DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208673

NDA APPROVAL

Sanofi US Services Inc.
Attention: Shefali Goyal
Director, Global Regulatory Affairs
55 Corporate Drive
Mail Stop: 55D-215A
Bridgewater, NJ 08807

Dear Ms. Goyal:

Please refer to your New Drug Application (NDA) dated and received December 21, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Soliqua 100/33 (insulin glargine and lixisenatide injection).

We acknowledge receipt of your major amendment dated August 12, 2016, which extended the goal date by three months.

This new drug application provides for the use of a long-acting human insulin analog with a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, IFU, Medication Guide). Information on submitting SPL files using eLIST may be found in the

guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 208673**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

DATING PERIOD

The dating period for Soliqua 100/33 is 18 months from the date of manufacture when stored at 2-8 °C.

The in-use period is 14 days when stored at room temperature (below 86° F (30 °C) after first use for the finished product.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement in patients aged 0 to < 10 years old for this application because necessary studies are impossible or highly impracticable. We are waiving the pediatric study requirement in patients aged 10 years to < 18 years old for this application because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age range **and** is not likely to be used in a substantial number of pediatric patients in this age range. This determination was made based on the following:

> Appropriate studies to support the safety and effectiveness of this fixed dose combination product would require enrollment of patients who require treatment with three or more

antidiabetic agents. The population of patients appropriate for such a study are small (estimated to be 1% of the pediatric type 2 diabetes mellitus population) and are impractical. Additionally, the fixed dose combination product does not provide any meaningful therapeutic benefit over the use of the separate individual products.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

As communicated to you in our approval letter for NDA 208471 dated July 27, 2016, we have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of the development of anti-drug antibodies (ADA) that could potentially neutralize the function of lixisenatide (i.e., neutralizing antibodies [Nab]) or cross-react with endogenous GLP-1 or glucagon and adversely impact regulation of glucose metabolism.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that this application is also subject to the PMR listed below, described in our July 27, 2016 approval letter:

3102-3 Perform immunogenicity testing on anti-drug antibody (ADA)-positive samples from clinical studies of type 2 diabetes patients treated with lixisenatide to determine the incidence of neutralizing antibodies (NAb) and anti-lixisenatide antibodies that are cross-reactive with endogenous GLP-1 and glucagon peptides and are capable of neutralizing these endogenous peptides. Assessments should be performed using assays demonstrated to be suitable for their intended purposes through formal validation studies that have been reviewed by the Agency prior to their use in clinical sample analysis. Samples used for these assessments should be archived under suitable conditions until testing, and should include sufficient quantity to allow for completion of required immunogenicity assessments. Study report(s) submitted to the Agency will include evaluation of the impact of NAb and cross-reactive antibodies on patient safety as well as PK, PD, and efficacy of lixisenatide.

The timetable you submitted on July 19, 2016, states that you will conduct this study according to the following schedule:

Interim Milestone 1 (Final Report –Assay Validation):	September 2017
Interim Milestone 2 (Studies EFC12404 and EFC12405 Completion):	June 2018
Interim Milestone 3 (Studies EFC12404 and EFC12405 Final Report Submission):	December 2018
Study Completion (EFC13794):	January 2019
Final Study Report Submission (EFC13794):	June 2019

You may choose to conduct this evaluation using appropriately scheduled samples collected from Phase 3 studies evaluating insulin glargine/lixisenatide injection; however, the adequacy of these data will depend on the demonstration of comparable anti-lixisenatide immunogenicity rates between the monotherapy and combination product trials.

Submit the protocol to your IND 062724, with a cross-reference letter to NDA 208471 and to this NDA. Submit all final reports to NDA 208471 with a cross-reference letter to this NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3138-1 Stability analysis to assess maintenance of the essential performance requirements of the final finished combination product (i.e. dose accuracy, dispense force, etc.) through the intended expiration date of 18 months using primary registration stability batches.

The timetable you submitted on November 9, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: January 2018

Submit clinical protocols to your IND 105157 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge receipt of your submission dated December 21, 2015, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for Soliqua 100/33 to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has also contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final reports. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to this evaluation.

If you have any questions, call Martin White, M.S., Regulatory Project Manager, at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

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

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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

/s/

JEAN-MARC P GUETTIER
11/21/2016