCs were caused by glass breakage of the cartridge due to unknown stress factors. Four cases were related to mishandling of the pen injector.

Table 2 - PTC cases for insulin lispro clinical pen injector used in the phase 3 trials

Clinical trial number	PTC cases [No.]	AE [No.]	Devices in study [No.]
EFC12619	6	0	~ 12.300
EFC13403	0	0	~ 8.300

AE = adverse event

Human Factors Validation

Because the design of the insulin lispro pen injector is based on the already marketed Lantus® SoloStar® pen injector (reference is made to NDA 21-081), a delta analysis was conducted to identify the differences in the user interface that required an assessment in the HF validation studies (see Table 2).

The HF validation studies were carried out in accordance with guidelines in the FDA Guidance document *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* (1), ANSI/AAMI/IEC 62366-1:2015 (2) and ANSI/AAMI HE75:2009 (3), section 5 on managing the risk of use error and section 9 on usability testing.

Post-market data from Lantus SoloStar and the HF validation studies confirmed that the intended users can safely and effectively use the final device (including its labeling and packaging) under simulated but realistic use conditions.

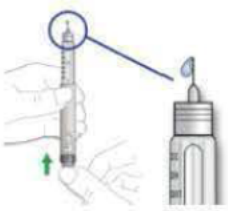
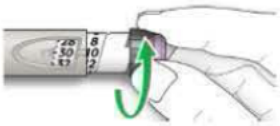
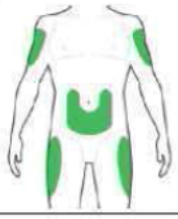
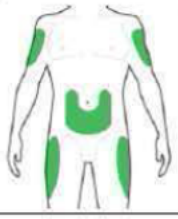
The main results of the HF validation studies, which were conducted in the U.S. with U.S. citizens, are shown in Table 1.

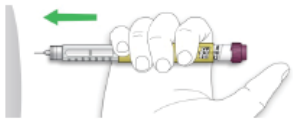
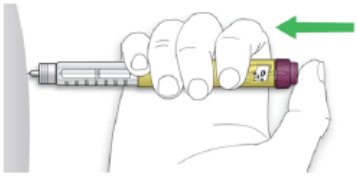
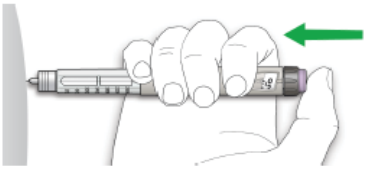
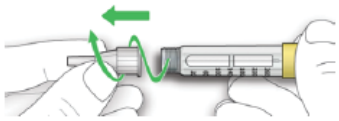
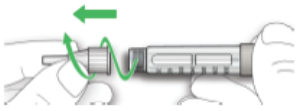
Table 1 - Summary of study results

Study item	Study results
Pen injector	The insulin lispro pen injector was found to be differentiable from other pen injectors and enabled users to select the correct pen based on a simulated prescription. The insulin lispro pen injector was also found to be differentiable from other pen injectors when users had to select the correct pen based on the pen color scheme and the respective pen label.
Pen package	The insulin lispro pen injector pen package was found to be differentiable from other pen injector packages and enabled users to select the correct package based on a simulated prescription.

Table 2 - User interface elements and user interactions with the insulin lispro pen injector and Lantus SoloStar

Task and related user group		Insulin lispro pen injector user interface elements and user interactions	Lantus SoloStar user interface elements and user interactions	Evaluation of equivalence or difference
Dispensing of correct pen package to the user in the pharmacy	Pharmacist	The outer packaging color and information for the insulin lispro pen injector will support the pharmacist to recognize and dispense the correct product to the patient 	The outer packaging design and information for the Lantus SoloStar supports the pharmacist to recognize and dispense the correct product to the patient 	The outer packaging color and the information for the insulin lispro pen injector are necessarily different from the outer packaging for Lantus SoloStar. Not equivalent.
Open the pen package	User			The packaging design, components, materials, user interactions and related risks are equivalent. Post-market data from Lantus SoloStar is acceptable.
Select the correct pen device	User			The colors of the packaging box and device cap, device body, injection button and dose selector are necessarily different to facilitate appropriate differentiation. Not equivalent.

Task and related user group		Insulin lispro pen injector user interface elements and user interactions	Lantus SoloStar user interface elements and user interactions	Evaluation of equivalence or difference
		Dispensing of safety shot 	Dispensing of safety shot 	Device design, components, materials, user interactions and related risks are equivalent. Post-market data from Lantus SoloStar is acceptable.
Select the dose	User			Device design, components, materials, user interactions and related risks are equivalent. Post-market data from Lantus SoloStar is acceptable.
Select the correct injection site	User	The injection sites are illustrated in the IFU 	The injection sites are illustrated in the IFU 	Information in the IFU, user interactions and related risks are equivalent. Post-market data from Lantus SoloStar is acceptable.

Task and related user group		Insulin lispro pen injector user interface elements and user interactions	Lantus SoloStar user interface elements and user interactions	Evaluation of equivalence or difference
Insert the needle into the skin	User			Device design, components, materials, user interactions and related risks are equivalent. Post-market data from Lantus SoloStar is acceptable.
Inject the dose	User	The dose will be injected by pressing on the injection button 	The dose is injected by pressing on the injection button 	Device design, components, materials, user interactions and related risks are equivalent. Post-market data from Lantus SoloStar is acceptable.
Remove the needle from the pen	User			Device design, components, materials, user interactions and related risks are equivalent. Post-market data from Lantus SoloStar is acceptable.

Task and related user group		Insulin lispro pen injector user interface elements and user interactions	Lantus SoloStar user interface elements and user interactions	Evaluation of equivalence or difference
Attach the pen cap	User			Device design, components, materials, user interactions and related risks are equivalent. Post-market data from Lantus SoloStar is acceptable.
Storage of pen injector which is in use	User	The insulin lispro pen injector can be stored for up to 4 weeks in room temperature after first use	Lantus SoloStar can be stored for up to 30 days after first use	Storage information description is equivalent for the products. Post-market data from Lantus SoloStar is acceptable.

Reviewer Comment

CDER DMEPA has requested CDRH's review of the HF validation study results submitted by Sanofi. Xin Feng from the human factors team was consulted to review the HF validation study results. The human factors study appears to be related only to the ability of the user to select the correct pen (differentiation).

Xin Feng provided the following deficiency:

> *Your Human Factors (HF) validation studies included T2DM patients, nurses and pharmacists. However, based on your description, the intended users of the subject combination product include T1DM patients, T2DM patients, lay caregivers, nurses and pharmacists. Your HF test participants did not include either T1DM patients or lay caregivers group. The participants in the HF validation testing should match the representative profile of the intended user. Please provide human factors testing data including T1DM patients and lay caregivers group; or provide justification on why T1DM patients and lay caregivers group can be excluded from the HF validation testing.*
>
> *Current Agency guidance applying human factors and usability engineering to medical devices can be found at: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm259760.pdf*

Ariane Conrad, DMEPA, sent the following email on April 17, 2017:

> *I just wanted to follow up to let you know our findings regarding the HF report submitted for NDA 209196. We understand your review determined that the study participants were not representative of the population because type 1 diabetes patients and caregivers were not included in the study. You also indicated that this deficiency could be resolved without additional data if there is an agreement between the agency and DMEPA on the participant recruitment plan presented in the HF report.*
>
> *DMEPA agreed with Sanofi's proposed patient population during our review of the study protocol in 2015. Sanofi indicated that lay caregivers were not included in the study "because this user population is adequately represented by the patient population with no pen experience." and we agree that inexperienced users would not be expected to perform differently for this differentiation study. In addition, because this study was designed to test product differentiation instead of usability, we would not expect that patients with type 1 diabetes perform differently. Therefore, we determined that the patient population is adequate to support safe and effective use of this product.*

Xin Feng provided the following response:

> *Based on the information that you have provided, I do not need further data or information from the sponsor.*

Design Verification Review

Table 3 - Trace matrix for essential performance and safety requirements

Essential performance and safety requirement	Specification	Verification data	Accelerated aging / simulated shipping[a] (Yes/No)	Batch release testing[b] (Yes/No)
Cap removal force	The cap removal force shall be within a range of (b) (4) F (b) (4) N.	**Summative information:** Section 3.2.1 of (b) (4) **Verification report extracts:** Figure 1 and Figure 2 of (b) (4)	Yes	No
Needle compatibility	The pen injector shall be compatible with standard disposable needles that meet the requirements of the screw on/off test defined in EN ISO 11608-2, ie the screw-on torque is (b) (4) Nm and the screw-off torque is (b) (4) Nm.	**Summative information:** Section 3.2.2 of (b) (4) **Verification report extract:** Figure 3 of (b) (4)	Yes	No
Dial torque	The torque for dialing a dose and back-dialing shall be (b) (4) Nmm (mean peak) and (b) (4) Nmm (break-loose/end peak), respectively.	**Summative information:** Section 3.2.3 of (b) (4) **Verification report extracts:** Figure 4 and Figure 5 of (b) (4)	Yes	No
Dose number visibility	The dose numbers and marking lines shall be visible and legible at environmental lighting conditions of (b) (4) from a reading distance of (b) (4) cm (requirement for visual inspection - ISO 11608-1).	Verification has been performed as part of the dose accuracy tests according to ISO 11608-1 (see below)	Yes	No
Dose Accuracy	The quantity of medication injected must correspond to the dialed amount and shall match the dose accuracy requirements of ISO 11608-1:2014 at standard atmospheric conditions (b) (4) See (b) (4) for dose accuracy specification limits.	**Summative information:** (b) (4) **Verification report extracts:** Table 5 to Table 12 of (b) (4) **Statistical analysis of dose accuracy data:** Section 2 of (b) (4)	Yes	Yes

Essential performance and safety requirement	Specification	Verification data	Accelerated aging / simulated shipping[a] (Yes/No)	Batch release testing[b] (Yes/No)
Dispense force	The maximum dispense force shall be (b) (4) N.	**Summative information:** Section 3.2.6 of (b) (4) **Verification report extracts:** Figure 6 and Figure 7 of (b) (4)	Yes	No
Cap attachment force	The cap attachment force shall be (b) (4) N.	**Summative information:** Section 3.2.1 of (b) (4) **Verification report extracts:** Figure 1 and Figure 2 of (b) (4)	Yes	No
(b) (4)			(b) (4)	

Dose Accuracy Testing

Table 4 - Results of dose accuracy testing [µL] according to ISO 11608-1

Condition (determinations per V_{set})	Set dose V_{Set}	Min	Max	Mean value $\bar{x}$	Standard deviation s	LSL	USL	(b) (4)	Test result[a]
Standard atmosphere (b) (4)	(b) (4)								complies
									complies
									complies
Cool atmosphere (b) (4)									complies
									complies
									complies
Warm atmosphere (b) (4)									complies
									complies
									complies
Last dose (b) (4)									complies
Preconditioning by free-fall (b) (4)									complies
									complies
									complies
Preconditioning in dry-heat (b) (4)									complies
									complies
									complies
Preconditioning in cold-storage (b) (4)									complies
									complies
									complies
Preconditioning by vibration (b) (4)									complies
									complies
									complies

a Results are noted as "complies" if the test requirements according to ISO 11608-1 were fulfilled
LSL: lower specification limit
USL: upper specification limit
Tolerance limit factor *k* see Table 2

During testing for last dose accuracy, the pen injector was investigated for its ability to deliver the labeled volume from the insulin cartridge. Table 5 provides the range of volumes (in units), which were delivered from the cartridges under investigation. All values met or exceeded the given labeled volume of 300 units.

Table 5 - Deliverable volume (Units)

Test condition (determinations)	Min	Max	Test result
Deliverable volume (b) (4)		(b) (4)	complies

Biocompatibility Evaluation

Parts of the pen injector with potential skin contact were tested according to ISO 10993-1 under consideration of duration and type of contact.

Table 1 - Parts of the insulin lispro pen injector with body contact

Component	Material	Color	Printing
Pen cap	(b) (4)	Light yellow	-
Pen body		Light yellow	-
Injection button		Burgundy	-
Cartridge holder		Transparent	Black
Dosage selector		Burgundy	-
Number sleeve		Inherent (White)	Black
Thread insert		Transparent	-

Pen components with potential skin contact (Table 1) were subjected to the following biocompatibility tests in accordance with ISO 10993-1 Annex A, taking into consideration the classification of the pen as a "surface device", the nature of body contact (intact skin) and the limited duration of contact (≤ 24 h):

- *Cytotoxicity tests according to ISO 10993-5;*
- *Irritation (including intracutaneous reactivity) testing according to ISO 10993-10;*
- *Skin sensitization testing according to ISO 10993-10.*

The test protocols and test reports were included under 3.2.P.2. The test article was named- SAR342434 solution and included the following components: body, cap, thread insert, dial grip, dose button
- number sleeve
- cartridge holder

Endpoint	Test Method	Extraction and Test Method Acceptability	Test Result
Cytotoxicity	(b) (4)	Acceptable	(b) (4) **Pass**
Sensitization		Acceptable	(b) (4) **Pass**
Irritation		Acceptable	(b) (4) **Pass**

(b) (4)

(b) (4)


(b) (4)


(b) (4)

D. Risk Analysis

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		

Summary of Risk Analysis

Based on the task analysis and the risk identification conducted by the risk management team, all known and foreseeable causes leading to hazardous situations were included in the risk analysis as can be seen in Section 3.2.P.2.4 "Pharmaceutical development – Container closure system – Overview of the results of risk management". This includes potential use errors as well as technical defects (device malfunctions).

Prior to the implementation of risk control measures, a total of 79 causes leading to 319 hazardous situations could be identified (see Figure 3). Of those, 70 risks were rated as "not acceptable" (red region) and 159 risks were identified within the yellow region before implementation of risk control measures. The detailed analysis of the risks before implementation of risk control measures can be found in Section 3.2.P.2.4 "Pharmaceutical development – Container closure system – Overview of the results of risk management".

With the implemented risk control measures, no risks remain in the red (unacceptable) region. The majority of all risks were mitigated to the green (acceptable) region. Some risks (63 in total) remain in the yellow region.

The following primary operating functions and user tasks were used as the basis to identify potential use errors that can occur on each task (located under 3.2.P.2.4 in Container closure system - Risk Management Summary (b) (4)

(b) (4)

(b) (4)

E. Labeling

Read this first

(b) (4)

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

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

/s/

CALLIE C CAPPEL-LYNCH
07/17/2017

CONSULTING REVIEW MEMORANDUM

DATE:	July 5, 2017
TO:	Callie CappelLynch CDER/OND/ODEII/DMEP
FROM:	Joshua M. Balsam, Ph.D. CDRH/OIR/DCTD/DDDB
APPLICANT NAME:	Sanofi Group
SUBJECT:	NDA 209196 SAR342434, Insulin Lispro
RECOMMENDATION:	Outstanding Device Issue

Review Team:
Joshua Balsam – Lead Consulting Reviewer
Jisun Yi – Clinical Consult
Stayce Beck – Diabetes Division Branch Chief

Consult Description:
The NDA Lead Reviewer requested a consult from CDRH to assess two studies provided by Sanofi: 1) a clinical safety study conducted by Sanofi to support the safe use of their insulin in two currently marketed insulin pumps, and 2) a bench study to demonstrate insulin stability in two currently marketed insulin pumps.

Consult Conclusion:
Based on the information currently available, Sanofi has an outstanding device issue because there is not currently a legally marketed insulin pump in the US which lists their insulin product as being compatible. However, CDRH is willing to work with CDER and Sanofi in order to resolve this outstanding issue.

I. Submission Description:

Sanofi has submitted a 505(b)(2) NDA application for SAR342434 solution for injection (100 U/mL). Sanofi intends SAR342434 to be comparable to Humalog (insulin lispro solution, 100 U/mL, NDA 020563). Sanofi is seeking approval for several administration routes, one of which is continuous subcutaneous insulin

infusion (CSII) via body-worn infusion pump.

II. Bench Studies Conducted:

Sanofi has conducted bench testing to demonstrate that their insulin is safe for use in two currently marketed insulin pumps. This testing included the following studies:

- A 14-day insulin stability in simulated use conditions (subject of this consult)
- An extractables study of the pump reservoirs (reviewed by CMC)
- A leachables study of the pump reservoirs (reviewed by CMC)

Consult Comment: *The extractables and leachables studies are not the subject of this review. It was confirmed via email on April 7, 2017 that Muthukumar Ramaswamy (CMC consult on this file) had reviewed the extractables and leachables studies and concluded that the levels found in these studies were acceptable.*

Pump Stability Study Review

A stability study was performed to investigate and compare the stability profile of Sanofi's insulin lispro solution and commercialized Humalog solution from Eli Lilly in marketed insulin pump systems. Two prevalent marketed insulin pump systems have been used exemplarily for the study. Three lots of Sanofi's drug product solution have been tested, and one batch of Lilly's Humalog. Where possible, multiple lots of device components (insulin pumps and infusion sets) have been used.

A randomly chosen commercial batch of Lilly's Humalog and commercial scale batches of Sanofi's insulin lispro solution for injection in 10 mL glass vials (all batches released for clinical use), were used for performing the study.

For this study, two marketed insulin pumps, namely Animas Vibe and Medtronic MiniMed 530G Model 751, were tested.

(b) (4)

Pumping Conditions and Analytical Methods

In order to mimic in-use conditions, the filled pumps were placed for a total duration of 14 days onto a laboratory shaker at a defined temperature of +37°C and defined shaking amplitude of 60 rpm. Sampling took place after 3, 7, 10 and 14 days for the test items appearance, assay, related compounds and impurities, high molecular weight proteins (HMWPs), bioassay and pH, and after 14 days for the test items particulates and sterility.

Additionally, reference samples of Sanofi's drug product and Lilly's Humalog were placed onto the laboratory shaker at the defined temperature of +37°C was tested to document the changes of the stability profile due to temperature effects without pumping. The reference samples were contained in glass vials.

The following tests were performed during stability testing: appearance, assay, related compounds and impurities, HMWPs, bioassay, particulates, pH, and sterility. The same analytical procedures were used as for normal batch release

testing.

A dosing scheme, consisting of basal dosing combined with bolus dosing, was applied. The dosing rate scheme has been established in order to mimic the use in patients as closely as possible. A slow pump rate represents a continuous interaction between the drug product solution and the pump equipment and is therefore considered as worst case. A variable dosing-rate scheme was chosen to balance the need for insulin exposure to pumping with the reservoir capacity. At each sampling day, solution from multiple pumps was pooled to obtain sufficient amount of solution for the test program. For the testing of the parameters “sterility” and “particulates”, solution coming from only one pump each was used in order to avoid artefacts through contamination.

The table below provides the pump rate scheme used during this study:

(b) (4)

Consult Comment: *The pumping scheme that Sanofi has used here appears to be generally adequate to assess stability of their insulin product in a typical insulin pump under a reasonable worst-case scenario. Sanofi has*

selected the longest infusion set available for both pumps [redacted] *The environmental conditions* [redacted] *are also typical for this type of study based on a review of other recently cleared insulin pumps. The light conditions were clarified with Sanofi during interactive review: pumps were exposed to typical bright lab lighting conditions continuously during the 14 day period.*

It is noted that the basal rate used in this study [redacted] *is not the absolute lowest that either pump is capable of* [redacted] *However this rate is a reasonable compromise between insulin residence time, the restriction of the duration of the study (14 days), and the volume of insulin needed for analysis.*

It is also noted that the higher basal rate used for both pumps [redacted] *is different:* [redacted] *is used for the Medtronic pump and* [redacted] *is used for the Animas pump.* [redacted] *n both cases the pump rate and time is sufficient to evacuate all fluid from the infusion set* [redacted]

The MiniMed 530G pump is a threshold suspend pump which can suspend basal insulin delivery for up to 4 hours per day. Therefore this study should have included 4 hours of pump suspension (basal rate set to zero) per day in order to provide a better approximation of worst case use in that system.

[redacted]

Stability Study Results

The batches of insulin lispro solution for injection and Humalog showed a comparable stability profile in both pump types. After the14 days in-use period the tests for sterility were passed for all batches of insulin lispro solution and for Humalog, for both pumps. No occlusion events have been observed during the study. [redacted] all stability tests were passed.

[redacted]

Complete study results for one batch of Sanofi's insulin product are provided in the following tables:


(b) (4)

(b) (4)


(b) (4)


(b) (4)

Consult Comment: *The acceptance criteria in each case are the criteria for release, and the test methods in each case are the same test methods used during release testing. These acceptance criteria are the same as or tighter than the criteria used during the assessment of insulin stability in other recently cleared infusion pumps.* ***The consult defers to CDER for assessment of the release test methods.*** *The tables above demonstrate that acceptance criteria were met for all test items*

(b) (4)

(b) (4)

(b) (4)

(b) (4)

found to be acceptable.

III. Clinical Study

Consulting reviewer: Jisun Yi, M.D. (CDRH/OIR/DCTD)

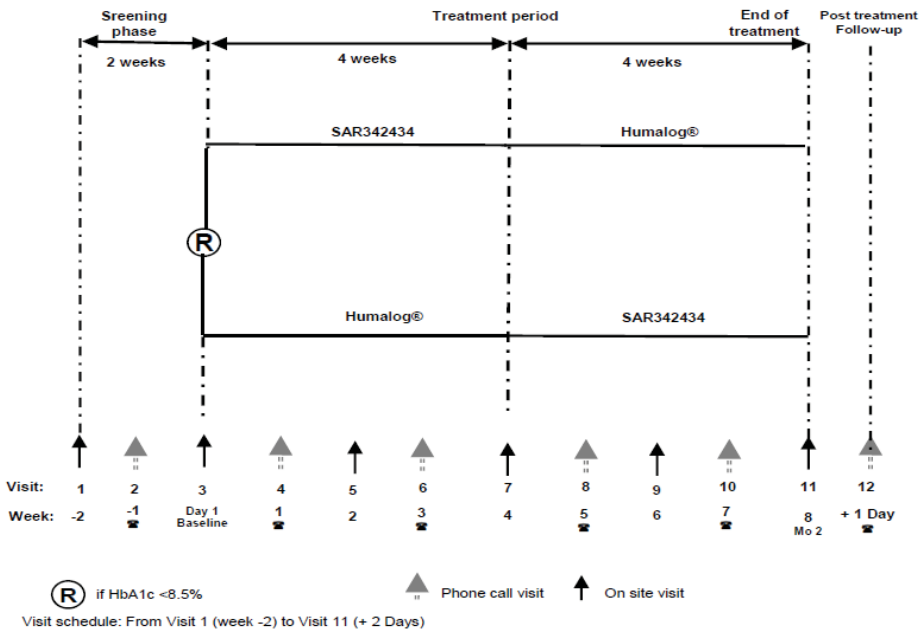
Consult Recommendation: *Outstanding device issue for SAR342434 U-100 insulin for use with insulin (CSII) pump(s), pending:*

(b) (4)

Study PDY13502 was a randomized, active-controlled, 2x4 week, open-label, comparative 2-treatment arm, 2-period crossover study in adult patients with T1DM conducted to compare the safety of SAR342434 and Humalog when used in external pumps. The primary safety outcome assessed was the incidence of infusion set occlusions defined as failure to correct hyperglycemia (plasma glucose ≥300 mg/dL) by insulin bolus via the insulin pump (excluding pump malfunction).

The treatment, either SAR342434 or Humalog US, was administered as solutions for injection containing 100 U/mL insulin lispro. The dose was individually titrated and self-administered at a basal rate and in bolus as guided by the Investigators. Each treatment period was 4 weeks, followed by a cross-over to either SAR342434 or Humalog, for another 4 weeks as illustrated in Figure 1 (below).

Figure 1 - Study design



Up to 28 patients were planned to enter the study in order to have 24 that complete the study. Patients were randomized 1:1 to receive SAR342434 then Humalog; or Humalog then SAR342434.

For each participant, the total study duration from screening through the post-study visit was 10 weeks:
• Screening: 14 days (+7 day visit window).
• Treatment periods: 28 days for each of the two treatment periods (±2 days for each visit).
• Post-study visit: 1 day after end of the second dosing period.

No interactive voice response system/interactive web response system was used for this study.
An ARAC was to adjudicate all allergic or possible allergic reactions occurring during the study.

Objectives:
The **main objective** of the study was to assess the safety of SAR342434 and Humalog when used in external pumps in terms of the incidence of infusion set occlusions. Infusion set occlusions is defined as failure to correct hyperglycemia (plasma glucose ≥ 16.7 mmol/L [300mg/dL]) by insulin bolus via the insulin pump.

The **secondary objectives** were to assess the safety of SAR342434 and Humalog used in CSII as determined by:

- Intervals for infusion set changes, either;
  - on a routine basis or
  - when occlusion occurred or was suspected, or
  - based on adverse events
- Incidence of insulin pump alarms for infusion set occlusion (independent of confirmation of occlusion by hyperglycemia and failure to correct hyperglycemia by insulin bolus via the insulin pump)
- Patient observation of infusion set occlusion recorded in patient diary (independent of confirmation of occlusion by hyperglycemia and failure to correct hyperglycemia by insulin bolus via the insulin pump)
- Adverse and serious adverse events including bruising at the infusion site, injection site and hypersensitivity reactions
- Incidence of hypoglycemic events (according to American Diabetes Association [ADA] Workgroup on Hypoglycemia)

Treatments Administered:

Investigational medicinal product (1): SAR342434 (insulin lispro)

- Formulation: Solution for injection containing 100 U/mL insulin lispro
- Route(s) of administration: Continuous subcutaneous insulin infusion (CSII) via a pump
- Dose regimen: Individually titrated to achieve the plasma glucose target: pre-prandial 3.9–7.2 mmol/L (70–130 mg/dL), postprandial <10.0 mmol/L (<180 mg/dL)

Investigational medicinal product (2): Humalog-U.S.

- Formulation: Solution for injection containing 100 U/mL insulin lispro
- Route(s) of administration: Continuous subcutaneous insulin infusion (CSII) via a pump
- Dose regimen: Individually titrated to achieve the plasma glucose target: pre-prandial 3.9–7.2 mmol/L (70–130 mg/dL), postprandial <10.0 mmol/L (<180 mg/dL)

The IMPs, SAR342434 and Humalog US were supplied as solutions for injection containing 100U/mL insulin lispro each.

The IMP was individually titrated and administered at a basal rate and in bolus doses via the patient's own insulin infusion pump: Medtronic 530G Model 751, or any other Medtronic pump with a 3 mL reservoir, or Animas Vibe or OneTouch Ping. The "Threshold Suspend" function (the suspension of insulin

basal rate delivery when a select low blood glucose threshold is reached) on the Medtronic pumps was not utilized during the study. Animas pumps used in the study do not have a similar function. Patients were instructed to change the infusion sets no later than every three days. The IMP in the insulin pump reservoir was changed at least once every 7 days, in accordance with the Humalog label.

Duration of observation:
For each participant, the total study duration from screening through the post-study visit was 10 weeks:

- Screening: 14 days (+7 day visit window)
- Treatment periods: 28 days for each of two treatment periods (±2 days for each visit)
- Post-study visit : 1 day after end of the second dosing period

Main safety parameter
The main safety parameter was the infusion set occlusion, defined as failure to correct hyperglycemia (plasma glucose ≥16.7 mmol/L [300 mg/dL]) by insulin bolus via the insulin pump. It was recorded in e-CRF with “Unexplained plasma glucose” as the primary reason and “Infusion set occlusion” in the specified field. In case of pump malfunction, the incidence was recorded in e-CRF with “Unexplained plasma glucose” as the primary reason and “Pump malfunction” in the specified field and was not counted as the main safety parameter.

Secondary safety parameters
The secondary safety parameters were:

• Average interval for infusion set changes: derived individually per treatment period as number of days in the treatment period divided by the number of infusion set changes in the treatment period. The calculation was performed for any infusion set change (regardless of the reason) and separately for:

- Infusion set changes performed on a routine basis (infusion set changes with “Scheduled infusion set change” recorded as the primary reason).

- Infusion set changes when occlusion occurred or was suspected (infusion set changes with “Unexplained plasma glucose” recorded as the primary reason and “Infusion set occlusion” in the specified field, or infusion set changes with “Pump alarm for infusion set occlusion” or “Visual infusion set occlusion” recorded as the primary

reason).

- Infusion set changes based on pump malfunction (infusion set changes with “Unexplained plasma glucose” recorded as the primary reason and “Pump malfunction” in the specified field).

- Infusion set changes based on adverse events (infusion set changes with “Pain or swelling at infusion site” recorded as the primary reason).

• Insulin pump alarms for infusion set occlusion (independent of confirmation of occlusion by hyperglycemia and failure to correct hyperglycemia by insulin bolus via the insulin pump): derived from infusion set changes with “Pump alarm for infusion set occlusion” recorded as the primary reason.

• Patient observation of infusion set occlusion (independent of confirmation of occlusion by hyperglycemia and failure to correct hyperglycemia by insulin bolus via the insulin pump): derived from infusion set changes with “Visual infusion set occlusion” recorded as the primary reason.

Disposition of Patients

A total of 27 patients with T1DM were randomized and treated. Of the 27 patients, 13 were treated with SAR342434 during the first 4-week study period, then treated with Humalog during the second 4-week study period (SAR342434/Humalog group); 14 received Humalog during the first 4-week study period, then SAR342434 during the second 4-week study period (Humalog/SAR342434 group).

Regardless of the treatment sequence, patients who were receiving SAR342434 were considered to be in the SAR342434 treatment group; similarly, the Humalog treatment group consisted of patients who were on Humalog regardless of the treatment sequence.

Three (3) patients (all in the Humalog arm) did not complete the study (Table 6). All 3 patients

• One (1) patient in the SAR342434/Humalog group discontinued during the second treatment period while on Humalog due to poor protocol compliance (failure to return the patient diary);

• Two (2) patients in the Humalog/SAR342434 group discontinued during the first treatment period while on Humalog; 1 voluntarily withdrew and another experienced SAEs.

Clinical Study Discussion

This 2x4-week crossover study (PDY13502) assessed the safety of SAR342434, a follow-on product to insulin lispro, and Humalog, when used in external pumps in terms of the incidence of infusion set occlusions. The definition of infusion set occlusions was appropriately designated as failure to correct hyperglycemia ≥ 300 mg/dL within 60 minutes by insulin bolus via the insulin pump. The objective for performing this study was to demonstrate that sAR342434 can be safely administered by CSII via external insulin pumps in patients with Type 1 Diabetes Mellitus.

This study was performed at 2 sites in the United States. The majority of patients utilized Medtronic insulin pumps (81.5%) versus Animas pumps (18.5%). The “Threshold Suspend” function on the Medtronic pumps was not utilized during the study, and the Animas pumps do not have a similar function.

Although there were more reports of infusion set occlusions during the treatment periods in the SAR342434 group compared to the Humalog group, as well as more patients who experienced infusion set occlusions when receiving treatment with SAR342434, compared to Humalog, these reported differences are unlikely to have clinical significance for several reasons. Firstly, none of these infusion set occlusions were reported to lead to DKA, so there was no associated clinical adverse event linked to any of these reports of infusion set occlusion. Further, the higher number of infusion set occlusions reported during treatment with SAR342434 were due to two more patients receiving SAR342434 who reported at least one infusion set occlusion. Further, given the limited size of the study population (27 patients), and the limited number of events in the study, the 95% confidence intervals surrounding the number of patients with at least one infusion set occlusion within each treatment group are wide, and cross, and the risk difference between the treatment groups also is wide, and crosses zero. Further, the sponsor has calculated the predictive probability of observing 2 or more patients with occlusions in the SAR342434 group than the Humalog group, assuming the same true rate (of occlusions), as at least 24%. Thus, although the reported number of infusion set occlusions and number of patients who experienced infusion set occlusions was higher, it is not possible to conclude from this study, that use of SAR342434 is associated with a truly higher risk of infusion set occlusion compared to Humalog. Although the low number of patients with infusion set occlusions during the SAR342434 period makes the interpretation of the data difficult, the results of the study do not suggest a difference in the risk of infusion set occlusion with SAR342434 and Humalog when used in CSII.

The overall incidence of treatment emergent adverse events was similar between the two groups, and there were no reports of allergic or hypersensitivity reactions during the study treatment phase. In addition, there were no reports of diabetic ketoacidosis or severe hypoglycemia during the study treatment phase. Thus, there does not appear to be a safety concern relating to other adverse events during the study treatment phase.
The proposed labeling specifying up to 3 days of infusion set wear (and infusion site change) as well as insulin change in reservoir at least every 7 days are supported by the insulin pump stability study and the insulin pump clinical safety study (PDY13502).

Clinical Recommendation
I have reviewed the relevant data provided in this NDA (NDA 209196) regarding the safety of SAR342434 for clinical use in insulin infusion pumps. I have made comments regarding the clinical study performed to support the safety of SAR342434 for use in insulin infusion pumps.

Based on the review and considerations discussed above, I recommend that SAR342434 receive Conditional Approval for SAR342434 U-100 insulin for use with insulin (CSII) pump(s), pending:

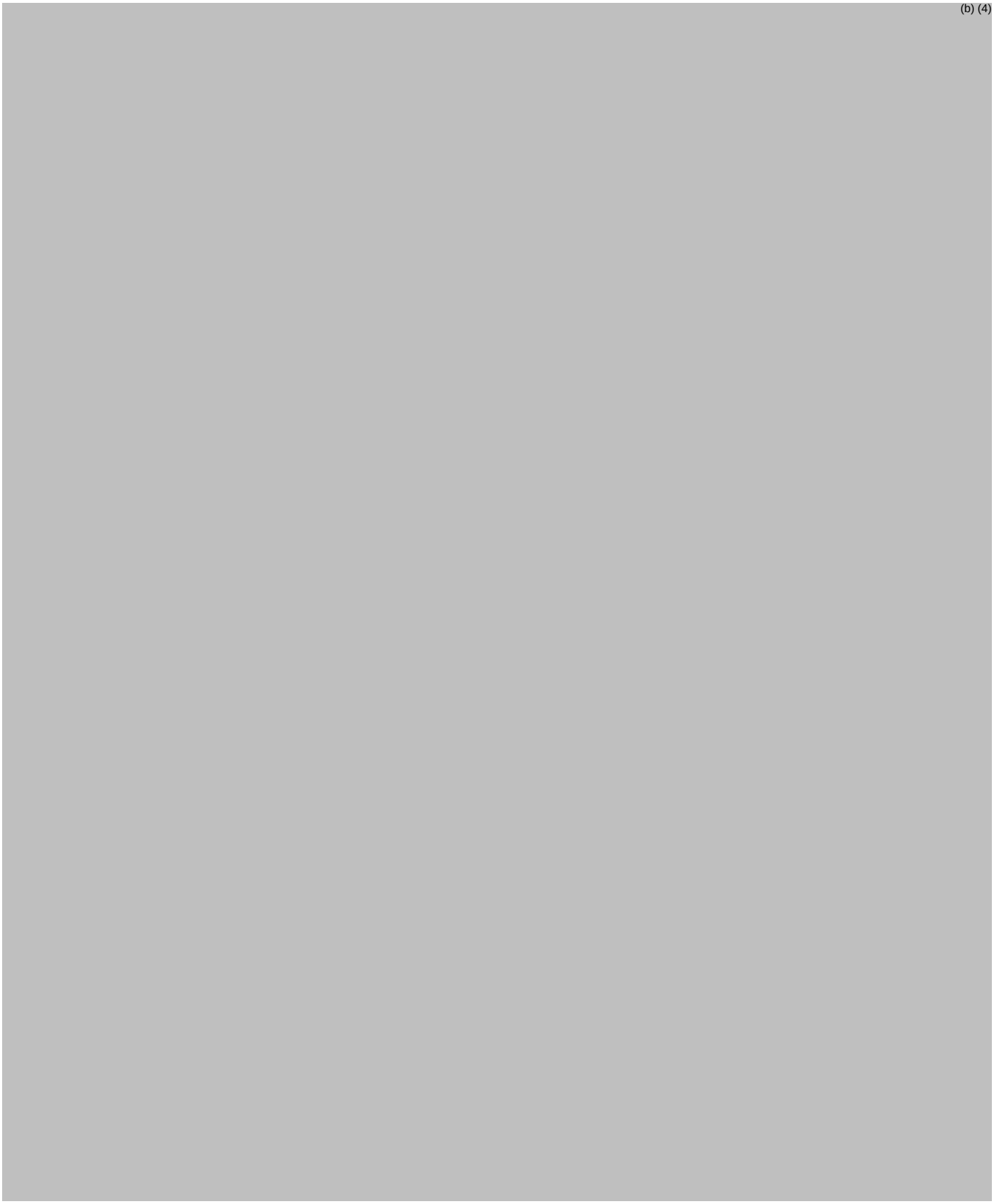
i) Inclusion of SAR342434 in labeling of at least one approved or cleared insulin pump by the time of NDA approval
ii) Agreement on labeling with CDER and Office of Combination Products (OCP)

IV. Communication with Sponsor:

(b) (4)

The following written feedback was provided to the sponsor:

(b) (4)


(b) (4)

FDA INFORMATION REQUEST DATED 10 JANUARY 2017
Provide an assessment of photostability of your drug product per ICH Q1B in the two representative infusion pumps you have previously identified. Testing should be conducted using worst-case delivery settings (i.e. slowest programmable basal delivery rate and longest typically available infusion sets).

Sanofi Response
As demonstrated in photostability studies according to ICH Q1B on the drug product, insulin lispro solution for injection is photosensitive and degrades under the conditions as outlined in the guideline. Therefore, the drug product has to be stored protected from light. Further information on the photostability can be found in sections 3.2.P.8.1. Stability Summary and Conclusion and 3.2.P.8.3 Stability Data.

Since insulins are known to be photosensitive, a test design was chosen matching as far as possible the patient use, ie. the insulin solution was exposed to room light under in-use study conditions for the pump infusion.

The experiments in the infusion pumps outlined in the dossier in Section 3.2.P.2.6 were performed at room light over 14 days. This setting is

considered realistic for the patient use since the infusion will occur at ambient light for limited durations (b) (4) .

A slow continuous flow through the pump system was chosen which represents a continuous interaction between the drug product solution and the plastic surface of the pump cartridge and infusion set.

A dosing scheme, consisting of basal dosing combined with bolus dosing, is applied. The dosing rate scheme has been established in order to mimic the use in patients as closely as possible. A slow pump rate is considered as worst case. A variable dosing-rate scheme was chosen to balance the need for insulin lispro exposure to pumping across the 14-day period with the reservoir capacity.

The batches of insulin lispro solution for injection and Humalog showed a similar stability profile in the tested pump types, as well as in photostability studies performed with cartridges and vials. Therefore, Sanofi proposes the identical label information as Humalog.

Consult Comment: *This response is adequate. Sanofi clarified that the insulin compatibility study was conducted under continuous exposure to room-light for the duration of the 14 day study. This study design was compared to studies used to support clearance of other recent insulin pumps and was found to be a similar or higher level of light exposure.*

FDA INFORMATION REQUEST DATED 10 MARCH 2017

In your clinical study report, PDY13502, you have reported a higher number of infusion set occlusions in the SAR342434 group compared to the Humalog group, particularly in the second treatment period. From the information you have provided, it is unclear whether there may have been other factors that may have contributed to infusion set occlusions. Please provide clarification regarding the following:

REQUEST NO. 1

You have provided information (PDY13502-16-2-7-ae-data, page 21 of 134) that the average interval of infusion set changes (in days) when occlusion occurs due to failure to correct hyperglycemia was a mean of 16.44 days with SAR342434 and 18.73 days with Humalog. This reported interval of infusion set changes is significantly beyond the 3 day intended use period for insulin pump infusion sets. Please provide line data from your study (which includes the duration of wear of

each infusion set all subjects in the study and highlight those subjects reporting with any infusion set occlusion; failure to correct or alarm) to help clarify whether utilization of the infusion sets beyond the intended use period may have contributed to the higher number of infusion set occlusions in the SAR342434 group, particularly during the second treatment period. Alternatively the subject's log/diary can be provided.

You have reported that "*The total number of infusion set occlusion events during the on treatment period was 23, with 14 occurring while receiving SAR342434 and 9 while receiving Humalog (Table 14). Only 1/23 event occurred >3 days (3.13 days) after a previous infusion set change (patient* (b) (6) *on Humalog during the 2nd treatment period).*" This statement appears to conflict with the data as presented in which, as stated above, the occlusions appeared to occur after the required period of infusion set change (every 3 days). Please provide clarification of this statement.

Sanofi response:
In study PDY13502 patients were instructed per protocol to change their infusion set no later than every 3 days, which is in agreement with the Humalog US Prescribing Information. The listing of infusion set changes was included in appendix 16.2.7.4 of the clinical study report PDY13502 submitted in the original NDA 209196 (Sequence 0000).

Mean intervals for infusion set changes were analyzed for any infusion set change, regardless the cause, and for infusion set changes due to infusion set occlusions defined as failure to correct hyperglycemia (plasma glucose ≥300 mg/dL) by insulin bolus via the insulin pump:

- The mean interval between infusion set changes independent of the cause for infusion set change observed in the study was 3.09 (SD 0.97) days for SAR342434 and 2.95 (SD 0.78) days for Humalog. This result is driven by the intervals between the regular infusion set changes and consistent with the recommendation to change infusion sets after 3 days at the latest.

- The mean intervals of 16.44 and 18.73 days refer to the intervals between infusions set changes that were due only to infusion set occlusions defined as failure to correct hyperglycemia (plasma glucose ≥300 mg/dL) by insulin bolus via the insulin pump. This analysis is independent of the regular infusion set changes and does therefore not support the conclusion that the occlusions occurred after the required period of infusion set change every 3 days. Indeed, as shown in Table 1, all but one infusion set occlusion in the Humalog group occurred within the 3-day wear period.

Line data of all infusion set changes presenting the duration of wear of each infusion set and the reason for infusion set change is provided in Appendix.

Table 1 - Duration of wear (days) of each infusion set when infusion set occlusion occurred

SAR342434		Humalog	
Patient number / date of infusion set change	**Duration of wear (days)**	**Patient number / date of infusion set change**	**Duration of wear (days)**
(b) (6)	2.13	(b) (6)	3.13
	0.39		1.06
	0.17		0.98
	1.62		2.97
	0.18		2.04
	1.90		0.09
	2.51		2.64
	0.60		2.77
	3.00		0.67
	0.31		
	0.15		
	0.27		
	1.11		
	0.11		

Clinical Consult Comment: *The sponsor provided clarification that the reported analysis of average interval of infusion set changes (in days) when occlusion occurs due to failure to correct hyperglycemia was a mean of 16.44 days with SAR342434 and 18.73 days with Humalog reported in both treatment groups is independent of the regular infusion set changes and does therefore not support the conclusion that the occlusions occurred after the required period of infusion set change every 3 days. The sponsor provided additional data regarding the duration of wear of each infusion set when occlusion occurred. This response is acceptable.*

REQUEST NO. 2

It is unclear from reviewing your study report as well as relevant appendices, if

lower insulin infusion rates may have contributed to the higher number of infusion set occlusions reported in the SAR342434 group, particularly during the second treatment period. Please provide information regarding the (mean) total daily dose of insulin used
during each treatment period per subject; identify the insulin used at each period and if an occlusion (failure to correct or alarm) occurred during that period.

Sanofi response:
Neither the insulin doses nor the infusion rates were reported in study PDY13502. The higher number of infusion set occlusions reported in the SAR342434 group are attributed to two patients (No. 840002001; No. 840002017) who reported infusion set occlusions under SAR342434 only ("discordant responses") and caused the numerical difference between treatments with 6/25 (24.0%) patients with infusion set occlusions while receiving SAR342434 and 4/27 (14.8%) patients while on Humalog. One of the 2 patients (No. 840002001 randomized to the treatment sequence SAR342434/Humalog) with a discordant response reported an unexplained hyperglycemia with a blood glucose value of 24.7 mmol/L (445 mg/dL). As plasma glucose had not fallen by at least 2.8 mmol/L (50 mg/dL) and to <16.7 mmol/L (300 mg/dL) after insulin bolus administration, the criteria for infusion set occlusion were met and following the study protocol, the infusion set was changed. Three hours after infusion set change plasma glucose was re-checked and was 24.7 mmol/L (444 mg/dL). The event only resolved after the pump reservoir was refilled. Blood glucose was checked again 6 hours after infusion set change and was 8.8 mmol/L (158 mg/dL). Therefore
the blood glucose value measured prior to infusion set change might not have been related to infusion set occlusion but to other factors such as an empty reservoir. However, taken the most conservative approach this event was counted as infusion set occlusion, because it met the criteria of the definition of infusion set occlusion.

Although the low number of patients with a discordant outcome make the interpretation of the data difficult, the results do not suggest a difference in the risk of infusion set occlusion with SAR342434 and Humalog as all of these patients completed the study as planned, no patient reported any adverse events linked to any occlusion event and no event of ketoacidosis was reported.

Clinical Consult Comment: *The sponsor has clarified that the insulin doses and infusion rates were not reported in study PDY13502. It remains unclear whether lower insulin infusion rates could have contributed to the higher number of infusion set occlusions (attributable largely to two patients in the SAR342434 group) that were reported in the SAR342434 group. This*

response is acceptable.

REQUEST NO. 3

You have reported that one patient died during the study – subject (b) (6) Please provide the full CRF for this patient, including the patient log/diary. (Or provide information as to where this information is contained within the NDA submission).

Sanofi response:

(b) (6)

REQUEST NO. 4

(b) (6)

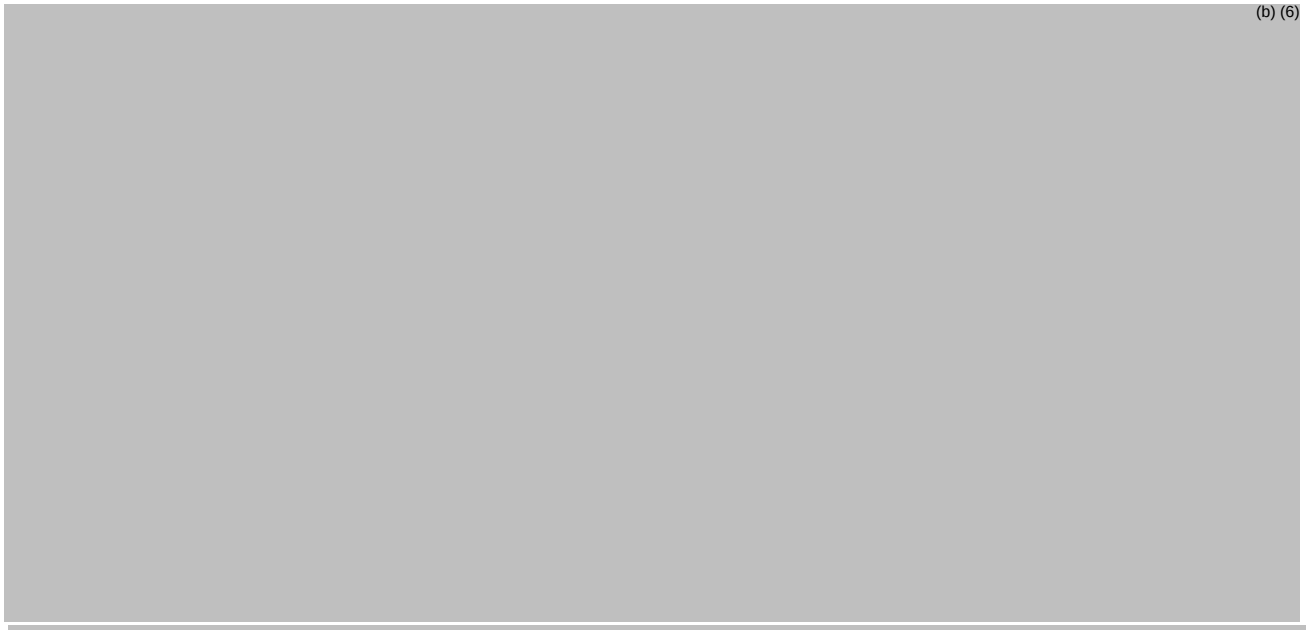
(b) (6)

Clinical Consult Comment: *The sponsor has provided clarification that blood glucose values (and not continuous glucose monitor glucose values) were used in determination of the safety endpoints. The sponsor has confirmed that the insulin bolus was administered according to the bolus calculator in the pump system, and based on the subject's insulin sensitivity factor. This response is acceptable.*

(b) (6)

(b) (6)


(b) (6)


(b) (6)


(b) (6)

(b) (6)

Joshua Balsam -S
2017.07.05 10:50:54 -04'00'

Joshua M. Balsam, Ph.D.

Stayce Beck -S
2017.07.05 10:54:58 -04'00'

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

/s/

CALLIE C CAPPEL-LYNCH
07/05/2017
signing for Joshua Balsam

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)

Date: June 7, 2017

To: Muthukumar Ramaswamy, CDER/ONDP/DNDPII/NDPBVI, E-mail: Muthukumar.Ramaswamy@fda.hhs.gov

CDER/OPQ/OPF: Juandria.Williams@fda.hhs.gov

Office of Combination Product at: combination@fda.gov

From: Jamie Kamon-Brancazio, REGO/DMQ/OC, CDRH, WO 66, Rm 3427, E-mail: Jamie.Kamon-Brancazio@fda.hhs.gov

Jamie Kamon-brancazio -A

Digitally signed by Jamie Kamon brancazio -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001568505, cn=Jamie Kamon brancazio -A
Date: 2017.06.27 21:36:07 -04'00'

Applicant: (b) (4).

Application #: NDA 209196

Insulin lispro solution for injection

Product Name: Site Inspection Review

(b) (4)

The Office of Compliance at CDRH received a consult request from CDER to evaluate NDA 209196, to review the results of the device constituent manufacturing inspection and to review the 21 CFR 820 requirements of the combination product.

Site inspection evaluation

A drug inspection was performed at the (b) (4) manufacturing facility in (b) (4). (b) (4) The current inspection revealed no deficiencies and a 483 was not issued to the firm.

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application NDA 209196 and has the following recommendations:

CDRH recommends approval for NDA 209196 based on the status of the recent inspection at (b) (4) This inspection was classified NAI and a 483 was not issued to the firm.

The desk review of the responses provide for compliance with the Medical Device Regulations showed no deficiencies, CDRH would recommend a review of the final validation data collected on the final combination product post-approval.

Crystal Lewis -S

Digitally signed by Crystal Lewis -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Crystal Lewis -S, 0.9.2342.19200300.100.1.1=2000430186
Date: 2017.06.07 11:17:37 -04'00'

Crystal Lewis

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
06/29/2017
Uploading on behalf of Crystal Lewis.

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 # 209196	NDA Supplement #: S- 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: TBD Established/Proper Name: insulin lispro Dosage Form: injection Strengths: 100 units/mL Route(s) of Administration: subcutaneous injection, continuous subcutaneous infusion, and intravenous infusion		
Applicant: Sanofi-aventis U.S., LLC Agent for Applicant (if applicable): N/A		
Date of Application: November 1, 2016 Date of Receipt: November 1, 2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: September 1, 2017	Action Goal Date (if different): same	
Filing Date: December 31, 2016	Date of Filing Meeting: December 19, 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 ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): to improve glycemic control in adults and children with diabetes mellitus		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: 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): 120511	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***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 electronic archive? ***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 electronic archive.***	☒	☐		

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:	☐	☐	X	
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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	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. Contact the User Fee Staff. If appropriate, send UN letter.	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 and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** *http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm* **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*	☐	☐		The applicant identified Humalog as the listed drug relied upon, and provided an appropriate patent certification or statement.

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)(14)]**? ***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: 3 ***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: ☒ 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?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

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, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in 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] ***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]	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

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 (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (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 Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☐ ☐	☒ ☒	☐ ☐	Will include comment in 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 PLLR format before the filing date.***	☐	☒	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576 htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/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 ☐ 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 OIR and GHDB were both consulted.
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** October 6, 2014	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** March 23, 2016	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐	X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 19, 2016

BACKGROUND: Sanofi has submitted NDA 209196 as a 505(b)(2) NDA for insulin lispro relying on finding of safety and efficacy of NDA 20563 for Humalog.

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)	William Chong		Y
Division Director/Deputy	Jean-Marc Guettier		Y
Office Director/Deputy	Curtis Rosebraugh		N
Clinical	Reviewer:	Sonia Doi	Y
	TL:	William Chong	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:	Johnny Lau	N
	TL:	Manoj Khurana	Y
• Genomics	Reviewer:	NN	
• Pharmacometrics	Reviewer:	NN	
Biostatistics	Reviewer:	Roberto Crackel	Y
	TL:	Mark Rothmann	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Dan Minck	Y
	TL:	Ron Wange	N
Statistics (carcinogenicity)	Reviewer:	NN	
	TL:	NN	
Product Quality (CMC) Review Team:	ATL:	Muthukumar Ramaswamy	Y
	RBPM:	Anika Lalmansingh	Y
• Drug Substance	Reviewer:	Xavier Ysern	N
• Drug Product	Reviewer:	Muthu Ramaswamy	N
• Process	Reviewer:	Khalid Khan	N
• Microbiology	Reviewer:	Zachary Cusumano	N
• Facility	Reviewer:	Krishna Ghosh	N
• Biopharmaceutics	Reviewer:	NN	
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Sharon Williams	N
	TL:	Shawna Hutchins	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Ankur Kalola	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Adriane Conrad	Y
	TL:	Hina Mehta	N
OSE/DRISK (REMS)	Reviewer:	Naomi Redd	N
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NN	
	TL:	NN	

Bioresearch Monitoring (OSI)	Reviewer:	NN	
	TL:	NN	
Controlled Substance Staff (CSS)	Reviewer:	NN	
	TL:	NN	
Other reviewers/disciplines			
CDRH	Reviewer:	OIR -Jisun Yi and Josh Balsam GHDB- Sarah Mollo	Y
	TL:	OIR Adrea Bell-Vlasov GHDB – Alan Stevens	N
Other attendees	Terrolyn Thomas- RPM OSE		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues:	☐ Not Applicable
o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
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):	1 clinical pharmacology study and 2 phase 3 studies were conducted to provide proof of similarity
• 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**: request PLLR compliant labeling	☐ 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**: request PLLR compliant labeling	☐ 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
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**: CDRH compliance is not recommending device inspection	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ 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 **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): April 5, 2017	
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- consult OBP, consult OSIS

Annual review of template by OND ADRAs completed: April 2016

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

/s/

CALLIE C CAPPEL-LYNCH
05/03/2017

LABEL AND LABELING AND HUMAN FACTORS RESULTS 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:	April 19, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209196
Product Name and Strength:	Admelog, insulin lispro, injection, 100 units/mL, 1000 units per 10 mL vial Admelog SoloStar, insulin lispro, injection, 100 units/mL,300 units per 3 mL pen
Product Type:	Single ingredient Single ingredient and Combination product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sanofi-Aventis
Submission Date:	November 1, 2016 and February 3, 2017
OSE RCM #:	2016-2516 and 2017-210
DMEPA Primary Reviewer:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested that DMEPA evaluate the human factors (HF) study report and proposed labels and labeling submitted under NDA 209196 for Admelog (insulin lispro) as part of the evaluation of the 505(b)(2) submission. The reference listed drug (Humalog, NDA 020563) was approved June 14, 1996.

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	C
Information Requests	D
Center for Devices and Radiological Health (CDRH) Human Factors Review	E
Labels and Labeling	F

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Sanofi-Aventis submitted NDA 209196 for Admelog, which will be supplied in a multiple dose vial and a disposable multiple dose pen injector containing 100 units/mL of insulin lispro, to improve glycemic control in adults and children with diabetes mellitus. The pen injector will use the currently marketed SoloStar platform approved for use for the administration of other Sanofi insulin products (i.e., Lantus SoloStar, Toujeo SoloStar, Apidra SoloStar).

DMEPA reviewed the human factors study results for the pen injector and the proposed labeling submitted by Sanofi for both the pen and vial preparations on November 1, 2016.[a] We agreed with Sanofi's strategy in terms of performing a differentiation study and we also agreed with the objectives and the methodology for the proposed differentiation study. On February 9, 2017, we consulted Center for Devices and Radiological Health (CDRH) Human Factors (HF) team to evaluate the report and to provide additional input from a device perspective. The CDRH HF team determined that the study participants are not representative of intended user

[a] Vee S. Human Factors Protocol Review for insulin lispro (IND 120511). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Nov 20. RCM No. 2015-2309.

population.[b] However, we agreed with Sanofi's proposed patient population during our review of the study protocol.[a] Sanofi indicated that lay caregivers were not included in the study "because this user population is adequately represented by the patient population with no pen experience." and we agree that inexperienced users would not be expected to perform differently for this differentiation study. In addition, because this study was designed to test product differentiation instead of usability, we would not expect that patients with type 1 diabetes perform differently. Therefore, we determined that the patient population is adequate to support safe and effective use of this product. On April 17, 2017, we communicated our conclusion regarding the adequacy of the data to the CDRH HF team and they agreed with our conclusion.

In addition, 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.

3.1 HUMAN FACTORS VALIDATION STUDY

Methodology

Sanofi-Aventis conducted a human factors differentiation study for Admelog. We previously reviewed the study protocol and provided written responses under IND 120511.[a] We confirmed that most of our comments for the study protocol were implemented; however, the sponsor did not fully implement the modifications recommended for the moderator script. Of note, we indicated that the proposed language would prompt participants to pay more attention to the visual cues for the pen injector than they may in actual use of the product and would not be representative of a real-world environment. We acknowledge that the sponsor did modify the moderator script; however, prompting statements like (b) (4) were still included in the script. We believe that this language is not representative of a real-world environment and may introduce bias; however, we determined that it is unlikely that Sanofi's use of this language had a negative impact on the study results.

The sponsor conducted two studies to evaluate pen and carton differentiation since the sponsor was relying on post-marketing data and previous HF validation studies for the currently marketed SoloStar pen injectors to confirm that the intended users can safely and effectively complete the injection process (e.g., dialing and administering a dose).

The first study was conducted with 60 participants (30 patients with type 2 diabetes, 15 nurses that train and treat patients with type 2 diabetes, and 15 dispensing pharmacists) and focused on pen and carton differentiation. The cartons and pens used in this study were labeled using the name (b) (4) Pharmacists were asked to select the correct product carton from a selection of comparator boxes based on a simulated prescription. Patients and nurses

[b] Mollo S. Human Factors Consult Memo for insulin lispro. Silver Spring (MD): FDA, CDRH, ODE, DAGRID, GHDB (US); 2017 Mar 10. NDA 209196.

(b) (4)

were asked to select the correct product carton and pen injector from a selection of comparator products based on a simulated prescription. This scenario was performed twice, each time the target pen was presented with two different sets of five comparators.

The second study was conducted with 45 participants (30 patients with type 2 diabetes and 15 nurses that train and treat patients with type 2 diabetes) and focused on pen differentiation. The pens for this study were labeled using the name Admelog SoloStar.[c] Patients and nurses were shown the Admelog SoloStar pen and then asked to select the correct pen injector from a selection of comparator products based its appearance rather than a prescription. This scenario was performed twice, each time the target pen was presented with two different sets of five comparators.

None of the study participants received training.

Results

Study I:

Fifteen pharmacists were presented with a prescription for (b) (4) and tasked to select the product carton. Fourteen pharmacists selected the correct product carton. One pharmacist selected the wrong product because she confused the names (b) (4) and "SoloStar," which lead her to select the Lantus SoloStar carton. The sponsor determined that this error is a study artifact because the error was due to the placeholder name used in the study and we agree with this assessment.

Thirty patients and fifteen nurses were presented with a prescription for (b) (4) and tasked to select the product cartons. Twenty-nine of the patients and all fifteen nurses selected the correct product carton. One patient confused the names (b) (4) and "SoloStar" and selected the Toujeo SoloStar packaging in error. This error was determined to be a study artifact and we agree with this assessment.

For the pen differentiation portion of this study the same participants (patients and nurses) were tasked to also select the correct pen. There was one error in which the patient (of note, it was not the same patient that selected the wrong product carton) chose the target pen when completing the task the first time (b) (4) but chose an incorrect pen when the task was repeated. This patient was confused because of the repetition of the task (selecting a pen injector twice in a row) and deliberately selected a different pen injector from the one initially selected. We consider this error to be an artifact of the study design.

Study II:

There were no use errors in this portion of the study. All of the nurse and patient participants identified the correct pen injector so we do not have any concerns regarding pen differentiation.

3.2 LABELS AND LABELING

In addition to the human factors study evaluation, DMEPA reviewed the proposed labels and labeling for Admelog to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We noted several areas that could be clarified within the proposed labels and labeling. We provide recommendations in section 4.1 and 4.2.

4 CONCLUSION & RECOMMENDATIONS

The HF differentiation study results are acceptable. We have provided recommendations for the proposed labeling to improve clarity.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)
    1. Highlights of Prescribing Information
        a. Remove the word (b) (4) from the phrase "TRADENAME (insulin lispro for injection)" (b) (4) (b) (4) Rephrase to state "TRADENAME (insulin lispro injection)".
    2. Full Prescribing Information-Section 16.2 Storage and Handling
        a. For consistency with the Humalog PI, we recommend including the following statement in the section titled "Use in an External Insulin Pump": "Insulin in the reservoir should be discarded after 7 days. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion set insertion site should be selected at least every 3 days."
B. Instructions for Use (IFU)-SoloStar pen
    1. We recommend adding the statements "Admelog SoloStar should not be used by people who are blind or have severe vision problems, without the help of a person who has good eyesight and who is trained to use the Admelog SoloStar the right way." immediately below the statement "Do not share your TRADENAME SoloStar pen...".
    2. We recommend adding the statements "Admelog SoloStar is a disposable prefilled pen used to inject Admelog. Each Admelog SoloStar has 300 units of insulin which can be used for many doses. You can select doses from 1 to 80 units in steps of 1 unit. The pen plunger moves with each dose. The plunger will only move to the end of the cartridge when 300 units of insulin have been given." immediately following the statement recommended in B.1.
C. Instructions for Use (IFU)-Vial
    1. For step 7, we recommend adding an image that shows all of the recommended sites for injection.

4.2 RECOMMENDATIONS FOR SANOFI-AVENTIS

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

A. Container Label-SoloStar pen
    1. Increase the prominence of "SoloStar" within the proprietary name "TRADENAME SoloStar" so that the full proprietary name has equal prominence on the label.
    2. Remove the abbreviation (b) (4) from the established name so that the name reads as follows: "insulin lispro injection".
    3. Replace the NDC placeholder with the NDC number and submit for Agency review.
    4. Move the net quantity statement "3 mL prefilled pen" so that it is not located directly below the product concentration statement "100 units/mL". We recommend placing the statement "3 mL prefilled pen" where you currently have the statement "501XXXXX" to increase prominence of the quantity statement and placing the statement "501XXXXX" closer to the bottom of the label near the manufacturer information.
    5. Add the statement "for subcutaneous use only" directly below the product concentration statement "100 units/mL." Consider increasing the size of the white area used for text to accommodate the addition of this information on the label.

B. Carton Labeling-SoloStar pen
    1. See comments A.1, A.2, and A.3.
    2. Revise the statement (b) (4) to read (b) (4) to clarify that this statement applies to each individual pen. In addition, we recommend placing this statement directly above or below the "Initial Use Date" fillable lines for improved visibility of the pen's beyond use information.

C. Container Label-Vial
    1. See comments A.2 and A.3.
    2. Consider moving the net quantity statement "10 mL vial" so that it is not located directly below the product concentration statement "100 units/mL" to minimize confusion of these numbers.
    3. Revise the statement (b) (4) to read "for subcutaneous or intravenous use" to improve clarity.

D. Carton Labeling-Vial
    1. See comments A 2 and A 3.
    2. Revise the statement (b) (4) to read "for subcutaneous use" then we recommend revising the statement (b) (4) to "For intravenous infusion after further dilution ONLY under direct medical supervision" for improved clarity of this recommendation.
    3. Improve the readability of the information currently placed on the (b) (4) colored side panel by making this panel white with black letters. The current

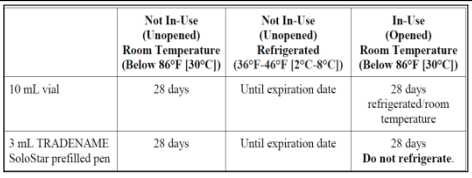
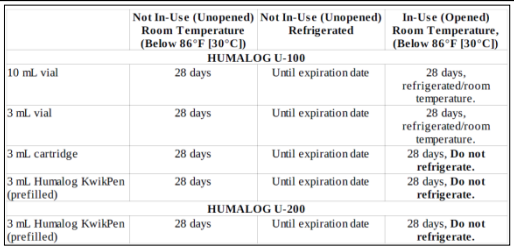
white lettering on a (b) (4) background may be difficult for users to distinguish and decrease user readability of this information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Admelog that Sanofi submitted on November 1, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Admelog and the Listed Drug

Product Name	**Admelog**	**Humalog (NDA 020563)**
Initial Approval Date	N/A	June 14, 1996
Active Ingredient	insulin lispro	insulin lispro
Indication	to improve glycemic control in adults and children with diabetes mellitus	to improve glycemic control in adults and children with diabetes mellitus
Route of Administration	subcutaneous or intravenous	subcutaneous or intravenous
Dosage Form	solution for injection	solution for injection
Strength	100 units/mL	100 units/mL or 200 units/mL
Dose and Frequency	individualized dose administered within 15 minutes before a meal or immediately after a meal	individualized dose administered within 15 minutes before a meal or immediately after a meal
How Supplied	10 mL vial and 3 mL prefilled pen	3 mL vial, 10 mL vial and 3 mL prefilled pen
Storage		

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 6, 2017, we searched the L:drive and AIMS using the term, insulin lispro, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review[d] for Sanofi's insulin lispro (submitted under IND 120511 or NDA 209196) and we confirmed that our most of our comments were implemented; however, the sponsor did not fully implement the modifications recommended for the moderator script.

[d] Vee S. Human Factors Protocol Review for insulin lispro (IND 120511). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Nov 20. RCM No. 2015-2309.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

3.2 DEVICE USE AND USE ENVIRONMENT

The insulin lispro pen injector is intended for single patient use, most often in non-clinical environments but also in clinical environments.

3.2.1 Intended Use Environments

Typically, the insulin lispro pen injector will be used in patients' homes, but depending on their daily routines the location may vary, for example:

- At home (eg, in the bathroom or bedroom, but also outdoors);
- At work or school (eg, in a restroom);
- In public places (eg, restaurants, parks).

HCPs are expected to use the insulin lispro pen injector primarily in clinical environments.

The intended users of the insulin lispro pen injector include patients (DMI and DMII), lay caregivers, nurses, and pharmacists.

3.2.3 Presence of other injection devices

As short-acting insulins are generally used in combination with intermediate- or long-acting insulins, other injection devices (eg, for delivery of long-acting insulins) are present in a patient's home use environment. Additionally, it is possible that more than one household member has diabetes mellitus and, therefore, other injection devices might be present in the home environment.

In a clinical setting and in a pharmacy, other injection devices are expected to be present in the environment of use.

4 DEVICE USER INTERFACE

The insulin lispro pen injector contains and provides a method of accurately injecting an individual dose which must be selected based on a patient's specific insulin needs.

To support this, insulin lispro pen injector allows:

- A one unit (1 U) increment dosing with each click when dialed;
- Injection of up to 80 U of insulin lispro per dose.

The intended injection sites for insulin lispro pen injector are:

- The abdomen (belly);
- The thigh;
- The upper arm.

7.2 STUDY GOALS

The following objectives were defined for the HF validation studies:

- Confirm that the insulin lispro pen injector can successfully be differentiated from other pen injectors (comparators) that might be present in the same use scenario;
- Confirm that the packaging for the insulin lispro pen injector enables users to differentiate the insulin lispro pen injector packaging from other packages (comparators) that might be present in the same use scenario.

7.3 PARTICIPANTS

A total of 60 participants participated in the HF validation study I. The participants were representatives of the intended users of the insulin lispro pen injector: patients, nurses and pharmacists (see Table 7).

A total of 45 participants participated in the supplemental HF validation study II. The participants were representatives of the intended users of the insulin lispro pen injector: patients and nurses (see Table 7).

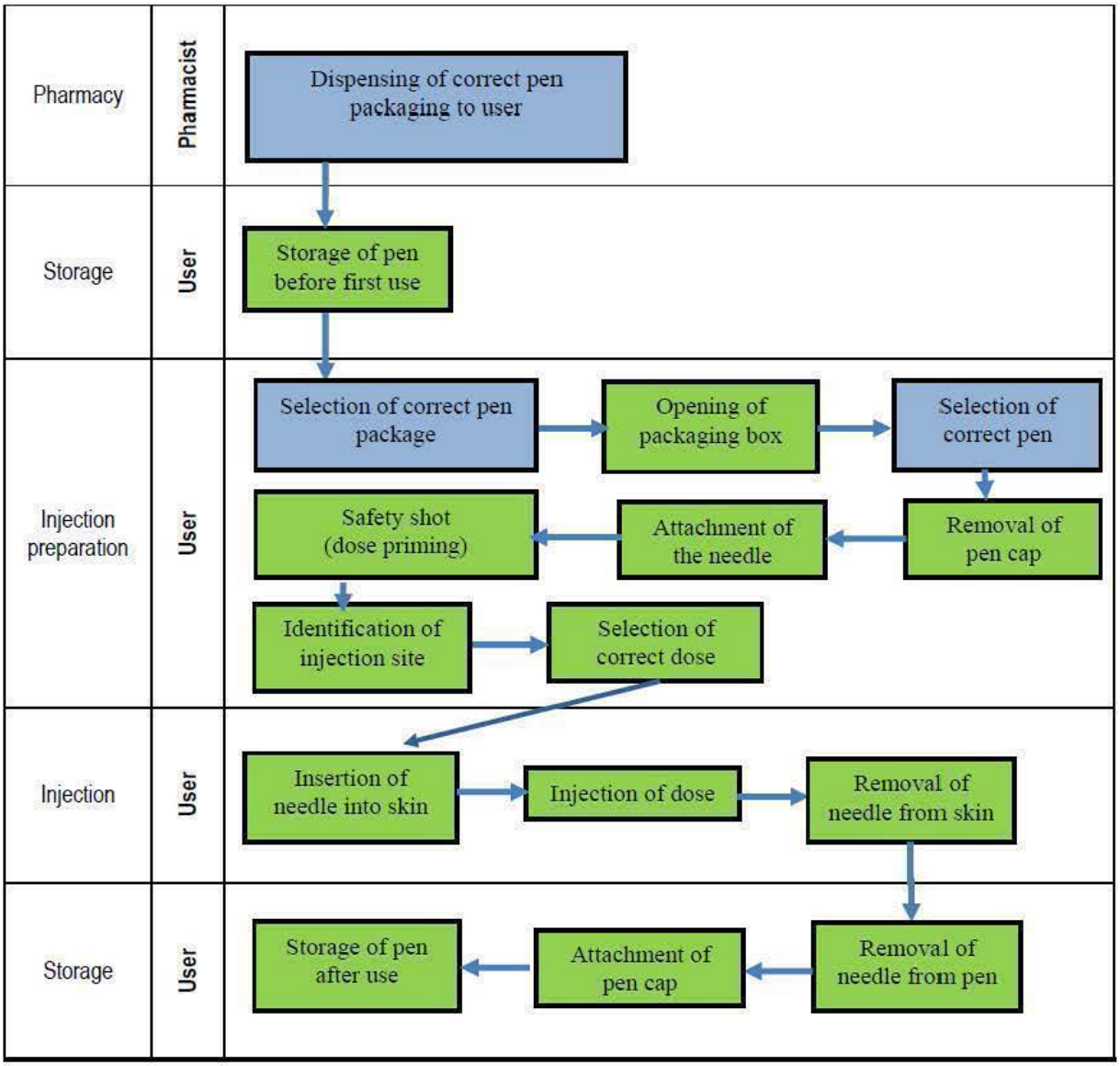
Table 7 - Participants involved in the HF validation study I and II

User group for HF validation study I (n = # of participants)	Sub-groups (if any) (n = # of participants)	Study tasks based on simulated prescription	
		Packaging differentiation	Pen differentiation
T2DM Patients (n=30)	Untrained and pen naive (n=15)	x	x
	Untrained but experienced in self-injection with a pen (n=15)	x	x
Nurses currently treating and training T2DM patients (n=15)		x	x
Pharmacists (n=15) who dispense insulin products		x	-

User group for HF validation study II (n = # of participants)	Sub-groups (if any) (n = # of participants)	Study tasks based on pen color and label
		Pen differentiation
T2DM Patients (n=30)	Untrained and pen naive (n=15)	x
	Untrained but experienced in self-injection with a pen (n=15)	x
Nurses currently treating and training T2DM patients (n=15)		x

Lay caregivers were not included in the study "because this user population is adequately represented by the patient population with no pen experience."

Table 5 - User interface elements and user interactions with insulin lispro pen injector and Lantus SoloStar



7.4 STUDY MATERIALS

All materials used in the HF validation studies were representative of the commercial product, with the exception of the brand name. (b) (4) or "Admelog" were used as dummy brand names for the insulin lispro pen injector in the HF validation studies for the purpose of blinding the product identity from the study participants.

The following materials were used in the HF validation study I:

- Pen packages for package differentiation session (for pharmacists, patients and nurses):
  - Pen package labeled as (b) (4) (Appendix C, Section 9.3)
  - Packages for the comparators (Appendix B, Section 9.2)
- Pre-filled pens for pen differentiation session (for patients and nurses):
  - Pen labeled as (b) (4) (Appendix D, Section 9.4)
  - Pre-filled pens for the comparators (Appendix B, Section 9.2)

The following materials were used in HF validation study II:

- Pre-filled pens for pen differentiation session (for patients and nurses):
  - Pen labeled as "Admelog SoloStar" (Appendix D, Section 9.4)
  - Pre-filled pens for the comparators (Appendix B, Section 9.2)

7.6.1 Training

In these studies, none of the participants (pharmacist, patient- and nurse-participants) was trained.

All the participants, including the nurses and pharmacists, were given only a high-level overview of the purpose of the therapy and the study.

Table 9 - Tasks to be performed by the study participant groups and definitions of task success

Task No.	Task	Study task	Range of acceptable performance
HF validation study I			
1.1	Dispensing of correct pen package to user in pharmacy.	Pharmacists: Were asked to identify the correct box from a set of boxes.	Pharmacists must be able to select the correct box from the set of boxes (including comparator boxes) based on simulated prescription.

Task No.	Task	Study task	Range of acceptable performance
HF validation study I			
2.1	Selection of correct pen package.	Patient and nurse participants: Were asked to identify the correct pen from a set of pens.	Patient and nurse participants must select the correct pen package (including comparator boxes) based on simulated prescription.
2.2a	Selection of correct pen.	Patient and nurse participants: Were asked to identify the correct pen from a set of pens.	Patient and nurse participants must select the correct pen (including comparator boxes) based on simulated prescription.
HF validation study II			
2.2b	Selection of correct pen.	Patient and nurse participants: Were asked to identify the correct pen from a set of pens.	Patient and nurse participants must select the correct pen (including comparator boxes) based on pen color and pen label design.

C.2 Results

Table 10 - Study results - critical handling tasks

Task No.	Task	Results		Observations	Root cause / comments
HF validation study I					
1.1	Dispensing of correct pen package to user in pharmacy based on simulated prescription	Pass	14/15 pharmacists	N/A	N/A
		Use Error	1/15 pharmacist	One pharmacist selected the Lantus SoloStar packaging when asked to collect the packaging corresponding to the prescription for (b) (4) She explained that she got confused due to the similarity of the names (b) (4) and "SoloStar" and therefore she collected the Lantus SoloStar packaging.	The study material used the dummy name (b) (4) which will be changed for the commercial product. This is considered an artifact of the artificial situation.
2.1	Selection of correct pen package based on simulated prescription	Pass	29/30 patients 15/15 nurses	N/A	N/A
		Use Error	1/30 patient	One patient selected the Toujeo SoloStar packaging when asked to collect the packaging corresponding to the prescription for (b) (4) She argued that both terms - (b) (4) and "SoloStar" - are quite similar and therefore she collected the Toujeo SoloStar packaging.	The study material used the dummy name (b) (4) which will be changed for the commercial product. This is considered an artifact of the artificial situation.
2.2a	Selection of correct pen based on simulated prescription	Pass	29/30 patients 15/15 nurses	N/A	N/A
		Use Error	1/30 patient	One patient chose the target pen (b) (4) correctly in his first draw but chose *Humalog Mix 75/25* in his second draw. This was due to a misinterpretation of the task. He stated he was confused based on the repetition of the study task and deliberately selected a pen that was different from the one he had selected in his first draw.	The patient participant was confused by the study procedure (two draws in a row). This is considered an artifact of the artificial situation.
HF validation study II					
2.2b	Selection of correct pen based on pen color and pen label	Pass	30/30 patients 15/15 nurses	N/A	N/A

7.8.2 Summary of use errors on the critical tasks

A total of three (3) use errors occurred in the HF validation study I on the following critical tasks:

- 1.1, Dispensing of correct pen package to user in pharmacy:
  - 1 of 15 pharmacists selected the wrong package (wrong product)
  - This use error was related to the dummy brand name used during this study.
- 2.1, Selection of correct pen package:
  - 1 of 30 patients selected the wrong package (wrong product)
  - This use error was related to the dummy brand name used during this study.
- 2.2a, Selection of correct pen:
  - 1 of 30 patients selected the wrong pen (wrong product)
  - This use error was related to the study set up, which confused the patient participant.

No use errors occurred in the HF validation study II.

7.9 CONCLUSION

Taking into consideration the post-market data from the Lantus Solostar, the results of the HF validation studies demonstrate the following:

- The insulin lispro pen injector is safe and effective for use by the intended users.
- The insulin lispro pen injector was found be differentiable from other pens.
- The package for the insulin lispro pen injector was found to enable users to recognize it and to differentiate it from other packages.

APPENDIX D. INFORMATION REQUESTS

On February 7, 2017, we issued an information request to Sanofi requesting an updated copy of the moderator scripts used in the Human Factors Usability report submitted on November 1, 2016. The complete response from Sanofi, submitted February 15, 2017, is available via the following link: \\cdsesub1\evsprod\nda209196\0005\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes-mellitus\5354-other-stud-rep\hfs\hfs-script.pdf.


response to DMEPA
IR submitted Feb 15 2

On March 14, 2017, we issued an information request to Sanofi requesting clarification of the study methodology. The complete response from Sanofi, submitted March 20, 2017, is available via the following link: \\cdsesub1\evsprod\nda209196\0010\m1\us\cmc-response-14mar2017.pdf.


response to DMEPA
IR submitted March 2(

APPENDIX E. Center for Devices and Radiological Health (CDRH) Human Factors Review[e]

HF Recommendation: Human Factors data is **inadequate** to demonstrate that the user interface of the subject combination product supports safe and effective use.

Reviewer Analysis/Comments:

Mismatch between the participants and the intended user. Neither T1DM patients nor caregivers were included.

HF Consult Response to communicate to sponsor

Deficiency 1:

Your Human Factors (HF) validation studies included T2DM patients, nurses and pharmacists. However, based on your description, the intended users of the subject combination product include T1DM patients, T2DM patients, lay caregivers, nurses and pharmacists. Your HF test participants did not include either T1DM patients or lay caregivers group. The participants in the HF validation testing should match the representative profile of the intended user. Please provide human factors testing data including T1DM patients and lay caregivers group; or provide justification on why T1DM patients and lay caregivers group can be excluded from the HF validation testing.

Current Agency guidance applying human factors and usability engineering to medical devices can be found at: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm259760.pdf.

To lead reviewer:

The HF protocol may be reviewed by the agency/DMEPA before. If there is an agreement between the agency and DMEPA on the participant recruitment plan presented in the HF report, then the above deficiency might be resolved without additional HF data.

[e] Mollo S. Human Factors Consult Memo for insulin lispro. Silver Spring (MD): FDA, CDRH, ODE, DAGRID, GHDB (US); 2017 Mar 10. NDA 209196.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Admelog labels and labeling submitted by Sanofi on November 1, 2016.

- Container Label
- Carton Labeling
- Instructions for Use (IFU)
- Patient Information (PPI)

F.2 Label and Labeling Images

Container Label-Vial

(b) (4)

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[f] 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
04/20/2017

HINA S MEHTA
04/20/2017

QUYNHNHU T NGUYEN
04/20/2017