

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208673Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208673

SUPPL # N/A

HFD # 510

Trade Name Soliqua 100/33

Generic Name insulin glargine and lixisenatide injection

Applicant Name Sanofi

Approval Date, If Known November 21, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021081 Lantus

NDA# 208471 Adlyxin

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

- [EFC12404]: A randomized, 30-week, active-controlled, open-label, 3-treatment arm, parallel-group multicenter study comparing the efficacy and safety of insulin glargine/lixisenatide fixed ratio combination to insulin glargine alone and to lixisenatide alone on top of metformin in patients with Type 2 diabetes mellitus (T2DM)
- [EFC12405]: A randomized, 30-week, active-controlled, open-label, 2-treatment arm, parallel-group, multicenter study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination to insulin glargine with or without metformin in patients with Type 2 diabetes mellitus (T2DM)
- [ACT12374]: ACT12374 - A randomized, 24-week, open-label, 2-arm parallel-group, multicenter study comparing the efficacy and safety of insulin glargine/lixisenatide fixed ratio combination versus insulin glargine on top of metformin in type 2 diabetic patients

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #3 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #3 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

- [EFC12404]: A randomized, 30-week, active-controlled, open-label, 3-treatment arm, parallel-group multicenter study comparing the efficacy and safety of insulin glargine/lixisenatide fixed ratio combination to insulin glargine alone and to lixisenatide alone on top of metformin in patients with Type 2 diabetes mellitus (T2DM)
- [EFC12405]: A randomized, 30-week, active-controlled, open-label, 2-treatment arm, parallel-group, multicenter study comparing the efficacy and safety of the insulin glargine/lixisenatide fixed ratio combination to insulin glargine with or without metformin in patients with Type 2 diabetes mellitus (T2DM)
- [ACT12374]: ACT12374 - A randomized, 24-week, open-label, 2-arm parallel-group, multicenter study comparing the efficacy and safety of insulin glargine/lixisenatide fixed ratio combination versus insulin glargine on top of metformin in type 2 diabetic patients

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 105157 YES !
! ! NO
! Explain:

Investigation #2
IND # 105157 YES !
! ! NO
! Explain:

Investigation #3
IND # 105157 YES !
! ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES !
! ! NO
Explain: ! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Martin White, M.S.

Title: Regulatory Project Manager

Date: November 21, 2016

Name of Division Director signing form: Jean-Marc Gueittier, MD

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MARTIN L WHITE
11/21/2016

JEAN-MARC P GUETTIER
11/21/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208673	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Soliqua 100/33 Established/Proper Name: insulin glargine and lixisenatide injection Dosage Form: injection		Applicant: Sanofi US Services Inc. Agent for Applicant (if applicable):
RPM: Martin White		Division: DMEP
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)	<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>	
❖ Actions		
- Proposed action - User Fee Goal Date is <u>11/21/2016</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		
		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 1- New Molecular Entity
(confirm chemical classification at time of approval)

☐ Fast Track	☐ Rx-to-OTC full switch
☐ Rolling Review	☐ Rx-to-OTC partial switch
☐ Orphan drug designation	☐ Direct-to-OTC
☐ Breakthrough Therapy designation	

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments: This application was a priority review because Sanofi submitted a priority voucher.

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	☐ Yes ☐ No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval on 11/21/2016

Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included: see approval letter
• Original applicant-proposed labeling	☐ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☒ Medication Guide: see approval letter ☐ Patient Package Insert ☒ Instructions for Use: see approval letter ☐ Device Labeling ☐ None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☐ Included
• Original applicant-proposed labeling	☒ Included : see approval letter
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	☐ Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>)	10/3/2016,9/28/2016,9/16/2016,7/15/2016,6/08/2016,5/11/2016,4/1/2016, 3/31/2016
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 2/18/2016 DMEPA: 11/8/2016,10/7/2016,4/13/2016 DMPP/PLT (DRISK): 11/15/2016 OPDP: 11/10/2016 SEALD: ☒ None CSS: ☒ None Product Quality see OPQ Review Other: ☒ DPMH 10/25/2016

Administrative / Regulatory Documents

❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	2/18/2016
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Completed 11/21/2016
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>7/13/2016</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	N/A
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	N/A
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	N/A
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	11/21/2016, 11/16/2016 11/8/2016, 11/3/2016, 10/12/2016, 10/6/2016, 9/29/2016, 9/6/2016, 8/17/2016, 6/3/2016, 5/20/2016, 5/9/2016, 4/26/2016(2), 4/20/2016, 4/8/2016, 3/25/2016, 3/22/2016 (2), 3/16/2016, 3/10/2016, 3/7/2016, 3/4/2016, 3/3/2016 (2), 2/22/2016 (2), 2/12/2016, 2/9/2016, 1/25/2016, 1/19/2016, 1/5/2016, 12/23/2015
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)September 28, 2015	☐ No mtg October 28, 2015
• EOP2 meeting (<i>indicate date of mtg</i>)June 25, 2010	☐ No mtg July 23, 2010
• Mid-cycle Communication (<i>indicate date of mtg</i>)March 23, 2016	☐ N/A April 5, 2016
• Late-cycle Meeting (<i>indicate date of mtg</i>)May 11, 2016	☐ N/A June 22, 2016 and May 5, 2016
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	

❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	May 25, 2016
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	11/21/2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	11/21/2016
PMR/PMC Development Templates (<i>indicate total number</i>)	1 (signed on 11.21.2016)
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review see CDTL review
• Clinical review(s) (<i>indicate date for each review</i>)	September 30, 2016, 1/29/2016
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	see clinical review, page 25
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	10/31/016, 6/2/2016, 4/27/2016, 4/13/2016
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management - REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) December 21, 2015 - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) N/A - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	N/A ☐ None August 16, 2016
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	10/10/2016 (2), 9/27/2016, 8/2/2016, 7/8/2016
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	7/21/2016, 1/25/2016

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	8/4/2016(2)
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	☐ None 7/19/2016, 1/22/2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☒ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	☒ None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	8/1/2016; 11/14/2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	See OPQ Executive Summary
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	The Applicant's claim of categorical exclusion from environmental assessment is acceptable. Proposed protein drugs are naturally occurring substances and readily metabolized in humans and degraded in the environment. EA for Lantus and lixisenatide was completed during review of NDA 206538 and NDA 208471 review and found acceptable.
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) <i>(only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change))</i>	☒ Acceptable (see OPQ Executive Summary) Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>) N/A
• Finalize 505(b)(2) assessment	☐ Done N/A
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done N/A (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> • Notify the Division of Online Communications, Office of Communications	☐ Done N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done N/A
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done 11/21/2016
❖ Ensure Pediatric Record is accurate	☒ Done 11/21/2016
❖ Send approval email within one business day to CDER-APPROVALS	☐ Done 11/21/2016

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

/s/

LEAH S HER
10/24/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.18.2016
Date: Friday, November 18, 2016 4:51:29 PM

Received, thanks.

Shefali

Shefali Goyal
Global Regulatory Affairs, Diabetes
Phone:(908) 981-6996



From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Friday, November 18, 2016 4:45 PM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.18.2016

Shefali,

The revised PI, medguide along with the IFU is attached. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return the revised labeling by **10:00am Monday, November 21, 2016**. If there are no changes, please submit the final agreed upon label to me via email.

Acknowledge receipt of this email and let me know if you have any questions.

Thanks
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [mailto:Shefali.Goyal@sanofi.com]
Sent: Friday, November 18, 2016 3:13 PM
To: White, Martin
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

Hi Martin,
Is there any chance of us getting the PI comments back today?

Thanks

Shefali

Shefali Goyal

Global Regulatory Affairs, Diabetes

Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]

Sent: Friday, November 18, 2016 8:42 AM

To: Goyal, Shefali R&D/US

Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

Shefali,

Emailing the documents is not required. I was able to locate the submission.

Regards,

Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]

Sent: Friday, November 18, 2016 8:28 AM

To: White, Martin

Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

Everything was submitted through the gateway yesterday. Did you also need it via email?

Shefali

Shefali Goyal

Global Regulatory Affairs, Diabetes

Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]

Sent: Friday, November 18, 2016 8:27 AM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

When will you be submitting the revised Medguide and IFU?

Thanks
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Friday, November 18, 2016 8:25 AM
To: White, Martin
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

Thanks Martin, we anxiously await your comments.

Best Regards

Shefali

Shefali Goyal
Global Regulatory Affairs, Diabetes
Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Friday, November 18, 2016 8:23 AM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

We are in receipt of the label.

Thanks
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Thursday, November 17, 2016 5:07 PM

To: White, Martin
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

Hi Martin,
Please see updated PI based on our discussion today and let us know if you have any comments. We will be submitting this and other label components later today via the gateway. Please confirm receipt of this email.

Thanks

Shefali

Shefali Goyal
Global Regulatory Affairs - Diabetes
Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Thursday, November 17, 2016 2:13 PM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

Thank you. We received the revised PI.

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Thursday, November 17, 2016 2:04 PM
To: White, Martin
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

Please confirm that you received it, thanks.

Shefali

Shefali Goyal
Global Regulatory Affairs - Diabetes
Phone:(908) 981-6996



From: Goyal, Shefali R&D/US
Sent: Thursday, November 17, 2016 1:30 PM
To: 'White, Martin'
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

Hi Martin,

To facilitate the discussion during this meeting, please see our current draft PI with the proposed changes and supportive comments.

Thanks and Best Regards

Shefali

Shefali Goyal

Global Regulatory Affairs - Diabetes

Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Thursday, November 17, 2016 12:15 PM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

Shefali,

We are available today at 3:00pm. The teleconference will be for 30 minutes. Please provide a call-in number.

Regards,
Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Thursday, November 17, 2016 10:00 AM
To: White, Martin
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

Hi Martin,

Please let me know about the requested meeting, it is very important that we discuss with the Agency today.

Can you also let us know if the carton and container labels can be considered final at this point?

Thanks

Shefali

Shefali Goyal

Global Regulatory Affairs - Diabetes

Phone:(908) 981-6996



From: Goyal, Shefali R&D/US

Sent: Wednesday, November 16, 2016 5:33 PM

To: 'White, Martin'

Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

Hi Martin,

We will need to discuss a few points with the Agency tomorrow prior to sending our responses back. Can we please have a short TC with the Agency in the early afternoon?

Thanks very much!

Shefali

Shefali Goyal

Global Regulatory Affairs - Diabetes

Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]

Sent: Wednesday, November 16, 2016 4:37 PM

To: Goyal, Shefali R&D/US

Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

Shefali,

FDA has compiled the attached comments for your draft labeling submitted for the above-mentioned NDA on December 21, 2015. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling by COB **Thursday, November 17, 2016**. **If there are no changes, please submit the final agreed upon label to me via email.**

Acknowledge receipt of this email and let me know if you have any questions.

Please note that we are scheduled to take action on November 21, 2016.

Regards,
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Thursday, November 10, 2016 3:44 PM
To: White, Martin
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

Great, thanks!

Shefali
Shefali Goyal
Global Regulatory Affairs - Diabetes
Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Thursday, November 10, 2016 3:39 PM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

We received the documents.

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Thursday, November 10, 2016 3:33 PM
To: White, Martin
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

Please confirm receipt, thanks.

Shefali
Shefali Goyal
Global Regulatory Affairs - Diabetes
Phone:(908) 981-6996



From: Goyal, Shefali R&D/US
Sent: Thursday, November 10, 2016 2:09 PM
To: 'White, Martin'
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

Hi Martin,
Please see attached PI, medication guide, carton and container labeling for your information. We will be submitting these formally later today. Let me know if you have any questions or comments.

Thanks and Best Regards

Shefali
Shefali Goyal
Global Regulatory Affairs - Diabetes
Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Thursday, November 10, 2016 1:57 PM
To: Goyal, Shefali R&D/US

Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

Thank you.

Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]

Sent: Thursday, November 10, 2016 1:33 PM

To: White, Martin

Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

Hi Martin,

I plan to send you the label components via email in about an hour to give you a head start, and will follow with a formal submission later in the day.

Best Regards

Shefali

Shefali Goyal

Global Regulatory Affairs - Diabetes

Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]

Sent: Tuesday, November 08, 2016 4:22 PM

To: Goyal, Shefali R&D/US

Subject: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

Good Afternoon Shefali,

FDA has compiled the attached comments for your draft labeling submitted for the above-mentioned NDA on December 21, 2015. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling by COB **Thursday, November 10, 2016**. At this time there are no comments for the IFU.

All of your proposed changes from this version should be marked via tracked changes.

In addition, we recommend the following be implemented prior to approval of this NDA for the

Carton and Container Label:

A. Carton Labeling

1. Revise the presentation of the established name to include parenthesis as follows for consistency with other product labeling: "(insulin glargine and lixisenatide injection)".
2. Revise the statement "[REDACTED] (b) (4)" as follows to remove the (b) (4) statement for improved clarity: "100 units/mL and 33 mcg/mL".

B. Container Label

1. Revise the presentation of the established name to include parenthesis as follows for consistency with other product labeling: "(insulin glargine and lixisenatide injection)".
2. Revise the statement "[REDACTED] (b) (4)" as follows to remove the (b) (4) statement for improved clarity: "100 units/mL and 33 mcg/mL".

Please note that the label is still undergoing tertiary review and we cannot rule out additional comments at a future point.

Acknowledge receipt of this email and let me know if you have any questions.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
11/21/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016
Date: Wednesday, November 16, 2016 4:43:55 PM

Received, thanks.

Shefali

Shefali Goyal
Global Regulatory Affairs - Diabetes
Phone:(908) 981-6996



From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Wednesday, November 16, 2016 4:37 PM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, IFU)_11.16.2016

Shefali,

FDA has compiled the attached comments for your draft labeling submitted for the above-mentioned NDA on December 21, 2015. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling by COB **Thursday, November 17, 2016**. **If there are no changes, please submit the final agreed upon label to me via email.**

Acknowledge receipt of this email and let me know if you have any questions.

Please note that we are scheduled to take action on November 21, 2016.

Regards,
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Thursday, November 10, 2016 3:44 PM
To: White, Martin
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and

Container)_11.08.2016

Great, thanks!

Shefali

Shefali Goyal

Global Regulatory Affairs - Diabetes

Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Thursday, November 10, 2016 3:39 PM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

We received the documents.

Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Thursday, November 10, 2016 3:33 PM
To: White, Martin
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

Please confirm receipt, thanks.

Shefali

Shefali Goyal

Global Regulatory Affairs - Diabetes

Phone:(908) 981-6996



From: Goyal, Shefali R&D/US
Sent: Thursday, November 10, 2016 2:09 PM
To: 'White, Martin'
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

Hi Martin,
Please see attached PI, medication guide, carton and container labeling for your information. We will be submitting these formally later today. Let me know if you have any questions or comments.

Thanks and Best Regards

Shefali

Shefali Goyal
Global Regulatory Affairs - Diabetes
Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Thursday, November 10, 2016 1:57 PM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

Thank you.

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Thursday, November 10, 2016 1:33 PM
To: White, Martin
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

Hi Martin,
I plan to send you the label components via email in about an hour to give you a head start, and will follow with a formal submission later in the day.

Best Regards

Shefali

Shefali Goyal
Global Regulatory Affairs - Diabetes
Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Tuesday, November 08, 2016 4:22 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

Good Afternoon Shefali,

FDA has compiled the attached comments for your draft labeling submitted for the above-mentioned NDA on December 21, 2015. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling by COB **Thursday, November 10, 2016**. At this time there are no comments for the IFU.

All of your proposed changes from this version should be marked via tracked changes.

In addition, we recommend the following be implemented prior to approval of this NDA for the Carton and Container Label:

A. Carton Labeling

1. Revise the presentation of the established name to include parenthesis as follows for consistency with other product labeling: "(insulin glargine and lixisenatide injection)".
2. Revise the statement (b) (4) as follows to remove the (b) (4) statement for improved clarity: "100 units/mL and 33 mcg/mL".

B. Container Label

1. Revise the presentation of the established name to include parenthesis as follows for consistency with other product labeling: "(insulin glargine and lixisenatide injection)".
2. Revise the statement (b) (4) as follows to remove the (b) (4) statement for improved clarity: "100 units/mL and 33 mcg/mL".

Please note that the label is still undergoing tertiary review and we cannot rule out additional comments at a future point.

Acknowledge receipt of this email and let me know if you have any questions.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
11/17/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016
Date: Tuesday, November 08, 2016 5:17:16 PM

Received, thanks Martin.

Shefali

Shefali Goyal
Global Regulatory Affairs, Diabetes
Phone:(908) 981-6996



From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Tuesday, November 08, 2016 4:22 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_FDA Comments for Labeling (PI, Medguide, Carton and Container)_11.08.2016

Good Afternoon Shefali,

FDA has compiled the attached comments for your draft labeling submitted for the above-mentioned NDA on December 21, 2015. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling by COB **Thursday, November 10, 2016**. At this time there are no comments for the IFU.

All of your proposed changes from this version should be marked via tracked changes.

In addition, we recommend the following be implemented prior to approval of this NDA for the Carton and Container Label:

A. Carton Labeling

1. Revise the presentation of the established name to include parenthesis as follows for consistency with other product labeling: "(insulin glargine and lixisenatide injection)".
2. Revise the statement [REDACTED] (b) (4) as follows to remove the [REDACTED] (b) (4) statement for improved clarity: "100 units/mL and 33 mcg/mL".

B. Container Label

1. Revise the presentation of the established name to include parenthesis as follows for consistency with other product labeling: "(insulin glargine and lixisenatide injection)".
2. Revise the statement [REDACTED] (b) (4) as follows to remove the [REDACTED] (b) (4) statement for improved clarity: "100 units/mL and 33 mcg/mL".

Please note that the label is still undergoing tertiary review and we cannot rule out additional comments at a future point.

Acknowledge receipt of this email and let me know if you have any questions.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
11/08/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_PMC list_11.3.2016
Date: Thursday, November 03, 2016 4:40:09 PM

Received, thanks.

Shefali

Shefali Goyal
Global Regulatory Affairs, Diabetes
Phone:(908) 981-6996



From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Thursday, November 03, 2016 4:35 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_PMC list_11.3.2016

Good Afternoon Shefali,

While review of your application continues, we are sending you a draft list of PMCs based on the data and internal analyses available to date. These brief study summaries are intended to describe the main objective and study characteristics of interest.

Please submit by email a copy of the PMC studies to us with milestone dates, which include **Final Report Submission**.

We would like to request that this be returned by COB Tues 11/8, if possible.

Please confirm receipt of this email.

Thanks
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 240.402.6018

Fax 301.796.9712

Martin.White@fda.hhs.gov

PMR/PMC list for NDA 208673

Soliqua 100/33 (insulin glargine and lixisenatide) injection, 100 units and 33 mcg per mL

While review of your application continues, we are sending you a draft list of PMCs based on the data and internal analyses available to date. These brief study summaries are intended to describe the main objective and study characteristics of interest.

Please submit by email a copy of the PMC studies to us with milestone dates, which include **Final Report Submission**.

- Note that milestone dates only need month and year
- For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.
- **For PMCs, include a statement that you agree to conduct these studies/trials.**

Postmarketing Commitments:

- 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.

Final Report Submission:

January 2018

Comment [A1]: FDA Comment:

(b) (4)

Please confirm your concurrence with this postmarketing requirement as described with this milestone

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/s/

MARTIN L WHITE
11/03/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_FDA Comments for Labeling (PI and IFU)_Round 2_10.11.2016
Date: Tuesday, October 11, 2016 11:13:48 AM

Thanks Martin, I confirm receipt.

Best Regards

Shefali

Shefali Goyal

Global Regulatory Affairs, Diabetes

Phone:(908) 981-6996



From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Tuesday, October 11, 2016 10:47 AM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_FDA Comments for Labeling (PI and IFU)_Round 2_10.11.2016

Good Morning Shefali,

FDA has compiled the attached comments for your draft labeling (PI and IFU) submitted for the above-mentioned NDA on December 21, 2015. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than **Tuesday, October 18, 2016**. All of your proposed changes from this version should be marked via tracked changes.

Acknowledge receipt of this email and let me know if you have any questions.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712

Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
10/12/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_Statistical Information Request 10-6-2016
Date: Thursday, October 06, 2016 2:01:50 PM

Received, thanks.

Shefali

Shefali Goyal
Global Regulatory Affairs - Diabetes
Phone:(908) 981-6996



From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Thursday, October 06, 2016 12:16 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_Statistical Information Request 10-6-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

We would like to request an additional analysis for Study EFC12405. Please impute missing HbA1c measurements in both arms using the “return to baseline” approach: baseline plus an error. The error should be normally distributed with mean zero and a standard deviation set equal to the estimated pooled standard deviation (pooling the treatment specific standard deviations computed after adjusting for meaningful covariates). Please perform such an analysis using an ANCOVA model including the same covariates used for the primary analysis.

Please provide your response by Friday, October 14, 2016.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products

WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
10/06/2016



NDA 208673

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Sanofi-Aventis U.S. LLC
55 Corporate Drive
Mail Stop: 55D-215A
Bridgewater, NJ 08807

ATTENTION: Shefali Goyal
Director, Global Regulatory Affairs

Dear Ms. Goyal:

Please refer to your New Drug Application (NDA) dated December 21, 2015, received December 21, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Glargine and Lixisenatide Injection, 100 units and 33 mcg per mL.

We also refer to your September 6, 2016, correspondence, received September 6, 2016, requesting review of your proposed proprietary name, Soliqua 100/33.

We have completed our review of the proposed proprietary name, Soliqua 100/33 and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Martin White, Regulatory Project Manager in the Office of New Drugs, at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
10/03/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673
Date: Thursday, September 29, 2016 9:01:24 AM

Thanks for the confirmation Martin.

Best Regards

Shefali

Shefali Goyal
Global Regulatory Affairs - Diabetes
Phone:(908) 981-6996



From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Thursday, September 29, 2016 8:59 AM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673

Shefali,

The team would like for you to submit all of the proposed documents in addition to the requested documents for review prior to approval.

Regards,
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [mailto:Shefali.Goyal@sanofi.com]
Sent: Wednesday, September 28, 2016 2:15 PM
To: White, Martin
Subject: RE: NDA 208673

Hi Martin,

So just to be clear, you do want us to submit all the updated documents mentioned in our table below for module 3 as soon as possible, in addition to the requested information in your email of September 27th. We had asked the question because potentially those changes could also be made via a CBE-30 or some other post-approval process. Please confirm.

Regards

Shefali

Shefali Goyal

Global Regulatory Affairs - Diabetes

Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]

Sent: Wednesday, September 28, 2016 1:26 PM

To: Goyal, Shefali R&D/US

Subject: RE: NDA 208673

Shefali,

Based on the short deadlines, we would like for you to submit the information as possible, if they are available.

Thanks

Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]

Sent: Wednesday, September 28, 2016 12:42 PM

To: White, Martin

Subject: RE: NDA 208673

Hi Martin,

We will provide the information you request below by October 4th. In addition, could you please clarify whether or not you would like us to submit the other documents mentioned in our original e-mail at a later date?

Thanks

Shefali

Shefali Goyal

Global Regulatory Affairs - Diabetes

Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Tuesday, September 27, 2016 1:10 PM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673

Shefali,

After review of your information submitted, the Agency would like for you to submit the following:

1. Detailed comparison of previous pen design and to-be-marketed pen design (i.e. engineering drawings, materials, functionality, labeling, etc.).
2. Comparison of the essential performance requirements/specifications between the previous pens and the to-be-marketed pen.
 - a. Traceability from essential performance requirements/specifications to the associated verification testing and clinical validation of the to-be-marketed pen.
 - b. Rationale for the acceptability of any performance testing and/or clinical validation conducted with the previous pen design intended to support the new pen design.
3. Updated risk analysis for the new pen design, highlighting any differences in the previous pen design.

Please provide the responses by Tuesday, October 4, 2016.

Regards,
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Thursday, September 15, 2016 3:43 PM
To: White, Martin
Subject: RE: NDA 208673

Ok, thanks Martin.

Shefali

Shefali Goyal
Global Regulatory Affairs - Diabetes
Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Thursday, September 15, 2016 3:43 PM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673

Shefali,

Thank you for the email. The questions have been forwarded to the review team. I will forward their responses to you once they are available.

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Wednesday, September 14, 2016 1:01 PM
To: White, Martin
Subject: NDA 208673

Hi Martin,

Hope you are doing well. I would like to follow up with you on two points regarding the ongoing NDA review as outlined below:

1. CMC

Based on the changes proposed for the device, Sanofi has identified relevant sections of Module 3 in the current NDA that should be updated to reflect the final product to be marketed (see table below). We request a teleconference with the CMC review team at the Division to discuss if they have also identified similar sections, and how and when these changes should be made.

Summary of proposed revisions

CTD Section	Section Title / Document	Content Information / Modification
<u>3.2.P</u>	<u>Drug Product</u>	
3.2.P.1	Description and composition of the drug product	Document "Brief description of the pen-injector" will be replaced by a new one describing the upcoming US-commercial pen-injector. No information on the former two pen-injectors will be kept.

3.2.P.2	Pharmaceutical Development	Section 3.2.P.2 will still include information on all formulations/dosage strengths developed and will also still describe the two pen-injectors of the two-pen-concept. Changes in documentation in Section 3.2.P.2 are described below.
3.2.P.2.4	Pharmaceutical Development – Container closure system	Document “Pharmaceutical development - Container closure system – pen-injector” will be amended with information on the pen-injector with the updated pen design. However, previous test results for functional requirements obtained for pen B remain valid for the new pen.
3.2.P.2.4	Pharmaceutical Development – Container closure system – Pen-injector comparison	The clinical pen-injectors used in phase 3 clinical trial will be compared with the upcoming US-commercial pen-injector. Information on the two pen-injectors of the two-pen-concept will be removed.
3.2.P.7	Container closure system – Pen-injector	Document “Container closure system – disposable pen-injector” will be replaced by a new one describing the upcoming US commercial pen-injector. No information on the former two pen-injectors will be kept.
3.2.P.8.2	Post-approval stability protocol and stability commitment	The stability commitment will be updated to reflect the removal of the product containing 50 µg/mL.

We also believe that the other sections do not need to be changed with respect to the product containing 100 U/mL insulin glargine and 50ug/ml lixisenatide since that information is considered supportive. Please let me know if we can have a quick teleconference with the appropriate reviewers to discuss this matter.

2. Labeling

In your Sep 2nd e-mail you had requested Sanofi to add the glargine/lixisenatide dose table to the USPI dosing section, and we had responded that we will add it in the next update, after we have received additional comments on the label form the Agency. Can you please give us an estimate of when we could expect additional labeling comments? Do you anticipate sending them to us in parts, as you get done with some sections while still working on others? Any input that you can provide on the timeframe will be greatly appreciated, and help us plan accordingly.

Thanks and best regards

Shefali

Shefali Goyal

Global Regulatory Affairs - Diabetes

Phone:(908) 981-6996



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/s/

MARTIN L WHITE
09/29/2016



NDA 208673

**PROPRIETARY NAME REQUEST
ACKNOWLEDGEMENT/WITHDRAWAL**

Sanofi-Aventis U.S. LLC
55 Corporate Drive
Mail Stop: 55D-215A
Bridgewater, NJ 08807

ATTENTION: Shefali Goyal
Director, Global Regulatory Affairs

Dear Ms. Goyal:

Please refer to your New Drug Application (NDA) dated December 21, 2015, received December 21, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Glargine and Lixisenatide Injection, 100 units and 50 mcg per mL and 100 units and 33 mcg per mL.

We also refer to your September 6, 2016, correspondence, received on September 6, 2016, notifying us that you are withdrawing your request for a review of the proposed proprietary name, [REDACTED] (b) (4). Therefore, [REDACTED] (b) (4) is considered withdrawn as of September 6, 2016.

Finally, we refer to your September 6, 2016, correspondence, received September 6, 2016, requesting review of your proposed proprietary name, Soliqua 100/33. Upon preliminary review of your submission, we have determined that it is a complete submission as described in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

Therefore, the user fee goal date is December 5, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Martin White, Regulatory Project Manager in the Office of New Drugs, at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

Terrolyn Thomas, MS, MBA
Senior Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TERROLYN THOMAS
09/16/2016

From: Shefali.Goyal@sanofi.com
To: White.Martin
Cc: Guettier.Jean-Marc; Barry.Sickels@sanofi.com
Subject: RE: NDA 208673
Date: Friday, September 02, 2016 4:45:58 PM

Hi Martin,

Thanks for your quick response. We will therefore stay with the number sleeve design from August 10th.

We will submit the formal request regarding the modifier as suggested.

Best Regards

Shefali

Shefali Goyal

Global Regulatory Affairs - Diabetes

Phone:(908) 981-6996



From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Friday, September 02, 2016 2:47 PM
To: Goyal, Shefali R&D/US
Cc: Guettier, Jean-Marc; Sickels, Barry R&D/US
Subject: RE: NDA 208673

Shefali,

We have determined that a numerical modifier is FDA's preferred approach for the proprietary name for your product. We recommend the following: Soliqua 100/33

We request that you submit a new request for proprietary name for our review, or that you submit an alternative approach and explain why you do not agree with our recommendation.

With regard to your query: *We were following the Agency's advice on the number sleeve design received on August 10th to have the 1-2 and then black out the other numbers between 3-14.*

[REDACTED] (b) (4)
[REDACTED]. Is this a critical requirement from the Agency that is mandatory to change?

No, this is not a mandatory requirement. *[REDACTED]* (b) (4)
[REDACTED], please move forward with the August 10th design. Critical questions are no longer relevant.

Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]

Sent: Friday, September 02, 2016 12:33 PM

To: White, Martin

Cc: Guettier, Jean-Marc; Barry.Sickels@sanofi.com

Subject: RE: NDA 208673

Hi Martin,

Thanks for your email below.

We were following the Agency's advice on the number sleeve design received on August 10th to have the 1-2 and then black out the other numbers between 3-14. (b) (4)

Is this a critical requirement from the Agency that is mandatory to change?

Key questions:

- 1) Is the FDA going to establish this as mandatory design for fixed ratio combination products going forward?
- 2) If it is not mandatory, is the design the we proposed and FDA accepted on August 10th acceptable?
- 3) If it is mandatory, does the FDA have a (b) (4) they want used?
- 4) Does FDA anticipate any further changes may be required to the device before approval?

We will add the dose table in the PI as requested after we receive other Agency comments on our draft labeling submitted on August 11th, please let us know if this is acceptable.

We would like the opportunity to discuss with the Agency today regarding the change of the number sleeve.

Thanks and best regards

Shefali

Shefali Goyal

Global Regulatory Affairs, Diabetes

Phone:(908) 981-6996



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Friday, September 02, 2016 11:15 AM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673

Shefali,

Please see the comments from the review team.

Let me know if you have additional questions.

Thanks
Martin

- For the sleeve option please go with (b) (4) (blackened) in numbers for doses between the priming dose (i.e., 2 units) and 15 units range (A modified version OPTION#2, slide #2, in your slides entitled "Revised 15 to 60 number sleeves"). (b) (4), (b) (4)
- For dosing, we agree that doses of the combination product should be based on units of insulin glargine. The unit markings on the pen sleeve between 15 and 60 would therefore not change.
- The tradename on the pen will most likely include a modifier designating the product as a mixture of two products (similar to the approach taken for pre-mixed insulin products). At this stage, a tentative modifier being considered would have the following number of characters XXX/XX but a final determination on the exact nature of the modifier has not been made. This tentative information is being shared solely to help you anticipate the amount of space that may be needed for the tradename on the pen label. We will share our final recommendations regarding the tradename and modifier in the next few weeks either through labeling negotiations or through an email communication.
- With regards to the full PI, The D&A Section of the full PI should have a table describing the amount of insulin glargine and lixisenatide for each dose increment on the pen (example is provided below).

Unit(s) of insulin glargine	mcg of lixisenatide
P Priming volume not for injection	P Priming volume not for injection
15	Fill cell with the exact corresponding Lixi dose
16	Fill cell with the exact corresponding Lixi dose
17	Fill cell with the exact corresponding Lixi dose

18	Fill cell with the exact corresponding Lixi dose
19	Fill cell with the exact corresponding Lixi dose
20	Fill cell with the exact corresponding Lixi dose
Etc...Fill rows for the entire dose range	Etc...Fill rows for the entire dose range
60*	Fill cell with the exact corresponding Lixi dose

Martin White, M.S.
 Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Wednesday, August 24, 2016 11:03 AM
To: White, Martin
Subject: NDA 208673

Hi Martin,

Hope you are doing well. I am writing to follow up on the conversation last week (August 18th) between Barry Sickels and Dr. Guettier in which Dr. Guettier mentioned that written feedback on the pen device may be forthcoming this week. This feedback would be to confirm the key points such as the number sleeve design, dosing, units and anything else pertaining to the device that we need to apply to the manufacturing process as soon as possible.

Could you please let us know when we can expect this information from the Agency?

Thanks and Best Regards

Shefali

Shefali Goyal
 Global Regulatory Affairs - Diabetes
 Phone:(908) 981-6996



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/s/

MARTIN L WHITE
09/06/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208673

**REVIEW EXTENSION –
MAJOR AMENDMENT**

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, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for insulin glargine/lixisenatide injection.

We received your major amendment to this application dated and received August 12, 2016. We also refer to your additional amendments to this application dated and received June 6, and August 11, 2016. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 21, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 21, 2016.

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

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/s/

JEAN-MARC P GUETTIER
08/17/2016

**PeRC Meeting Minutes
July 13, 2016**

PeRC Members Attending:

Lynne Yao
Gettie Audain
Wiley Chambers
Robert “Skip” Nelson
Gerri Bauer
Lily Mulugeta
Hari Cheryl Sachs
Barbara Buch
Adrienne Hornatko-Munoz
Jackie Yancy
Greg Reaman
Ruthie Davi
Peter Starke
Meshawn Payne
John Alexander
Raquel Tapia
Thomas Smith
Ikram Elayan
Lisa Falcon
Dionna Greene

Agenda

NON-RESPONSIVE



NON-RESPONSIVE

	NDA 208673	Insulin Glargine/Lixisenatide (Full Waiver) with an Agreed iPSP	DMEP	Martin White	Treatment of Type 2 Diabetes Miletus

NON-RESPONSIVE

4 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

Insulin Glargine/Lixisenatide (Full Waiver) with an Agreed iPSP

- Proposed Indication: Treatment of Type 2 Diabetes Miletus
- The PDUFA goal date is August 21, 2016.
- *PeRC Recommendations:*
 - The PeRC agreed with the division to grant a full waiver of the pediatric patients because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups.

NON-RESPONSIVE

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/s/

GETTIE AUDAIN
08/10/2016



NDA 208673

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Sanofi-Aventis U.S. LLC
55 Corporate Drive
Mail Stop: 55D-215A
Bridgewater, NJ 08807

ATTENTION: Shefali Goyal
Director, Global Regulatory Affairs

Dear Ms. Goyal:

Please refer to your New Drug Application (NDA) dated December 21, 2015, received December 21, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Glargine and Lixisenatide Injection, 100 units and 50 mcg per mL and 100 units and 33 mcg per mL.

We acknowledge receipt of your June 16, 2016, correspondence, received June 16, 2016, requesting a review of your proposed proprietary name, Soliqua.

The user fee goal date will be September 14, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Martin White, Regulatory Project Manager in the Office of New Drugs, at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

Terrolyn Thomas, MS, MBA
Senior Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TERROLYN THOMAS
07/15/2016

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 17, 2016
TIME: 12:30 PM (EST)
LOCATION: White Oak, Building 22, Room 4157
APPLICATION: NDA 208673
DRUG NAME: Soliqua (Insulin Glargine and Lixisenatide)
TYPE OF MEETING: Teleconference

MEETING CHAIR: Lubna Merchant
MEETING RECORDER: Terrolyn Thomas

FDA ATTENDEES:

Kellie Taylor, Deputy Director, Office of Medication Error Prevention and Risk management
Lubna Merchant, Deputy Director, Division of Medication Error Prevention and Analysis
Hina Mehta, Acting Team Leader, Division of Medication Error Prevention and Analysis
Yelena Maslov, Team Leader, Division of Medication Error Prevention and Analysis
Ariane Conrad, Reviewer, Division of Medication Error Prevention and Analysis
Suchitra Balakrishnan, Medical Officer, Division of Metabolism and Endocrinology Products
Terrolyn Thomas, Senior Safety Project Manager, Office of Surveillance and Epidemiology
Nichelle Rashid, Team Leader, Office of Surveillance and Epidemiology

SPONSOR ATTENDEES:

Molly Story, Head Human Factors Engineering
Steffen Raab, Human Factors
Suresh Ghai, Regulatory Affairs Devices
Verena Siefke-Henzler, Chemistry, Manufacturing and Controls
Udo Stauder, Devices
Volker Korger, Devices
Shefali Goyal, Regulatory Affairs iGlarLixi Global Lead
Gerrit-Jan Nijveldt, Regulatory Affairs Labelling
Marissa Cipriani, Regulatory Affairs US
Sebastien Delarive, Global Brand Leader
Chris Cann, US iGlarLixi Brand Leader
Christine Soltys-Robitaille, Global Project Manager

BACKGROUND: The Applicant submitted a request for proprietary name request on January 8, 2016 to review the proposed proprietary names, Soliqua (b) (4) and Soliqua (b) (4). (b) (4) OSE issued a denial letter on April 1, 2016 indicating that Soliqua, and the modifier, (b) (4), are acceptable but the proposed name modifiers, (b) (4) are unacceptable because they may cause medication errors. In a previous teleconference dated April 26, 2016, DMEPA agreed to provide preliminary feedback on the modifiers that Sanofi submits. DMEPA requested a teleconference to provide feedback on the names (modifiers) that the Applicant proposed via email dated May 3, 2016.

MEETING OBJECTIVES: The purpose of this meeting is to discuss the modifiers proposed by the Applicant following the teleconference between DMEPA and Sanofi on April 26, 2016.

DISCUSSION

DMEPA provided preliminary feedback on the proposed modifier(s) submitted by the Applicant. DMEPA noted that none of the modifiers seemed like viable for the reasons listed below;

- Modifier (b) (4),” may imply that there are (b) (4), which is incorrect.
- Modifier (b) (4) could be misinterpreted as the (b) (4)

- Modifier (b) (4) DMEPA specifically advised the sponsor (b) (4) for the modifiers during the April 26, 2016 teleconference.

-
- Modifier (b) (4)

DMEPA recommended the Applicant continue to think about the best option for their modifiers and also consider some of the options discussed in the last teleconference. DMEPA recommended the Applicant submit an informal proposal for preliminary review for viability of the names via email after the upcoming Advisory Committee Meeting.

ACTION ITEMS

- Applicant will submit an informal proposal to DMEPA to obtain preliminary feedback on the viability of the names via email prior to official submission through EDR.

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/s/

TERROLYN THOMAS
06/08/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](mailto:White.Martin@fda.hhs.gov)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_Clinical Pharmacology Information Request 6-3-2016
Date: Friday, June 03, 2016 3:48:13 PM

Received.

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Friday, June 03, 2016 3:45 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_Clinical Pharmacology Information Request 6-3-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

For model validation purpose, please provide the simulated HbA1c and SMPG time profiles for patients in study ACT12374, using the same strategies you used for study EFC12404 and EFC12405, overlaid with observed data.

Please provide the response by June 13th, 2016.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
06/03/2016



NDA 208471
NDA 208673

GENERAL ADVICE

Sanofi US Services Inc.
Attention: David Faunce and Shefali Goyal
55 Corporate Drive
Mail Stop: 55D-215A
Bridgewater, NJ 08807

Dear Mr. Faunce and Ms. Goyal:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lixisenatide injection and insulin glargine/lixisenatide injection.

We also refer to your email dated May 11, 2016, concerning Sanofi US Services Inc., comments on FDA Briefing Material for the May 25, 2016, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee for NDA 208471 lixisenatide injection and NDA 208673 for insulin glargine/lixisenatide injection.

Thank you for citing sections in the FDA briefing materials that needed corrections or clarification. Below please find our response to your comments. Note that we will not issue written Errata. Corrections will be included in FDA presentations where indicated.

Specific Sanofi US Services Inc., comments are listed below. FDA responses are in **bold font**.

1. Page 18 – Clinical Pharmacology Summary: Last paragraph on page 18 should be changed to: (b) (4)

FDA Response: We acknowledge the additional language you have suggested. We do not believe that this additional language is necessary. No corrective action is warranted.

2. Table 4 (DRI6012, any TEAE, GI SOC AE) Typo % in the placebo: should be (b) (4)% instead of 29%. Additionally, (b) (4) (GI SOC for the placebo group), not 19%.

FDA Response: We acknowledge this typographical error. We will not be discussing the incidence of any treatment emergent adverse event from the placebo group for this study. Correct decimal places will be used in the FDA presentations. No additional corrective action is warranted.

3. Page 23: Incorrect sentence (proposed changes in red): Comparing the effect on glyemic control, the (b) (4) 2-step titration appeared to result in numerically greater placebo-adjusted reduction in HbA1c than (b) (4) 1-step titration, but this difference was small (<0.2%, Table 5)

FDA Response: We acknowledge this error. This error will be acknowledged and corrected in FDA presentations on the day of the meeting. No additional corrective action is warranted.

4. Table 5 (HbA1c 1-step and 2-step: EFC6018 and EFC10743): (1) Results were switched between 2-step and 1-step lixi groups (except for "N" in EFC6018). (2) For EFC6018, MMRM (FDA) results not consistent with those in Table 10 (from Sponsor's ISE and verified by FDA). (3) For EFC10743 where results are missing in Table 10, numbers are different from those in the Sponsor ISE.

FDA Response: We acknowledge this error. This error will be acknowledged and corrected in FDA presentation on the day of the meeting. No additional corrective action is warranted.

5. Table 10 (HbA1c pivotal studies: 6018, 6015, 6016): EFC10743 was considered to be a key study per Table 7, but the results are missing in this table that showed pivotal study results.

FDA Response: We acknowledge this omission. Results for study EFC10743 will be included with this grouping of studies in the FDA presentation. No additional corrective action is warranted.

6. Table 14 (SAEs [HLT> Ph3 PCT, entire period): For the SOC "Infections and infestations," the n (%) in the FDA BB is from the (b) (4) not the intended SOC = "Infections and infestations." For the SOC "Infections and infestations," n (%) would be (b) (4)% in placebo and (b) (4)% in lixisenatide according to the quoted source 1.4.4.2 of the ISS appendix (module 5.3.5.3).

Also, PT = "Coronary artery disease" appears twice under HLT "Coronary artery disorder NEC" (the second one seems redundant).

FDA Response: This change in numbers does not substantially change the interpretation of the values. We will not be discussing serious adverse events in this detail. The second coronary artery disease is redundant. This redundancy does not substantially change the interpretation of the values. No corrective action is warranted.

7. Table 16 (common AE Ph3 PCT, main): For HLT "Hypoglycaemic conditions NEC," n(%) in the FDA BB is from (b) (4), not the intended HLT = "Hypoglycaemic conditions NEC." For HLT "Hypoglycaemic conditions NEC," n (%) would be (b) (4)% in placebo and (b) (4)% in lixisenatide according to the quoted source 1.4.2.2 of the ISS appendix.

FDA Response: This change in numbers does not substantially change the interpretation of the values. We will not be discussing adverse events at this level of detail. No corrective action is warranted.

8. Page 37 (first paragraph): For the lixisenatide-treated subjects, the proportion with measurable concentrations of ADA increased over time (b) (4)

FDA Response: Use of “over time” is reasonable as the proportion of subjects with measurable ADAs increase from week 24 to week 76. No corrective action is warranted.

9. Page 37 (Table 19): Week 12 / < 100 nmol/L; column for n: 55 should be changed to (b) (4).
Week 12 / < 100 nmol/L; column for %: 59.1 should be changed to (b) (4)

FDA Response: This change in numbers does not substantially change the interpretation of the data. No corrective action is warranted.

10. Page 37 (last paragraph): Table 20 is for the entire period, while considering the PY data did not show “higher AE for any” in the ADA positive versus “ADA-.” Therefore introductory sentence of this paragraph may be considered misleading.

FDA Response: While we acknowledge that event rates and incidence are different, the language in the text and table both refer to incidence. No corrective action is warranted.

11. Page 39 (sentence before Table 21): However, it is notable that high ~~titr~~ concentration subjects had a smaller reduction in HbA1c.

FDA Response: We agree that “concentration” is the correct term to use. This will be corrected in the FDA presentations. No additional corrective action is warranted.

12. Anaphylaxis and Allergic Reactions (Page 41): NIAID/FAAN criteria were not used by ARAC to rule out anaphylaxis. In particular, there was no requirement to have reduced blood pressure or associated symptoms of end-organ dysfunction to confirm the diagnosis of anaphylaxis. Of the total 10 cases adjudicated as drug related anaphylaxis in the lixisenatide clinical development programs, 7 did not satisfy the anaphylaxis definition as outlined by NIAID/FAAN criteria.

FDA Response: We acknowledge this comment. We will not be emphasizing adjudication criteria, and will not be presenting NIAID/FAAN criteria. No correction is warranted.

13. Table 22 (HbA1c Week 76 by ADA data): FDA BB says the upper bound of the 95% CI for > 100 nmol/L is “-0.0188,” but the source says “-0.188.” Seems one extra “0” was added to the first decimal point by mistake.

FDA Response: This typographical error is noted. We do not intend to discuss the 76 week data, but if discussed will present corrected numbers. No corrective action is indicated.

14. Table 32 (calcitonin % in Ph2/3):

- a) "N=5580" in Lixisenatide for "Total" category in the FDA BB, but the source says "N=6404."
- b) For the "Other" group results
 - "N=2097" for the "Total" category, but the calculation from the source gives "N=1003"
 - For % for ">upper limit of reference to <20 pg/mL" under "Total", FDA BB says "3.5%" but calculation from the source ="7.4%"
 - For % for ">=20 pg/mL to <50 pg/mL" under "Total," FDA BB says "0.5%" but source calculation ="1.1%"
- c) N for ">upper limit of reference to <20 pg/mL" in the "below upper limit of reference at baseline" category should be 20, not "17" as shown in the BB, and thus the corresponding % should be "2.9%," not "2.4%."

FDA Response: We acknowledge the error. Correction of these numbers does not substantially change the conclusions from these data. We do not intend to present the details of the calcitonin data. If discussed, the corrected numbers will be presented. No corrective action is warranted.

15. Table 34 (Ph3 CV meta in 2012): This is a summary (meta-analysis) of old data from the withdrawn 2012 NDA submission without the addition of a new phase 3 study from the 2015 submission, (b) (4) Final data from the analysis of ELIXA is now available and should be considered for the review.

FDA Response: We agree that the data from the final analysis of ELIXA should serve as the basis of conclusions. However we believe inclusion of this discussion is informative with regard to explaining the reasons for withdrawal and issues with using interim data. FDA presentations will present final results only, and we will stress that the final results of ELIXA are the results to be considered. (b) (4)
(b) (4) as the study is completed and knowledge of the interim results cannot impact the integrity of the completed study.

16. Table 35 (ELIXA interim): Given that the final analysis from this study is available and was submitted with the NDA, the Sponsor does not see any value of the interim analysis as part of this NDA evaluation. Additionally, this data is not available to Sanofi outside of the original firewalled team, nor the public, (b) (4)

FDA Response: We agree that the data from the final analysis of ELIXA should serve as the basis of conclusions. However we believe inclusion of this discussion is informative with regard to explaining the reasons for withdrawal and issues with using interim data. FDA presentations will present final results only, and we will stress that the final results of ELIXA are the results to be considered. (b) (4)
(b) (4) the study is completed and the knowledge of the interim results cannot impact the integrity of the completed study.

17. Table 39 (on-treatment MACE+, MACE): Seems typos in FDA MACE on-treatment results: ELIXA CSR has 342/3034 (11.3%) for placebo, and 334/3034 (11.0%) for lixisenatide, but FDA has 342 (21.7%) for placebo and 334 (21.8%) for lixisenatide. ELIXA CSR shows the correct percentages.

FDA Response: We acknowledge this error in data entry. While the numbers are incorrect, the overall interpretation remains the same. Corrected numbers will be used in FDA presentations. No additional corrective action is warranted.

18. Table 53 (deaths and SAEs in Ph3): The row “Nonfatal serious adverse events” presents the number of patients with both fatal and non-fatal SAEs during on- treatment period. The n (%) of patients with non-fatal SAEs during on-treatment period is 8 (3.4%) in lixisenatide, 33 (4.0%) in glargine, and 35 (4.2%) in FRC. Non-fatal SAEs were not presented in ISS.

FDA Response: We acknowledge the error in the presented percentages. The FDA presentation will correct these numbers. No additional corrective action is warranted.

19. Table 54 (Summary of nonfatal SAEs (HLT>0.4%)): *FDA BB presented this table in a very unusual way for on and post TEAEs using multiple SOC's (primary and one or more secondary SOC's) and “N = number of events,” not “number of patients” and used “# events/# in the safety population” for calculating “%,” not the usual way of “# patients with an event/# in the safety population.*

Details of the FDA algorithm:

- Included both on- and post- treatment AEs
- N for each SOC/HLT/PT was event count, not patient count. % = # events / # patients, on which the cutoff (HLT>0.4%) was based.
- - Included all SOC's, ie, primary SOC and/or 1 or more secondary SOC's. Some PTs/HLTs appeared more than once under different SOC's. For example, HLT” Hypoglycaemic conditions NEC” and its PTs “Hypoglycaemia,” “Hypoglycaemic seizure,” “Hypoglycaemic unconsciousness” appeared twice under SOC's “ENDOCRINE DISORDERS” and “METABOLISM AND NUTRITION DISORDERS.”

FDA Response: We acknowledge that the presented table did not present incidence using number of subjects with event/number of subjects. A corrected table for High Level Terms in >4% of subjects is included below. Review of this does not appear to substantially change the interpretation of safety. We note your comment. We will not be presenting information on serious adverse events for the insulin glargine and lixisenatide injection. No corrective action is warranted.

	Lixi N=233		Insulin glargine N=832		FRC N=834	
Cerebrovascular and spinal necrosis and vascular insufficiency	2	0.9	1	0.1	1	0.1
Coronary necrosis and vascular insufficiency	0	0.0	4	0.5	6	0.7

	Lixi N=233		Insulin glargine N=832		FRC N=834	
Heart failures NEC	0	0.0	5	0.6	1	0.1
Hypoglycaemic conditions NEC	0	0.0	1	0.1	4	0.5
Ischaemic coronary artery disorders	0	0.0	4	0.5	5	0.6
Pain and discomfort NEC	0	0.0	4	0.5	0	0.0
Respiratory signs and symptoms NEC	0	0.0	4	0.5	0	0.0

20. Table 55 (Summary of common AEs (PT>2%) in Ph3 studies): **Same comment as above**

FDA Response: We acknowledge that the presented table did not present incidence using number of subjects with event/number of subjects. A corrected table for Preferred Terms in >2% of subjects is included below. Review of this does not appear to substantially change the interpretation of safety. We note your comment. We will not be presenting the entirety of the table for the insulin glargine and lixisenatide injection. Safety concerns presented will reflect number of subjects with event/number of subjects. No additional corrective action is warranted.

	Lixi N=233		Insulin glargine N=832		FRC N=834	
Abdominal pain	5	2.1	9	1.1	7	0.8
Back pain	8	3.4	15	1.8	23	2.8
Bronchitis	5	2.1	20	2.4	17	2.0
Diarrhoea	21	9.0	30	3.6	58	7.0
Dizziness	7	3.0	12	1.4	24	2.9
Dyspepsia	5	2.1	8	1.0	11	1.3
Fatigue	5	2.1	7	0.8	7	0.8
Gastroenteritis	5	2.1	6	0.7	10	1.2
Headache	18	7.7	25	3.0	45	5.4
Influenza	4	1.7	22	2.6	31	3.7
Nasopharyngitis	16	6.9	58	7.0	59	7.1
Nausea	56	24.0	19	2.3	83	10.0
Pain in extremity	5	2.1	10	1.2	12	1.4
Upper respiratory tract infection	12	5.2	35	4.2	46	5.5
Urinary tract infection	6	2.6	13	1.6	19	2.3
Vomiting	15	6.4	9	1.1	29	3.5

21. Table 57 (EFC12404 hypo): For Documented symptomatic, the numbers presented in this table were actually not for documented symptomatic hypo but for all symptomatic hypo.

FDA Response: This is noted and numbers presented in the FDA presentation will be for "Documented symptomatic." No additional corrective action is warranted.

22. Table 7 (Ph3 study design for key studies): For EFC10743: planned N for lixisenatide is

(b) (4), and (b) (4) for placebo For EFC6016 population: (b) (4) in objective, missing.

FDA Response: We do not consider this to meaningfully change the understanding of the study description or results. We will not be discussing this level of detail in the presentations. No corrective action is warranted.

23. Table 9 (Ph3 ACT design): For EFC10780, planned N is (b) (4) not "160."
For EFC12626, planned N is (b) (4), not "300."

FDA Response: We do not consider this to meaningfully change the understanding of the study description or results. We will not be discussing this level of detail in the presentations. No corrective action is warranted.

24. Table 11 (HbA1c for other 6 Ph3 PCT): For EFC6017, missing (b) (4) in the study title.

FDA Response: We do not consider this to meaningfully change the understanding of the study description or results. We will not be discussing this study in the presentations. No corrective action is warranted.

25. Table 12 (HbA1c for 3 Ph3 active-controlled): For EFC12626, should state (b) (4) not "double-blind" in the study title

FDA Response: Descriptions of this study will be corrected in the FDA presentation. No additional corrective action is warranted.

26. Table 20 ($\geq 3\%$ AE by ADA): Would add "entire period" in the title, since we provided both "main" and "entire" period results. Also, due to different treatment exposure, would add PY data to adjust for different treatment exposure.

FDA Response: We acknowledge these comments. No corrective action is warranted.

27. Table 21 (HbA1c Week 24 by ADA data): FDA BB says LS mean (95% CI) for $\geq$ LLOQ to $\leq$ 100 nmol/L is -0.63 (-0.732, -0.534), while the source table in the SCE says (b) (4)

FDA Response: We do not consider this to meaningfully change the understanding of the results. These numbers will be corrected in the FDA presentation. No additional corrective action is warranted.

28. Page 40 (2nd paragraph under c): It says "372" events, but it should be (b) (4) events

FDA Response: We acknowledge this typographical error. This does not substantially change the interpretation of the findings. No corrective action is warranted.

29. Table 23 (adjudicated allergic events): "n" in the column header for this table in the FDA

BB is different from the quoted source. The FDA BB used all 20 Ph2/3 patients in the safety population (including ACT6011), while the quoted source is based on 19 Ph2/3 with ARAC adjudication (ie, excluded "N" from ACT6011). Not sure if this was a typo or on purpose

FDA Response: This was a typographical error. The sample size numbers were carried over from previous tables. As the presented incidence is correct, we do not believe this substantially changes the interpretation of the findings. No corrective action is warranted.

30. Table 24 (possibly IP related allergic events): "n" in the column header for this table in the FDA BB is different from the quoted source. The FDA BB used all 20 Ph2/3 patients in the safety population (including ACT6011), while the quoted source is based on 19 Ph2/3 with ARAC adjudication (ie, excluded "N" from ACT6011). Not sure if this was a typo or on purpose

FDA Response: This was a typographical error. The sample size numbers were carried over from previous tables. As the presented incidence is correct, we do not believe this substantially changes the interpretation of the findings. No corrective action is warranted.

31. Table 27 (pancreatitis Ph2/3): For any event % in the "other" group, this table says "0.1%," but the source says "(b)(4) %."

FDA Response: We do not consider this to meaningfully change the understanding of the study results. We will not be discussing this level of detail in the presentations.

32. Table 30 (malignancies of interest): Typos in the % for the thyroid (1)Missing "." In the lixisenatide group; (2) "<0.1%" not "(b)(4)%" in the "Other" group; A similar typo for the "papillary thyroid cancer" in the "Other group."

FDA Response: We do not consider this to meaningfully change the understanding of the study results. We will not be discussing this level of detail in the presentations.

33. Table 31 (mean calcitonin Ph3 PCT): FDA BB says "N=1517" for Placebo and "N=2630" for Lixisenatide for the Last value on-treatment, but the source says "(b)(4)" for Placebo and "(b)(4)" for Lixisenatide.

FDA Response: We do not consider this to meaningfully change the understanding of the study results. We will not be discussing this level of detail in the presentations.

34. Table 33 (hypo Ph3 PCT main): Results for EFC10887 are for all (basal insulin +/- sulfonylurea), not just for basal insulin+SU as noted in the BB.

FDA Response: We acknowledge this typographical error. We do not think this to meaningfully change the understanding of the study results. No corrective action is warranted.

35. Table 36 (ELIXA baseline): (1) United states under "Region:" Number for Placebo and Lixi

are switched. It should be 347 placebo and 349 Lixi randomized patients from United states. (2) Antidiabetic medications under “Concomitant medications (at randomization) of Metformin, SU, TZD, insulin. In footnote, FDA indicates reference from ELIXA CSR. The numbers (%) for these anti-diabetic medications are copied from the CSR “on- study” antidiabetic medication (ELIXA CSR Table 18), instead from “prior antidiabetic medication” (ELIXA CSR Table 17).

FDA Response: We acknowledge the error in numbers from the United States. We acknowledge that the error in concomitant antidiabetic medications. We do not believe that this substantially impacts the interpretation of the study results. No corrective action is warranted.

36. Figure 12 (forest plot of mortality subgroup results): “Female” and “Male” results seem to be switched: the results for “Male” subgroup is actually for “Female” and the results for “Female” subgroup is actually for “Male.”

FDA Response: We acknowledge this error. We do not intend to discuss sub-group findings for mortality. If discussed, this will corrected. No additional corrective action is indicated.

37. Table 47 (HbA1c): Inconsistent presentation of n in the column header between EFC12405 and EFC12404: EFC12404: “n” represents the number in the mITT population EFC12405: “n” represents those included in the HbA1c analysis, ie, patients had HbA1c measurements at both baseline and post- baseline

FDA Response: We do not believe this substantially alters the interpretation of the data. Consistent populations will be used in the FDA presentations. No additional corrective action is warranted.

38. Table 48 (2-hr glucose excursion): EFC12404 typos: (1) for the baseline value with lixisenatide: FDA BB has 91.36 but the source CSR Table 4 quoted in the footnote shows 91.26 (2) for LS mean diff vs. insulin glargine and the upper bound of the 95% CI: FDA BB has -38.45 with the upper bound as - 31.89, but the source CSR Table 4 quoted in the footnote shows -38.44 and UB = -31.88.

EFC12405 typos: For LS mean diff vs. insulin glargine (95% CI): FDA BB has -61.83 (95% CI: -70.71, -52.96), but the source CSR Table 5 quoted in the footnote shows -61.82 with 95% CI as (-70.70, -52.95).

FDA Response: We do not believe these substantially alter the interpretation of the data. No corrective action is warranted.

39. Table 50 (% of final lixisenatide dose summary): The data in this table referred to as the source were based upon the safety population that had no category of <5ug. However, numbers presented in this table were based upon the mITT population. The right source data should be section 16.2.6.6.1.2 of the Appendix to the study report for study EFC12404 and section 16.2.6.7.1.2 of the Appendix to the study report for study EFC12405.

FDA Response: We acknowledge this comment. The numbers presented are identical. No corrective action is indicated.

40. Page 79: Page 79 sentence “Based on mean insulin glargine dose (Figure 25), lixisenatide doses above 10 µg were not achieved on average until week 6 “ is not correct as based on 16.2.6.2.76 (Average daily insulin glargine dose (U) by visit) as well as Fig 25, it is already reached at week 5.

FDA Response: We note that mean dose achieved with the fixed ratio combination at week 5 was 20.5 “units.” Mean dose achieved at week 6 was 22.6 “units.” This translates to a mean lixisenatide dose of 10.25 and 11.3 micrograms, respectively. We acknowledge that 10.25 is greater than 10. In considering the timepoint, we rounded to the nearest microgram leading us to conclude that the dose did not exceed 10 micrograms until week 6. While there is a difference of 1 week, we do not believe that this should substantially change the interpretation of the findings. We have examined adverse events up to an earlier timepoint (i.e., 28 days) and seen similar findings (see table below for high level terms in >2% of any arm). As the overall interpretation of the data to not substantially change with using 28 days or 42 days, we do not

	Lixi N=233		Insulin glargine N=464		IGlarLixi N=467	
Nausea and vomiting symptoms	46	19.7	9	1.9	26	5.6
Upper respiratory tract infections	3	1.3	10	2.2	18	3.9
Upper respiratory tract infections NEC	3	1.3	10	2.2	18	3.9
Diarrhoea (excl infective)	9	3.9	9	1.9	15	3.2
Headaches NEC	11	4.7	8	1.7	13	2.8
Neurological signs and symptoms NEC	4	1.7	4	0.9	12	2.6
Cardiac signs and symptoms NEC	5	2.1	5	1.1	11	2.4
Circulatory collapse and shock	4	1.7	5	1.1	11	2.4
Asthenic conditions	6	2.6	3	0.6	3	0.6

41. Table 52 (safety pool) For EFC12405, the source table is also Table 36 of the EFC12405 CSR, not Table 26 as quoted in the FDA BB

FDA Response: We acknowledge this typographical error. No corrective action is warranted.

42. Table 54 (summary of non-fatal SAEs): There were a total of 4 patients with 5 events of serious hypoglycemia, not 5 patients.

FDA Response: We acknowledge this error. This will be corrected in the FDA presentation. No additional corrective action is warranted.

The FDA considers this to be its final position on the FDA briefing materials for NDA 208471 for lixisenatide injection and NDA 208673 for insulin glargine/lixisenatide injection.

NDA 208471
NDA 208673
Page 11

If you have any questions, call Martin White, 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

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
05/20/2016

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 26, 2016
TIME: 11:00 AM (EST)
LOCATION: White Oak, Building 22, Room 3157
APPLICATION: NDA 208673
DRUG NAME: Soliqua (Insulin Glargine and Lixisenatide)
TYPE OF MEETING: Teleconference

MEETING CHAIR: Lubna Merchant
MEETING RECORDER: Terrolyn Thomas

FDA ATTENDEES:

Lubna Merchant, Deputy Director, Division of Medication Error Prevention and Analysis
Hina Mehta, Team Leader, Division of Medication Error Prevention and Analysis
Yelena Maslov, Team Leader, Division of Medication Error Prevention and Analysis
Ariane Conrad, Reviewer, Division of Medication Error Prevention and Analysis
William Chong, CDTL, Division of Metabolism and Endocrinology Products
Terrolyn Thomas, Senior Safety Project Manager, Office of Surveillance and Epidemiology

SPONSOR ATTENDEES:

Molly Story, Head Human Factors Engineering
Steffen Raab, Human Factors
Anthony Watson, Head Regulatory Affairs - Devices
Suresh Ghai, Regulatory Affairs Devices
Verena Siefke-Henzler, Chemistry, Manufacturing and Controls
James Collins, Head Device Development Unit
Udo Stauder, Devices
Volker Korger, Devices
Don Gieseke, Regulatory Affairs Diabetes
Shefali Goyal, Regulatory Affairs iGlarLixi Global Lead
Gerrit-Jan Nijveldt, Regulatory Affairs Labelling
Marissa Cipriani, Regulatory Affairs US
Joanne Robinett, Regulatory Affairs US
Sebastien Delarive, Global Brand Leader
Chris Cann, US iGlarLixi Brand Leader
Christine Soltys-Robitaille, Global Project Manager

BACKGROUND: The sponsor submitted a request on January 8, 2016 to review the proposed proprietary names, Soliqua (b) (4) and Soliqua (b) (4). OSE issued a denial letter on April 1, 2016 indicating that Soliqua, and the modifier, (b) (4) are acceptable. However, the modifiers (b) (4) are unacceptable because they may cause medication errors. DMEPA requested a teleconference to discuss the sponsor's proprietary naming strategies for this product and offer some alternatives for them to consider.

MEETING OBJECTIVES: The purpose of this meeting is to discuss proprietary naming strategies and offer some alternatives for the sponsor to consider.

DISCUSSION

DMEPA informed the sponsor that the alternative modifiers proposed via slides from Sanofi prior to the teleconference, (b) (4), may be misleading because they are typically used in proprietary names (b) (4). However, Sanofi is proposing these modifiers be added for the pen device that actually contains the lower ratio of insulin glargine:lixisenatide.

DMEPA inquired if the sponsor had considered using the modifiers (b) (4) and 100/33,. The sponsor has concerns (b) (4)

However, the pens were designed (b) (4)

DMEPA inquired if the sponsor considered using (b) (4) as modifiers for the proprietary name. The sponsor has not considered expressing the name with (b) (4) and believed that this method would be misleading because (b) (4)

The Sponsor inquired about using the (b) (4) modifiers to differentiate the pens. DMEPA noted that (b) (4) as the modifiers (b) (4) and explained that this method may not be advisable.

Sponsor asked if DMEPA had any advice for them. DMEPA suggested to the sponsor may consider the use of a nonsensical modifier (i.e., the modifier that does not convey preconceived meaning) for differentiation of the two pens (e.g., (b) (4) for one pen and Soliqua “Modifier” (b) (4) for another pen).

DMEPA recommended that Sanofi submit their proposal via email for our preliminary feedback prior to the official submission.

REGULATORY OPTIONS

- The Sponsor said they would discuss the various options internally and may consider submitting the proposed proprietary name with nonsensical modifier(s) for one of their pens.

ACTION ITEMS

- Applicant will submit an informal proposal to DMEPA for preliminary review for viability of the names via email prior to official submission through EDR.

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

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

/s/

TERROLYN THOMAS
05/11/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_CDRH Information Request 5-09-2016
Date: Monday, May 09, 2016 3:47:04 PM

Received, thanks

Shefali

Shefali Goyal
(908) 981-6996

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Monday, May 09, 2016 3:30 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_CDRH Information Request 5-09-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

1. In document QUA-FD-2015-19978 you executed a simulated shipping study and performed functional inspection and dose accuracy testing to confirm the pen-injectors maintained functionality after shipping. The Agency believes that certain essential performance requirements such as dispensing force, injection time, and visual/audible/tactile feedback should be verified after shipping in order to establish that the device continues to meet all essential performance requirements. Please provide this testing in order to verify the essential performance requirements after shipping. Alternatively, please provide greater detail regarding the 'functional testing' performed in accordance with ISO 11608-1 Section 10.1 d) and if the functional testing included testing for the other essential performance requirements of your device besides dose accuracy.

Please provide the responses by Thursday, May 12, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 240.402.6018

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Martin.White@fda.hhs.gov

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

/s/

MARTIN L WHITE
05/09/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](mailto:White.Martin@fda.hhs.gov)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_Clinical Information Request 4-26-2016
Date: Tuesday, April 26, 2016 4:57:08 PM

Received, thanks.

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Tuesday, April 26, 2016 4:26 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_Clinical Information Request 4-26-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

Please summarize how many patients switched from PenA to PenB or vice-versa over the course of the studies EFC12404 and 12405. If the information is already available, please point to the location in the eCTD. Also summarize information for these patients related to hypoglycemia, gastrointestinal side-effects and dosing errors.

Please provide the responses by Tuesday, May 3, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
04/26/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_CDRH Information Request 4-26-2016
Date: Tuesday, April 26, 2016 4:56:54 PM

Received, thanks.

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Tuesday, April 26, 2016 4:17 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_CDRH Information Request 4-26-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

1.



(b)(4). Please provide a justification for why the vehicles you have used are appropriate for this test. Alternatively, please provide a method validation demonstrating that the extracts from the chosen vehicles are able to detect potential sensitizers. For more information, please refer to ASTM F2148: standard practice for evaluation of delayed contact hypersensitivity using the murine local lymph node assay.

2. In response to an information request dated March 2, 2016, you stated that the glargine/lixisenatide pen-injector is operated manually and therefore essential performance requirements associated with automated features do not apply. The Agency accepts this rationale for certain performance criteria, however the Agency notes that a specification should be developed for the injection time per unit dose so that the users have an expectation of how long it should take to inject given a maximum dispensing force of less than or equal to (b)(4) N. Please state the minimum time to inject (i.e. at a dispensing force of (b)(4) N) the minimum and maximum dose for both pen A and pen B. This minimum time to inject should be included in the labeling of the device to inform users the minimum time they must sustain the injection (independent of any audible/visual/tactile feedback for the end of injection). Alternatively, please provide a more detailed rationale for not including an estimated injection time for the minimum and maximum dose of the pen-injectors.
3. The Agency notes that your pen-injectors include tactile/visual/audible feedback per ISO 11608-1. However, you have not provided any verification of this feedback. Please develop a specification for this feedback as a part of your essential performance requirements and provide verification that the feedback functions as intended.

4. The Agency notes that of your essential performance requirements you have only included extractable volume as a test of dose accuracy within your current batch release (document QUA-FR-2014-23122). The Agency notes that all essential performance requirements should be verified during batch release including dose selection, dispensing force, injection time (based on results of request for specification), audible/visual/tactile feedback, and dose accuracy. Please provide documentation as evidence that you have included dose selection, dispensing force, and audible/visual/tactile feedback within your batch release testing.

5. In response to an information request dated March 2, 2016, you stated that the tests performed during in-use and long term stability studies are performed according to ISO 11608-1:2012 and require full functional assessment of the pen-injector, including steps to set up the pen for an injection and dispense the dose. However, you have not stated specifically what essential performance requirements were tested post-aging besides dose accuracy. It seems that you are asserting that a test for dose accuracy is a downstream effect of all functional characteristics of the pen-injector and therefore is representative of all other essential performance criteria. The Agency believes that certain essential performance requirements such as dispensing force, injection time, and visual/audible/tactile feedback should be verified after aging and preconditioning the device in order to establish that the device meets all essential performance requirements up to the labeled date of expiry for the device. Please provide this testing on a currently available batch within the long-term stability study in order to verify the essential performance requirements after aging. Alternatively, please provide greater detail regarding the full functional testing based on the instructions for use completed post-aging and if the functional testing included testing for the other essential performance requirements of your device besides dose accuracy.

Please provide the responses by Monday, May 2, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
04/26/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_Statistical Information Request 4-19-2016
Date: Wednesday, April 20, 2016 2:23:08 PM

Received.

Regards
Shefali

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Wednesday, April 20, 2016 2:20 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_Statistical Information Request 4-19-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015 and to the White Paper submitted in submission dated April 15, 2016, we have the following information request:

Please submit the SAS code for the sensitivity analyses of study results in Section 2.1.5 of the white paper. Please provide the code used for analysis only and omit the code used to generate tables.

Provide the response by Monday, April 22, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
04/20/2016

From: Shefali.Goyal@sanofi.com
To: White.Martin
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_Information Request 4-6-2016
Date: Wednesday, April 06, 2016 4:39:14 PM

Received, thanks.

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Wednesday, April 06, 2016 4:19 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_Information Request 4-6-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

Regarding Table 16.2.2.2.1 in the CSR for study EFC 12405:

Please summarize the initiation dose deviations by each component of the FRC i.e. -number of patients who were initiated on a higher dose of insulin glargine than recommended by protocol, higher dose of lixisenatide than recommended by protocol, and similarly for patients who were initiated on a lower dose by each component.

Please provide the responses by Monday, April 11, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
04/08/2016



NDA 208673

MID-CYCLE COMMUNICATION

Sanofi US Services Inc.
Attention: Shefali Goyal
Associate 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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for insulin glargine and lixisenatide injection.

We also refer to the teleconference between representatives of your firm and the FDA on March 23, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

Martin White, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: March 23, 2016 - 3: 00 PM to 4:00 PM

Application Number: NDA 208673
Product Name: insulin glargine and lixisenatide injection
Indication: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Applicant Name: Sanofi US Services Inc.

Meeting Chair: William Chong, M.D.
Meeting Recorder: Martin White, M.S.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D.	Director
William Chong, M.D.	Clinical Team Leader
Suchitra Balakrishnan, M.D.	Clinical Reviewer
Pamela Lucarelli, B.S.	Chief, Project Management Staff
Martin White, M.S.	Regulatory Project Manager

APPLICANT ATTENDEES

Rene Belder, M.D.	Project Head
Elisabeth Niemoeller, M.D.	Lead Clinician
Elisabeth Souhami, M.D.	Clinical Director
Yujun Wu, PhD.	BioStatistician
Peng-Liang Zhao, PhD.	Head Diabetes BioStatistics
Sandeep Kumar, M.D.	LixiLan Safety Officer
Jean-Luc Delhay, M.D.	Lixisenatide Safety Officer
Kirsten Sharma, M.D.	Head Diabetes Pharmacovigilance
Wolfgang Schmider, PhD.	Pharmacokinetics
John Newton, PhD.	Head Pharmacokinetics
Aleksandra Vljajnic, M.D.	Medical Affairs
Riccardo Perfetti, M.D.	Head Diabetes Medical Affairs
Verena Siefke-Henzler, PhD.	Chemistry, Manufacturing and Controls
Volker Korger, PhD.	Devices
Molly Story, PhD.	Head Human Factors Engineering
Caroline Ruf, PhD.	Human Factors
Anthony Watson, PhD.	Head Regulatory Devices
Julie Doerr, Regulatory	CMC
David Faunce, M.S.,	Lixisenatide Regulatory Affairs

Shefali Goyal, M.S., MSc.
Barry Sickels, PhD.
Sebastien Delarive,
Reinhold Roessler, PhD.

LixiLan Regulatory Affairs
Head North America Regulatory Affairs
Global Brand Leader
Project Manager

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Review issue # 1: Risk of anaphylaxis with lixisenatide

The potential for anaphylaxis with lixisenatide (a component of insulin glargine and lixisenatide injection) remains under consideration. Assessment of the risk with lixisenatide will contribute to the safety considerations for the insulin glargine and lixisenatide injection.

Review issue # 2: Interpretability of efficacy data due to study design

Given that insulin glargine doses were capped in the phase 3 studies and the limited scope of titration seen in EFC12405, we are considering whether the comparisons are unbiased and how to interpret the findings.

There is limited data on the contribution of lixisenatide to the effect of the insulin glargine and lixisenatide injection at lixisenatide doses < 10 mcg. This is further limited by the fact that the lixisenatide development program evaluated a maintenance dose of 20 mcg. Your post-hoc analyses and modeling remain under review.

Review issue # 3: Limitation of insulin dosing

The data submitted from the (b) (4) Database to support the statement that a majority of the target population will require a daily dose of insulin glargine between 10 and 60 units remains under review.

Review issue # 4: Medication errors

The revised dosage recommendations for patients already treated with insulin are not consistent with the algorithm used in your clinical trials. Similarly, the proposed dial display for the to-be marketed device differs in that doses below 10 units (or 30 units) are presented. Whether these

differences will impact dosing and the risk for medication errors is under consideration. The human factors validation study is still being reviewed.

Discussion: *The Division stated that the human factors testing remains under consideration and that the potential for medication errors remains a concern. Sanofi inquired whether a meeting with the Division of Medication Error Prevention and Analysis would be helpful in addressing the concerns. The Division stated that such a meeting would not be viewed as helpful at this time. Additional internal discussion and consideration would be needed first. If such a meeting would be helpful, the Division will contact Sanofi to request one.*

3.0 INFORMATION REQUESTS

There are no information requests at this time.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

The new data submitted regarding the risk of anaphylaxis with lixisenatide remains under review at this time.

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have made a preliminary determination that a risk evaluation and mitigation strategy (REMS) will not be necessary to ensure that the benefits of the insulin glargine and lixisenatide injection outweigh the risks of pancreatitis. A final determination will be made upon completion of our review. Updates will be provided when they become available.

5.0 ADVISORY COMMITTEE MEETING

We anticipate that the insulin glargine and lixisenatide injection will be discussed at an Advisory Committee meeting.

Discussion: *The anticipated format of the Advisory Committee meeting was discussed. The Division expects that both products will be presented during a single presentation by Sanofi and by the Division. The amount of time for each presentation is expected to be consistent with other Advisory Committee meetings. Sanofi inquired regarding the expectations for discussion of lixisenatide alone. The Division stated that a discussion point on the efficacy and safety of lixisenatide can be expected. Whether a voting question on this point will be included remains to be determined.*

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late Cycle Meeting will occur on May 11, 2016.
We expect to send labeling to you on or before July 22, 2016.

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/s/

MARTIN L WHITE
04/05/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208673

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Sanofi-Aventis U.S. LLC
55 Corporate Drive
Mail Stop: 55D-215A
Bridgewater, NJ 08807

ATTENTION: Shefali Goyal
Director, Global Regulatory Affairs

Dear Ms. Goyal:

Please refer to your New Drug Application (NDA) dated December 21, 2015, received December 21, 2015, submitted under section 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act for Insulin Glargine and Lixisenatide Injection, 100 units and 50 mcg per mL and 100 units and 33 mcg per mL.

We also refer to:

- Your January 8, 2016, correspondence, received January 8, 2016, requesting review of your proposed proprietary names, Soliqua (b)(4) and Soliqua (b)(4)
- Your amendment to the Request for Proprietary Name Review, dated January 20, 2016, and received January 20, 2016.

We have completed our review of the proposed proprietary names, Soliqua (b)(4) and Soliqua (b)(4), and have concluded that the name, Soliqua, and the modifier, (b)(4) are acceptable but the proposed name modifiers, (b)(4) are unacceptable because they may cause medication errors for the following reasons:

1. The modifiers, (b)(4), may be misinterpreted as demonstrated in the human factors study results where:
 - a. One physician misinterpreted the modifier as the ratio of medication contained within the pen injector. While this misinterpretation did not result in a dosing error, the prescriber could have given the wrong dose based on an incorrect assumption regarding the medication, which could result in a potentially harmful under or overdose of the medication. Two nurses and two patients also misinterpreted the modifiers to indicate a ratio statement. Moreover, we have other marketed insulin products where the numerical modifier denotes the ratio of the insulin components (e.g., Novolog 70/30, Novolin 70/30, and Humalog 50/50). Given the precedence of this nomenclature in the market, we are concerned that prescribers may misinterpret the modifiers as ratio statements.

- b. One patient misinterpreted the modifier as the dose he was supposed to prepare (i.e., (b) (4)) after receiving instructions to prepare a 20 unit dose.

The above findings are concerning and indicate that the modifiers, (b) (4) may be confused or misinterpreted by end users as ratios or dose.

2. In addition to the misinterpretations in the human factors study results, we also note the following in our FDA Name Simulation Studies for Soliqua (b) (4) and Soliqua (b) (4)

- a. One participant misinterpreted the (b) (4) modifier as (b) (4).
- b. One participant misinterpreted the (b) (4) modifier as (b) (4).
- c. One participant commented that he/she was unsure if the (b) (4) was part of the product name or a dose range when interpreting a verbal order for Soliqua (b) (4)
- d. One participant commented that there was no dose on the written order when transcribing the order for Soliqua (b) (4), which may indicate that the practitioner could not distinguish the dose (b) (4) from the modifier (b) (4)
- e. Two participants transcribed the order for Soliqua (b) (4) as “before dinner” without including a dose to administer, which may indicate that these practitioners interpreted the (b) (4) as the dose prescribed.

We also note the report from Med-ERRS (IND 105157) in which it was stated that these modifiers pose a high risk for confusion and may be misinterpreted as a patient specific dose or dosage range instead of the modifier for the pen injector.

3. The modifiers, (b) (4), can be misleading because each of the proposed devices can deliver doses outside of the labeled dose range (i.e., (b) (4))

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 240-402-3981. For any other information regarding this application, contact Martin White, Regulatory Project Manager in the Office of New Drugs, at 240-402-6018.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
04/01/2016

From: Shefali.Goyal@sanofi.com
To: White, Martin
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 3-23-2016
Date: Thursday, March 24, 2016 3:45:54 PM

Great, thanks Martin.

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Thursday, March 24, 2016 3:33 PM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 3-23-2016

Shefali,

Hopefully, we will be able to get these minutes to you next week.

Dr. Guettier was also on the call.

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Thursday, March 24, 2016 11:58 AM
To: White, Martin
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 3-23-2016

Ok, I will let them know.

When do you plan to send us the meeting minutes from yesterday? Also, was Dr. Guettier on the phone?

Regards
Shefali

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Thursday, March 24, 2016 11:55 AM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 3-23-2016

Yes, please.

Thanks
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Wednesday, March 23, 2016 5:33 PM
To: White, Martin
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 3-23-2016

Hi Martin,
Would you want these labeled as well?

Regards
Shefali

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Wednesday, March 23, 2016 4:12 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 3-23-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

We request that you submit a total of twenty (20) additional sample pen devices for insulin glargine/lixisenatide NDA 208673 (i.e., 10 of the 10 to 40 pens and 10 of the 30 to 60 pens) to aid in our review process.

The samples should be provided to the following address:

Martin White, M.S.
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3389
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code 20903 if shipping via United States Postal Service (USPS).
Use zip code 20993 if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

We request that you submit these samples to us no later than close of business on Friday, April 15, 2016.

Confirm receipt of this email.

Thanks
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
03/25/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_ Device Information Request 3-22-2016
Date: Tuesday, March 22, 2016 3:42:20 PM

Received, thanks.

Shefali

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Tuesday, March 22, 2016 3:33 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_ Device Information Request 3-22-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

On March 2, 2016, you provided test reports for cytotoxicity testing and chemical characterization data on the Lantus SoloStar pen components, which contains the (b) (4) that will be used in the to-be marketed glargine/lixisenatide pen-injectors. On March 15, 2016, the Agency requested that you provide a comparison of the materials in the proposed glargine/lixisenatide pen-injector to the Lantus SoloStar, in order to determine that no additional (b) (4) of the proposed pen, resulting in a cytotoxic response that would not occur with the Lantus SoloStar pen. Additionally, the Agency requested information to address the sensitization and irritation endpoints. On March 18, 2016, you provided irritation and sensitization test reports on the to be marketed pen-injector (b) (4). However, you are still using the cytotoxicity testing from the Lantus Solostar pen to evaluate the cytotoxicity of the device. Please provide a description of the materials in the Lantus SoloStar pen compared to the to-be marketed glargine/lixisenatide pen-injector and provide a rationale as to why any difference in materials between the two pens would not result in increased amounts of (b) (4) of the to-be marketed device.

Please provide a response by COB, Thursday, March 24, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389

10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
03/22/2016

From: Shefali.Goyal@sanofi.com
To: White_Martin
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_ Statistical Information Request 3-21-2016
Date: Monday, March 21, 2016 3:56:21 PM

Received, thanks.

Shefali

Shefali Goyal
(908) 981-6996

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Monday, March 21, 2016 3:24 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_ Statistical Information Request 3-21-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

Please provide the actual day from baseline when the 30-Week measurement for HbA1c used in the primary analysis was taken for each subject in both Phase 3 studies.

We notice some minor discrepancies between the analysis timepoint number (avisitn) and the MMRM analysis timepoint number (avisitn2) in your analysis dataset:

STUDYID	SUBJID	ARM	PARAMCD	AVAL	AVISIT	AVISITN	AVISIT2	AVISITN2
EFC12404	840095005	Lixisenatide	HBA1C	6.8	V18/WEEK24	180	V20/WEEK30/FINAL	200

STUDYID	SUBJID	ARM	PARAMCD	AVAL	AVISIT	AVISITN	AVISIT2	AVISITN2
EFC12404	642004002	Fixed Ratio Combination	WEIGHT	80.0	V9/WEEK4	90	V14/WEEK12	140
EFC12404	840095005	Lixisenatide	WEIGHT	83.30	V18/WEEK24	180	V20/WEEK30/FINAL	200

Please provide explanations by Thursday, March 24, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
03/22/2016

From: Shefali.Goyal@sanofi.com
To: White, Martin
Subject: Re: NDA 208673_insulin glargine/lixisenatide injection_CDRH Information Request 3-15-2016
Date: Tuesday, March 15, 2016 2:28:27 PM

Received, thanks.

Sent from my iPhone

On Mar 15, 2016, at 2:09 PM, White, Martin <Martin.White@fda.hhs.gov> wrote:

Shefali,

In your response to FDA Request for Information dated March 2, 2016, you provided biocompatibility testing on the insulin glargine/lixisenatide pen-injector; however, a new (b) (4) will be used for the commercial product. You have provided test reports for cytotoxicity testing and chemical characterization by GC/MS fingerprint and ICP-OES investigation on another pen, the Lantus® SoloStar® pen components with that contains the (b) (4)

<!--[if !supportLists]-->a. <!--[endif]-->Provide a description of the materials in the Lantus® SoloStar® pen compared to the proposed device and provide a rationale as to why any difference in materials between the two pens would not result (b) (4) of the proposed device.

<!--[if !supportLists]-->b. <!--[endif]-->Provide a risk assessment using the potential exposure values obtained in the chemical characterization of the Lantus SoloStar pen that specifically address the irritation and sensitization endpoints not assessed directly by biocompatibility testing.

Alternatively, please provide the primary irritation and sensitization testing on the final finished device that will be marketed.

Please provide the responses by Friday, March 18, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: White, Martin

Sent: Wednesday, March 02, 2016 1:53 PM
To: 'Shefali.Goyal@sanofi.com'
Subject: NDA 208673_insulin glargine/lixisenatide injection_CDRH Information Request 3-02-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

1. You have not provided the test reports regarding the biocompatibility of the pen-injector that you reference in the document titled "Biocompatibility of the pen-injector – ISO 10993-1 – QUA-FD-2015-01951". Please provide these test reports.
2. You note that a difference between the clinically used pen-injectors and the to-be marketed pen-injectors is that the dosage range above the intended limit of 40 or 60 units (depending on the model) is physically blocked for the to-be marketed pen-injectors. Please provide any verification/validation testing you have to support the functionality of this design feature.
3. Please provide a traceability matrix that lists the essential performance requirements of your pen-injector, the specification for each requirement, and the title of the provided test report that verifies your device to meet the specification. An example table can be seen below:

Essential Performance Requirement	Specification	Verification Test Report
Injection depth		
Injection accuracy		
Injection volume		
Injection time		
Activation force (initial and sustaining)		
Needle Connection Type		
Needle Length		
Needle Gauge		
....		

Please note that specifications should include performance up to the labeled date of expiry of the device (i.e. after preconditioning, aging, and shipping). If a requirement is controlled by another manufacturer (i.e. needle length/gauge) please provide the intended component specification (i.e. the pen-injector is intended for use with X needles) and how it is being controlled (i.e. labeling, warning statements, etc.) with reference to your risk assessment.

<!--[if !supportLists]-->4. <!--[endif]-->You note that you intend to continue in-use stability dose accuracy testing on your pen-injectors, however the Agency can not locate a requirement or statement of the intended shelf-life of your device.

<!--[if !supportLists]-->a. <!--[endif]-->Please provide information regarding the intended shelf-life of your device.

<!--[if !supportLists]-->b. <!--[endif]-->The Agency notes (b) (4) within your submitted stability data. Please provide a trend analysis of the dose accuracy of your device out to the labeled date of expiry with any available stability data you have acquired for both of your pen-injectors.

<!--[if !supportLists]-->c. <!--[endif]-->You are proposing to leverage accelerated aging testing data acquired from the Lantus SoloStar pen-injector, (b) (4)

Please clarify at what temperature the accelerated aging dose accuracy testing was completed for the Lantus SoloStar pen-injector. Furthermore, please clarify the corresponding shelf-life confirmed by the accelerated aging dose accuracy testing if performed at a lower temperature.

<!--[if !supportLists]-->5. <!--[endif]-->The Agency notes that you performed functional testing on the pen-injector after preconditioning in dry-heat atmosphere for at least 96 hours. However, you state that the pen-injectors are intended to be stored for up to 14 days. Please provide a justification for why the preconditioning of your device is representative of the intended storage duration.

Please provide the responses by Monday, March 07, 2016.

Confirm receipt of this email.

Thanks
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712

Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
03/16/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_ Clinical Information Request 3-10-2016
Date: Thursday, March 10, 2016 9:50:52 AM

Hi Martin,
Received, thanks.

Shefali

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Thursday, March 10, 2016 9:39 AM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_ Clinical Information Request 3-10-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

Refer to Tables 17 and 18 in the CSR for EFC 11319, (located in NDA 208471); and Table 2 of the submission to NDA 208673 dated March 7, 2016, displaying an exposure summary for patients on background basal insulin.

On comparison of patient numbers, there seems to be a large difference (i.e. (b) (4)% vs. (b) (4)% of the population), even considering the fact that the CSR tables include any insulin. Can you explain the discrepancy?

Also, can you point out the variable values in the "Chemical class" and "Medication analysis classification" in the adcm.xpt dataset, or any other variables you used to derive the number of patients on basal background insulin treatment.

Please provide the responses by Monday, March 14, 2016.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712

Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
03/10/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_ Statistics Information Request 3-07-2016
Date: Monday, March 07, 2016 11:23:34 AM

Received, thanks.

Shefali

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Monday, March 07, 2016 11:22 AM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_ Statistics Information Request 3-07-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

Please provide simplified SAS code for the primary and key secondary analyses for the two Phase 3 studies EFC12404 and EFC12405 (those included in the proposed product label). Please provide the code used for analysis only and omit the code used to generate tables and descriptive statistics, and minimize the number of macro variables.

Please provide the responses by Monday, March 14, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
03/07/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_Clinical Pharmacology Information Request 3-03-2016
Date: Thursday, March 03, 2016 5:16:08 PM

Received, thanks.

Shefali

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Thursday, March 03, 2016 4:39 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_Clinical Pharmacology Information Request 3-03-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

1. Develop dose-response or exposure-response model for Insulin glargine based on available individual level data from relevant trials (including ACT12374), where insulin glargine was well titrated to FPG target. The dose range of insulin data should be wide enough to characterize the DR or ER relationship at higher doses (> 60 units). You should account for differences in patient population if data from different trials are pooled. Using the developed model, simulate HbA1c profiles in the following scenarios. Include PK/PD variability in the simulation. Provide the simulation results along with the modeling dataset, codes and define files.
 - a. Follow the same insulin glargine regimen and same patient population in study 12404, overlaid with observed data.
 - b. Follow the same insulin glargine regimen and same patient population in study 12405, overlaid with observed data.
 - c. Follow the same insulin glargine regimen and same patient population in phase 2 study 12374, overlaid with observed data.
 - d. Follow an uncapped insulin glargine regimen in the patient population of study 12404.
 - e. Follow an uncapped insulin glargine regimen in the patient population of study 12405.
 - f. Follow an uncapped insulin glargine regimen in the patient population of study 12404, but use the titration algorithm in phase 2 study 12374.
 - g. Follow an uncapped insulin glargine regimen in the patient population of study 12405, but use the titration algorithm in phase 2 study 12374.
2. Conduct dose-response analysis of lixisenatide (preferably, using the Phase 2 HbA1c data for the QD dose levels from Lixisenatide development program) and submit the results of the analysis along with the model codes.

Please provide the responses by Friday, March 25, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
03/04/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 3-03-2016
Date: Thursday, March 03, 2016 9:40:54 AM

Received. Thanks

Shefali

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Thursday, March 03, 2016 9:35 AM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 3-03-2016

Shefali,

We have identified some additional questions regarding your human factor study results (documents titled Container Closure System – Human Factors/Usability Report and Container Closure System – Human Factors Report for Prescribing Information) submitted on December 21, 2015 and the protocol document (Human Factors Validation Study Protocol LixiLan Ratio Pen Injectors Moderator Guides and Scripts) submitted on February 26, 2016.

- We noted that Section A.4 of the Moderator Guide includes IFU assessment questions to determine participants' ability to proceed with changes in therapy. The results data submitted for the questions addressed in Sections A.4.1.1 and A.4.1.2 appear to be lumped into the summary data results provided in Table 13 of the Human Factors/Usability Report but that is unclear. Therefore, we request that you provide additional details regarding the errors that occurred with this specific assessment by outlining the following:
 - The number of correct and incorrect responses
 - Any subjective feedback provided by participants regarding this task
 - Any strategies to address deficiencies based on these errors
- In addition, we noted [REDACTED] (b) (4) [REDACTED]. However, both pens dial starting at "0" units and are able to dial doses below 10 units or 30 units respectively. Please clarify if the pens are actually able to dispense medication at doses dialed below 10 units or 30 units.

We request that you respond to this information request no later than the close of business on **Friday, March 4, 2016**. Thank you in advance.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.

Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
03/03/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_CDRH Information Request 3-02-2016
Date: Wednesday, March 02, 2016 2:12:43 PM

Received, thanks Martin.

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Wednesday, March 02, 2016 1:53 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_CDRH Information Request 3-02-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

1. You have not provided the test reports regarding the biocompatibility of the pen-injector that you reference in the document titled "Biocompatibility of the pen-injector – ISO 10993-1 – QUA-FD-2015-01951". Please provide these test reports.
2. You note that a difference between the clinically used pen-injectors and the to-be marketed pen-injectors is that the dosage range above the intended limit of 40 or 60 units (depending on the model) is physically blocked for the to-be marketed pen-injectors. Please provide any verification/validation testing you have to support the functionality of this design feature.
3. Please provide a traceability matrix that lists the essential performance requirements of your pen-injector, the specification for each requirement, and the title of the provided test report that verifies your device to meet the specification. An example table can be seen below:

Essential Performance Requirement	Specification	Verification Test Report
Injection depth		
Injection accuracy		
Injection volume		
Injection time		
Activation force (initial and sustaining)		
Needle Connection Type		
Needle Length		
Needle Gauge		
....		

Please note that specifications should include performance up to the labeled date of expiry of the device (i.e. after preconditioning, aging, and shipping). If a requirement is controlled by another manufacturer (i.e. needle length/gauge) please provide the intended component specification (i.e. the pen-injector is intended for use with X needles) and how it is being

controlled (i.e. labeling, warning statements, etc.) with reference to your risk assessment.

4. You note that you intend to continue in-use stability dose accuracy testing on your pen-injectors, however the Agency can not locate a requirement or statement of the intended shelf-life of your device.
 - a. Please provide information regarding the intended shelf-life of your device.
 - b. The Agency notes [REDACTED] (b) (4) within your submitted stability data. Please provide a trend analysis of the dose accuracy of your device out to the labeled date of expiry with any available stability data you have acquired for both of your pen-injectors.
 - c. You are proposing to leverage accelerated aging testing data acquired from the Lantus SoloStar pen-injector, [REDACTED] (b) (4)
[REDACTED]
[REDACTED] Please clarify at what temperature the accelerated aging dose accuracy testing was completed for the Lantus SoloStar pen-injector. Furthermore, please clarify the corresponding shelf-life confirmed by the accelerated aging dose accuracy testing if performed at a lower temperature.
5. The Agency notes that you performed functional testing on the pen-injector after preconditioning in dry-heat atmosphere for at least 96 hours. However, you state that the pen-injectors are intended to be stored for up to 14 days. Please provide a justification for why the preconditioning of your device is representative of the intended storage duration.

Please provide the responses by Monday, March 07, 2016.

Confirm receipt of this email.

Thanks
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
03/03/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_Clinical Information Request 2-22-2016
Date: Monday, February 22, 2016 3:38:55 PM

Hi Martin,
Received, thanks.

Shefali

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Monday, February 22, 2016 3:27 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_Clinical Information Request 2-22-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

Please provide an exposure table for the integrated database of patients on background insulin therapy from the lixisenatide program similar to Table 12 (overall exposure to FRC and insulin glargine in the FRC Phase2/3 studies) in the Summary of Clinical safety by Monday, March 7, 2016.

Confirm receipt of this email.

Regards,

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
02/22/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 2-19-2016
Date: Friday, February 19, 2016 4:46:35 PM

Hi Martin,
Confirming receipt. I will pass these requests on to the Human Factors group for their response.

Best Regards

Shefali

Shefali Goyal
(908) 981-6996

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Friday, February 19, 2016 4:12 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 2-19-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

We have identified some preliminary issues regarding your human factor study results (documents titled Container Closure System – Human Factors/Usability Report and Container Closure System – Human Factors Report for Prescribing Information).

- We noted that both of the above reports appear to provide a summary of the study results without providing detailed information outlining the following:
 - The moderator’s transcript including the specific user tasks and use scenarios that were studied
 - The specific knowledge questions that were used for each study population, the desired correct responses to those questions, the number of and root causes for incorrect responses, and any subjective feedback provided by participants, including those providing correct responses.
 - Definition of performance success and performance failure
 - Root cause analysis data for all use errors, difficulties, and close call errors
 - Subjective feedback provided by participants regarding all use errors, difficulties, and close call errors

Therefore, we request that you provide additional details regarding the methodology and study results to address these deficiencies.

- In addition, we note that there were errors in the Human Factors/Usability Report that involved incorrect pen selection associated with user interpretation of the name’s modifiers, (b) (4) Therefore, please provide a response on how you plan to address this issue.

Please provide the responses by Friday, February 26, 2016.

Confirm receipt of this email.

Thanks

Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
02/22/2016



NDA 208673

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Sanofi US Services Inc.
Attention: Shefali Goyal
Associate 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, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for insulin glargine/lixisenatide injection.

We also refer to your amendments dated January 8, 12 (2), and 20, February 2, and 3, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is August 21, 2016. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 22, 2016.

In addition, the planned date for our internal mid-cycle review meeting is March 21, 2016. We are currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issue:

Office of Pharmaceutical Quality

- Executed batch records were not in English

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the complete English translation of the executed batch records (EBR) with data entries for our review. Include EBRs for concentrate, compounding, and filling for both strength products.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list

each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and instruction for use (IFU). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
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>).

Do not submit launch materials until you have received our proposed revisions to the PI, Medication Guide, and IFU, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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 acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

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 & Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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/s/

JEAN-MARC P GUETTIER
02/19/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 2-12-2016
Date: Friday, February 12, 2016 3:00:56 PM

Ok, thanks.

Shefali

Shefali Goyal
(908) 981-6996

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Friday, February 12, 2016 2:59 PM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 2-12-2016

That is correct.

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Friday, February 12, 2016 2:57 PM
To: White, Martin
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 2-12-2016

Thanks Martin,

So it is also OK that they are (b) (4)

Regards

Shefali

Shefali Goyal
(908) 981-6996

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Friday, February 12, 2016 2:46 PM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 2-12-2016

Shefali,

Thank you for the email.

At this time, the team would like for you to ship the unlabeled products you have in the US (3 sets

of the 2 pens) to arrive next week.

The team would also like to receive at least 1 labeled pen (to-be-marketed pens) for each strength as soon as available. The team understands that these pens would be shipped from Europe.

Thanks
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]
Sent: Friday, February 12, 2016 1:14 PM
To: White, Martin
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 2-12-2016

Hi Martin,
We need a few clarifications for this request:

1. Can you please confirm if you need labeled product, or if we can provide representative pens currently available for a planned clinical study which are identical to our to-be-marketed pens?
2. Depending on the purpose of these samples, we would either ship them [REDACTED] (b) (4), can you please let us know specifically regarding the purpose so we can ship accordingly?
3. Additionally, as I mentioned previously, these pens have to shipped from Europe so would take 2-3 weeks to reach you, particularly since they need to get through customs.

We do have 3 sets of the 2 pens available in the US that are unlabeled [REDACTED] (b) (4), that we can ship to you immediately if they will suffice for your purpose. We can then follow up with additional pens as needed. Please let me know.

Thanks and Best Regards

Shefali

Shefali Goyal
(908) 981-6996

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Friday, February 12, 2016 9:59 AM
To: Goyal, Shefali R&D/US
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 2-12-2016

Thank you.

Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: Shefali.Goyal@sanofi.com [<mailto:Shefali.Goyal@sanofi.com>]

Sent: Friday, February 12, 2016 9:31 AM

To: White, Martin

Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 2-12-2016

Hi Martin, confirming receipt.

However, since the pens are manufactured in Germany, I need to check if we have samples here to send you by next week or they need to come in from Germany. Will let you know ASAP.

Regards

Shefali

Shefali Goyal

(908) 981-6996

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]

Sent: Friday, February 12, 2016 9:05 AM

To: Goyal, Shefali R&D/US

Subject: NDA 208673_insulin glargine/lixisenatide injection_DMEPA Information Request 2-12-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

Please submit five (5) sample pen devices to aid in our review process.

The samples should be provided to the following address:

Martin White, M.S.

Food and Drug Administration

Center for Drug Evaluation and Research

White Oak Building 22, Room: 3389

10903 New Hampshire Avenue

Silver Spring, Maryland

Use zip code 20903 if shipping via United States Postal Service (USPS).

Use zip code 20993 if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

Please provide the pen devices by Thursday, February 18, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
02/12/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_Clinical Pharmacology Information Request 2-8-2016
Date: Monday, February 08, 2016 4:15:07 PM

Received, thanks Martin.

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Monday, February 08, 2016 3:54 PM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_Clinical Pharmacology Information Request 2-8-2016

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

Please provide the following information for the Population PK reports (eCTD Module 5.3.3.5):

1. **Study PMH0118:** (a) NONMEM code and control stream files, and all datasets (including .xpt and ASCII) that were used for the NONMEM run; (b) R-Scripts and datasets
2. **Study SIM0266:** (a) NONMEM code and control stream files, and all datasets (including .xpt and ASCII) that were used for the NONMEM run; (b) R-Scripts and datasets
3. **Study PMH0172:** R-Script and datasets used for the model-based meta-analysis

If the requested data was already provided, please indicate the location in the eCTD.

Please Note that following are the general expectations for submitting the pharmacometric data and models:

- *All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.*
- *Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).*
- *A model development decision tree and/or table which gives an overview of modeling steps.*
- *For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.*

In terms of where the code and data should be submitted, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ctl.txt, run1.lst.txt, plot1.R.txt) with a define pdf file to explain the role of each file and sometimes with a pdf file as the revieweraid.pdf to explain the flow of running the code if necessary. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file."

Please provide your responses by February 18, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
02/09/2016

From: White, Martin
To: "Shefali.Goyal@sanofi.com"
Subject: NDA 208673_insulin glargine/lixisenatide injection_Clinical Information Request_1-25-2016
Date: Monday, January 25, 2016 10:35:00 AM

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

On December 4, 2014, the Food and Drug Administration published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR went into effect on June 30, 2015. According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

Together with submission of the proposed labeling for PLLR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).

Your submitted labeling did not provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made.

Submit the following information on insulin glargine and lixisenatide use in pregnant and lactating women by February 8, 2016:

- a) A review and summary of all available published literature regarding insulin glargine and lixisenatide;
- b) A review and summary from your pharmacovigilance database,
- c) Interim ongoing or final report on a closed pregnancy registry (if applicable);
- d) Revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Please confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue

Silver Spring, MD 20903

Phone 240.402.6018

Fax 301.796.9712

Martin.White@fda.hhs.gov

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MARTIN L WHITE
01/25/2016

From: White, Martin
To: "Shefali.Goyal@sanofi.com"
Subject: NDA 208673_insulin glargine/lixisenatide injection_Clinical Information Request_1-19-2016
Date: Tuesday, January 19, 2016 4:14:00 PM

Shefali,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

1. For all three clinical trials (EFC12404, EFC12405, and ACT 12374), provide information on the proportion of patients that achieved fasting plasma glucose targets at each study visit (see sample shell table below). We are interested in seeing this data for each treatment arm and by subgroups based on insulin glargine dose, similar to what you have presented in table 16.2.6.6.3.30 for EFC12404 at week 30.

Visit		Lixisenatide-Insulin glargine N (%)	Insulin glargine N (%)
Baseline	Total		
	< 10 U		
	10 to < 20 U		
	20 to < 30 U		
	30 to < 40 U		
	40 to < 50 U		
	50 to < 60 U		
	> 60 U		
Etc.			

2. We note that some patients received more than 20 mcg of lixisenatide in the fixed ratio arm (see Tables 16.2.6.6.1.2 in the CSR for EFC12404 and 16.2.7.1.2 in the CSR for EFC12405). Provide an explanation for this as well as the actual dose of lixisenatide each patient received.

Please provide your responses by February 2, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389

10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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MARTIN L WHITE
01/19/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208673_insulin glargine/lixisenatide injection_Clinical Information Request_1-5-2016
Date: Tuesday, January 05, 2016 10:37:35 AM

Hi Martin,
Confirming receipt, we will provide the information as requested.

Best Regards

Shefali

Shefali Goyal
Global Regulatory Lead – LixiLan

(908) 981-6996

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Tuesday, January 05, 2016 10:29 AM
To: Goyal, Shefali R&D/US
Subject: NDA 208673_insulin glargine/lixisenatide injection_Clinical Information Request_1-5-2016

Good Morning,

With reference to your above-mentioned NDA submitted on December 21, 2015, we have the following information request:

Please indicate if any investigators participated in the LixiLan program only and not in the Lixisenatide program. To assist in our consideration of the impact of these investigators (participating in the LixiLan program only, if any) on study conduct and findings, submit tables similar to those provided in your response dated December 14, 2015 to NDA 208471, indicating:

- a. Total number of investigators
- b. Number of investigators with relevant financial disclosures including the name of the investigator along with the associated site number and the number of patients enrolled by each corresponding site.

Please provide your responses by January 13, 2016.

Confirm receipt of this email.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research

Division of Metabolism and Endocrinology Products

WO22 - Room 3389

10903 New Hampshire Avenue

Silver Spring, MD 20903

Phone 240.402.6018

Fax 301.796.9712

Martin.White@fda.hhs.gov

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MARTIN L WHITE
01/05/2016



NDA 208673

NDA ACKNOWLEDGMENT

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

Dear Ms. Goyal:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: insulin glargine/lixisenatide injection

Date of Application: December 21, 2015

Date of Receipt: December 21, 2015

Our Reference Number: NDA 208673

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 19, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

Martin White, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARTIN L WHITE
12/23/2015



IND 105157

MEETING MINUTES

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

Dear Ms. Goyal:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for insulin glargine/lixisenatide.

We also refer to the meeting between representatives of your firm and the FDA on September 28, 2015. The purpose of the meeting was to discuss your upcoming new drug application (NDA) submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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 & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 28, 2015 and 11:00 AM – 12:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1417
Silver Spring, MD 20903

Application Number: IND 105157
Product Name: insulin glargine/lixisenatide
Indication: An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate

Sponsor: Sanofi US Services Inc.

Meeting Chair: Jean-Marc Guettier, M.D.
Meeting Recorder: Martin White, M.S.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D.	Director
Jennifer Rodriguez Pippins, M.D., M.P.H.	Deputy Director for Safety
William Chong, M.D.	Clinical Team Leader
Suchitra Balakrishnan, M.D.	Clinical Reviewer
Andreea Lungu, M.D.	Clinical Reviewer
Mitra Rauschecker, M.D.	Clinical Reviewer
Todd Bourcier, Ph.D.	Nonclinical Team Leader
Pamela Lucarelli, B.S.	Chief, Project Management Staff
Martin White, M.S.	Regulatory Project Manager

Office of Biostatistics, Division of Biometrics II

Mark Rothmann, Ph.D.	Statistical Team Leader
Jiwei He, Ph.D.	Biometrics Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Jayabharathi Vaidyanathan, Ph.D.	Clinical Pharmacology Team Leader
Sang Chung, Ph.D.	Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality, Office of New Drug Products
Suong Tran, Ph.D. CMC Lead

Division of Medication Error Prevention and Analysis

Yelena Maslov, Pharm.D. DMEPA Team Leader
Sarah Vee, Pharm.D. DMEPA Reviewer

Office of Surveillance and Epidemiology

Amarilys Vega, M.D., M.P.H. Risk Management Analyst, Division of Risk Management

Center for Devices and Radiologic Health

Richard Chapman, Ph.D. Chief, General Hospital Devices Branch
Biomedical Engineer
Ryan McGowan, B.S. General Hospital Devices Branch
Biomedical Engineer

Office of Scientific Investigations

Cynthia Kleppinger, M.D. Senior Medical Officer

EASTERN RESEARCH GROUP ATTENDEES

Peggh Khorrami, Independent Assessor

SPONSOR ATTENDEES

Wolfgang Schmider, Ph.D., Metabolism and Pharmacokinetics
Elisabeth Niemoeller, M.D., Clinical Lead, Late stage Clinical Development,
Global Diabetes Division
Rene Belder, M.D., Vice President, Deputy Head Clinical Development,
Global Diabetes Division
Riccardo Perfetti, M.D., Vice President, Medical Affairs, Global Diabetes Division
John Newton, Ph.D. Vice President, Head Pharmacokinetics
Yujun Wu, Ph.D., Associate Director, Biostatistics
Peng-Liang Zhao, PhD. Associate Vice President, Biostatistics
Sandeep Kumar, M.D., Senior Director, Pharmacovigilance
Verena Siefke-Henzler, Ph.D., iCMC New Products Program
Molly Story, Ph.D., Head, Global Usability Engineering and Risk Management
Julie Doerr, Associate Director, Regulatory CMC
Christopher Morabito, M.D., Global Project Head
Shefali Goyal, M.S., MSc., Director, Global Regulatory Affairs
Barry Sickels, Ph.D., Vice President, North America and Global, Global Regulatory Affairs
Amy Jennings, Ph.D., Associate Vice President, Global Regulatory Affairs

1. BACKGROUND

The purpose of this meeting is to discuss the sponsor's upcoming NDA submission for the insulin glargine/lixisenatide combination.

IND 105157 for insulin glargine/lixisenatide combination has been in effect since April 2009. Insulin glargine/lixisenatide is a combination of insulin glargine, approved as the long-acting insulin Lantus and lixisenatide, a GLP-1 agonist.

The fixed-ratio combination of insulin glargine and lixisenatide will contain a solution of insulin and lixisenatide in two ratios, to be delivered by two prefilled disposable pen injectors such as SoloSTAR.

The clinical development to support the lixilan NDA plan includes:

- Six completed Phase 1 studies,
- One completed Phase 2 Proof-of Concept study ACT12374,
- Two completed Phase 3 studies: EFC12404 (OAD failure patients) and EFC12405 (Patients already treated with basal insulin).

The End of Phase 2 meeting was held on June 25, 2010, during which the nonclinical, clinical, chemistry and device issues relevant to the proposed (b) (4) combination product of insulin glargine and lixisenatide were discussed.

On July 12, 2013, the Agency provided Type C written responses. The response included feedback on the sponsor's new fixed-ratio concept of LixiLan.

On May 1, 2015, the Agency provided Type C written responses. The response included comments on the analysis and presentation of clinical data for the NDA.

FDA sent Preliminary Comments to Sanofi US Services Inc. on September 24, 2015.

2. DISCUSSION

2.1. Nonclinical

Question 1: As described below, the nonclinical program to support LixiLan includes the following studies:

- 14 non-clinical in-vitro pharmacology and 3 non-clinical in-vivo pharmacology studies (in dog and mouse);
- 1 safety pharmacology study (for cardiovascular safety in the dog);
- 1 non-clinical single-dose PK study (in dogs);
- 2 Local Tolerance Studies in female rabbits and 1 Other Toxicity Study (additional 13-week subcutaneous toxicity study in rats for impurity qualification (HOE901)).

Does the Agency agree that the above non-clinical data together with cross-referenced programs for the individual components can support the evaluation of the LixiLan NDA for the proposed indication?

FDA Response to Question 1: Yes, your proposal is acceptable.

Discussion: No discussion occurred.

2.2 Clinical Pharmacology

Question 2: As described below, six biopharmaceutical studies have been conducted with insulin glargine/lixisenatide combination. Two definitive studies (BDR10880 and BDR12547), two preliminary studies (BDR11578 and BDR11540), and two exploratory studies with insulin glargine concentrations in the injection solution other than in the final combination product (BDR11038 and BDR12406). In addition, three lixisenatide monotherapy studies submitted with the lixisenatide NDA 208471 (ACT6011, PDY12545, and DRI6012), which provide information on the pharmacodynamic effects of lixisenatide at doses below 20 µg, will be briefly summarized and cross-referenced to the respective sections of the lixisenatide NDA 208471. These combination and monotherapy studies together will form the basis for the PK and PD of LixiLan to be provided in the NDA.

Does the Agency agree with presentation of the results according to their contribution to the phase 3 program and that the clinical pharmacokinetics/pharmacology package is adequate to support evaluation of the LixiLan NDA for the proposed indication?

FDA Response to Question 2: We agree that your clinical pharmacology package is adequate to evaluate biopharmaceutical and/or drug interaction perspectives of your proposed product. However, note that evaluation of the clinical pharmacology data supporting additive benefits between insulin glargine and lixisenatide including pharmacodynamic and/or dose-response information will be critical part of our review in terms of its adequacy in supporting the proposed indication (see Responses to Question 4).

We have following additional comments:

Please clarify whether the to-be-marketed presentation (i.e., formulation and device) is the same as that used in your Phase 3 studies.

We recommend that you include the subject level electronic data sets for all clinical pharmacology studies supporting the proposed NDA in your submission, preferably as SAS transport (*.xpt) files.

Discussion: The Sponsor stated during the meeting that they intend to provide the following information for the six phase 1 studies:

- **Data pool for demography, adverse events, disposition, exposure;**

- **PK concentration and parameters on study level.**

In addition, the Sponsor suggests providing PD data from the 3 phase 1 studies BDR10880, BDR11038, BDR11578 on a study level, if requested.

Data from the supportive lixisenatide studies PDY12545, ACT6011, DRI6011 were already submitted in the lixisenatide dossier. Only a reference to the lixisenatide dossier is planned.

Additional Post-meeting Comments: The Sponsor had the additional questions for the FDA which were not discussed at the meeting due to time constraints. These are repeated below followed by the FDA response.

1. ***Could the FDA please specify the meaning of “subject level data sets?”***

FDA Response to Additional Question 1: By “subject level data sets,” we mean that for each clinical pharmacology study include data files containing pharmacokinetic and pharmacodynamic data, by subject, for all subjects.

2. ***Could the FDA please comment on the need of the PD data?***

FDA Response to Additional Question 2: Please submit glucose infusion rate and plasma glucose during clamp data from the clinical pharmacology studies that involved clamp procedure.

3. ***Is it acceptable for the FDA that we reference to the lixisenatide dossier?***

FDA Response to Additional Question 3: Yes.

4. ***Could the FDA please confirm that all requested data have to be available at the time of submission of the dossier?***

FDA Response to Additional Question 4: All data necessary to support approval should be available at the time of submission.

2.3 Clinical

Question 3: Two phase 3 studies, (EFC12404 and EFC12405) and one phase 2 study (ACT12374) were conducted to support the safety and efficacy of LixiLan. High level clinical data from the phase 3 studies is presented below for the Agency’s information. Additional information is provided in [Section 10.2].

Does the Agency agree that these three studies together with cross-referenced programs for the individual components can support the evaluation of the LixiLan NDA for the proposed indication?

FDA Response to Question 3: While the three studies together with the cross-referenced programs for the individual components may be sufficient to allow for review of the LixiLan NDA for the proposed indication we continue to have concerns with regard to the adequacy of the data to support the proposed drug product. As communicated previously in our correspondence dated June 8, 2015, included in the Type B pre-NDA Meeting Minutes for IND 062724, it is unclear whether the available data supports that there is a contribution of each component to the observed effect over the proposed range of your proposed drug product. See responses to questions 4 and 5 for additional comments.

Discussion: See discussion under questions 4 and 5.

Question 4: In their pre NDA written correspondence for lixisenatide dated June 8 2015, the Agency stated “We have concerns about the glargine/lixisenatide product you are developing, particularly with regard to the availability of data to support a contribution of each component over the entirety of the proposed dosing range of your fixed combination product.” To address the Agency’s concerns, the Sponsor plans to perform benefit-risk evaluations of the phase 3 efficacy results according to final insulin and lixisenatide dose levels. These analyses are currently ongoing and will include key efficacy end points such as HbA1c and body weight, as well as safety aspects. Analyses are planned to be available for discussion at the time of the pre-NDA meeting.

Does the Agency concur with the Sponsor’s understanding and will these plans adequately address the Agency’s concerns?

FDA Response to Question 4: Your understanding of this concern is correct. As communicated in the July 12, 2013, correspondence under IND 105157, and also in the June 8, 2015, pre-NDA Meeting Minutes for IND 062724, we have concerns with regard to contribution of each of the components toward the stated effect for your proposed product. We would expect your program to show that there is a contribution of both lixisenatide and insulin glargine at the lowest dose available for patients as well as at the highest dose.

Efficacy of lixisenatide was studied for only the 20 µg dose in the phase 3 lixisenatide clinical program. In your meeting package, you refer to studies DRI6012 and ACT6011 from the lixisenatide development program to support a contribution of each component (i.e. doses of lixisenatide between 5-<20µg) over the entirety of the proposed dosing range. Only post-prandial glucose was assessed in study ACT6011, and study DRI6012 was a 13 week study for evaluating dose-response relationship. Only around 50 subjects each were exposed to lixisenatide 5 µg and 10 µg qd and the durability of HbA1c effect was not demonstrated, given the short duration of the study. We do not agree that this is adequate to demonstrate efficacy for the doses studied.

While you propose to provide additional analyses from the phase 3 studies from the LixiLan development program, we are concerned that this will not be adequate as your proposed subgroup analyses are based on post-randomization variables (i.e., final insulin and lixisenatide dose levels). Such analyses will not provide a valid estimate for treatment differences. Further,

we are concerned that there will be a limited number of subjects at the lower dose range (e.g., < 10 µg of lixisenatide).

We await your presentation of the results of these additional analyses, but have reservations that this approach will be adequate to support an NDA.

Discussion: Preliminary results from the proposed subgroup analyses of efficacy and safety endpoints comparing patients on insulin glargine versus the LixiLan fixed ratio combination across different dose ranges of insulin and lixisenatide were presented. The Agency stated that we remain concerned that the data may be insufficient to demonstrate a contribution of both components to the claimed effect as required by the combination rule [21CFR 300.50(a)] for the entirety of the dosing range, particularly at the lower doses. Whether the data support that this convenience product offers favorable benefit-risk remains an issue that will require significant consideration during the review.

Question 5: In the same pre NDA correspondence for lixisenatide, The Agency stated, “We further have concerns about the utility of a product that limits dose flexibility for a titratable product, such as insulin.” We interpret “utility” to refer to the ability of titratable product to produce additive benefit with minimal additional risk. We interpret the “limitation of dose flexibility” expressed by the Agency to refer to the capping of the maximum dose at 60 units, since titration is possible from 10 through 60 units with two pens (10 to 40 and 30 to 60) according to the patient FPG. (see proposed dosing, Appendix 1) Based on insulin glargine 100 U/ml use in US practice, this dose range of LixiLan is expected to meet the insulin requirements of approximately 90% of patients with T2DM and achieve additional clinical benefits with lixisenatide. The patients who need doses higher than 60 units of insulin glargine would not be able to use LixiLan.

Does the Agency concur with the Sponsor’s understanding of FDA’s concerns?

FDA Response to Question 5: You are correct in your understanding of this concern. Provide the source data supporting your statement that (b) (4) % of patients using insulin glargine 100 U/ml fall within the proposed dose range for your drug product.

Discussion: The sponsor stated that data supporting the claim that (b) (4) % of patients with T2DM using insulin glargine 100 U/mL fall within the proposed dose range of 10-60 U/day were generated based on prescriber and patient questionnaires conducted by (b) (4). Source data were not available.

Additional Post-meeting Comment: Additional information relating to the number of surveyed prescribers and patients should be included in the NDA submission, as well as demographic information to support that these findings are representative of the U.S. T2DM population.

Question 6: The Sponsor proposes the e-data submission plan (see Appendix 3) for the Phase 1 and Phase 2-3 studies for LixiLan, including the datasets for the integrated analyses and BIMO.

For lixisenatide placebo controlled studies with basal insulin background, the Sponsor plans to submit only the integrated safety database necessary to support the analyses included in the LixiLan NDA. The individual study datasets for the lixisenatide studies had been included in the lixisenatide NDA 208471 and will not be resubmitted in the LixiLan NDA.

Does the Agency agree with the e-data submission plan?

FDA Response to Question 6: Yes, your proposal is acceptable.

Discussion: No discussion occurred.

Question 7: Narratives will be provided for phase 2 and phase 3 studies. The presentation will follow the approach applied in the lixisenatide NDA for the confirmatory studies EFC12404 and EFC12405 but will be slightly different for the phase 2 study. The proposals are shown below.

Does the Agency agree with the Sponsor's narrative generation plan (including case report forms) for the dossier as described below?

FDA Response to Question 7: This is acceptable. Additional narratives may be requested depending on issues identified during the review cycle.

Discussion: No discussion occurred.

Question 8: The LixiLan NDA will include results of assessments of safety and effectiveness of the device for the intended users. These assessments include (a) Pen Related Events Questionnaire (PREQ, Appendix 4) that was implemented to evaluate prospectively device-related events in the two phase 3 trials via Amendment, and (b) a Human Factors Validation (HFV) Study (Appendix 5) to assess whether patients, nurses and pharmacists are able to dose and dispense correctly both strengths of the product. Both (a) and (b) were discussed in detail with the Agency prior to implementation.

As briefly summarized below, patients in the phase 3 trials reported pen related events in all treatment groups. None of these events was associated with a clinical event.

As previously communicated to the Agency, the pen, pen labeling, IFU, and prescribing information (USPI) used in the clinical trials and the planned commercial materials were different in some respects. The planned commercial materials were used in the HFV Study.

The HFV Study showed that the design of the LixiLan pens and their labeling are adequate to enable users (nurses and both pen-naïve patients and pen-experienced patients) to recognize the pens correctly and to differentiate them from other similar pens. The results also showed that users can dose the pen correctly, understand the intended dose ranges and understand that they should not use the LixiLan pens for daily injections that are not within the intended dose range. The results also showed that pharmacists can dispense the product correctly.

An additional study was conducted to assess the dosing and administration information in the commercial version of the USPI. The results showed that physicians can prescribe the pens correctly based on that information.

- a. *Does the Agency agree that the PREs and dose initiation deviations are adequately addressed?*
- b. *Does the Agency agree that the results of the HFV study conducted with the commercial pens, labeling, IFU and packaging demonstrate safety and effectiveness of the device with regard to differentiation, dispensing and dosing of the product?*
- c. *Does the Agency agree that the results of the additional study demonstrate the adequacy of the USPI with regard to prescription of the product?*

FDA Response to Question 8a: Pen related events and dose initiation deviations will be reviewed as part of NDA review. Please note, that the Agency will use these data to supplement the review of the HFV study results as well as product design and labels and labeling. However, we will not solely rely on these data to make any decisions regarding usability issues with the product as clinical trials are not designed to provide sufficient information regarding usability issues since patients are closely monitored and have a network of support from the investigators. Thus, clinical trials environment does not represent an actual use environment.

Discussion: Sanofi provided the Agency with four broad categories of pen related events (PREs) during the meeting. The Agency asked Sanofi to provide specific counts, details, and root cause analyses regarding each category of PREs to the Application submission as a separate document in conjunction with Human Factors (HF) Summative Study. This document will be included in Module 3.

FDA Response to Question 8b: The acceptability of the human factors validation study results is a review issue thus we will review that information once you submit the NDA to the Agency.

In addition to the device information referenced within your briefing package, you are reminded that you must provide non-clinical evidence for the performance and safety of the device constituent parts of the combination product, including information which establishes essential performance requirements for the combination product, information verifying those requirements and information validating the device is fit and clinically acceptable for its intended use. You should also provide a device-specific risk analysis documentation characterizing and evaluating the risks to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states.

Additionally, after inspection of your proposed stability plan, it is not clear how you intend to support stability of the device constituent parts of your combination product to a period equal to or greater than the labeled expiration.

Discussion: No discussion occurred.

FDA Response to Question 8c: Refer to our response for Question 8b.

Discussion: No discussion occurred.

Question 9: Regarding the Agency's OSI requirement of subject level data listings by site, there are 10 required listings for each site (listing "a" through "j"). In the LixiLan program, there are 494 sites in the 3 Phase 2/3 studies, generating more than 4900 listings for the submission. However, of these, about 62% had fewer than five randomized patients and a majority had three or fewer randomized patients. In order to focus on larger sites (about 188 sites with at least five randomized patients) and to ease the Agency's review process, the Sponsor proposes that the subject data listing is provided in the NDA as requested for sites that have at least 5 randomized subjects in Phase 2/3 studies. For sites with fewer than five randomized patients, the Sponsor can provide the subject data listing if requested by the Agency during the NDA review.

Does the Agency agree with this proposal?

FDA Response to Question 9: Yes, your proposal is acceptable.

Discussion: No discussion occurred.

2.4 Safety

Question 10: Since the Sponsor was advised to submit a REMS for lixisenatide (submitted NDA), the Sponsor plans to submit a similar proposal for LixiLan. If the lixisenatide REMS requirements change during the course of the NDA evaluation, the Sponsor will take that into account and modify accordingly.

Does the Agency agree with the Sponsor's proposal?

FDA Response to Question 10: Yes, your proposal is acceptable.

Discussion: No discussion occurred.

Question 11: The Sponsor requests a waiver for the 120-day safety update

(b) (4)

(b) (4)

Does the Agency agree with the Sponsor's proposal?

FDA Response to Question 11: Given the limited amount of additional information that is expected to be available, this seems acceptable provided that the required safety reports are submitted to the IND.

Discussion: No discussion occurred.

2.5 Regulatory

Question 12: A Table of Contents for the e-CTD is provided in Appendix 8. As discussed previously with the Agency, the Sponsor plans to cross-reference the nonclinical summaries, clinical summaries and study reports submitted in the original paper Lantus NDA and the lixisenatide NDA currently under review. The details on cross referenced documents will be provided in the NDA Module 1.4.4, Cross Reference to Other Applications.

Does the Agency agree with the proposed Table of Contents for the e-CTD?

FDA Response to Question 12: To use m1.4.4 for cross referencing, a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (e.g. paper and/or non- eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.) of the referenced document along with a hypertext link to the location of the information, whenever possible.

If during review of the NDA we have difficulty accessing previous paper submissions, we may request submission of an electronic version.

Additional Combination Products Comments:

Other than data analogous to batch records, all device constituent and combination product information data should be integrated in the eCTD with conceptually similar drug constituent information. The data should be organized based on the following principles:

1. For eCTD format and use of the electronic submission system, please adhere to eCTD headings as defined per ICH and FDA specifications. In the specifications, these may be identified as leaf nodes or elements. Specifically, any title that is associated with a numerical item should not change; i.e., Item 3.2.P.7 should say “Container Closure System.”
2. Do not use "node extensions" to create new elements. Although this is described in the eCTD specification, and may be acceptable in some regions, it is not acceptable in submissions to FDA.
3. When including and referencing device information, we recommend the following:
 - a. You may reference files under 3.2.P.7, which are not currently listed as numerical items in ICH and FDA specifications and guidance.

- b. In Module 3.2.P.7, you could include a leaf titled similar to the following, “Table of Contents for Pen-Injectors. This leaf/document could provide reference links to the other files in module 3.2.P.7.
 - c. The leaf titles should be clear, concise, and indicative of the document's content.
4. Module 1.4.4 “Cross-reference to other applications” is a location where you can provide references to other applications and you can include copies of an application’s table of contents, reference tables, or other similar documents. If you are cross referencing another company's application or master file, include the appropriate letters of authorization from the other companies in modules 1.4.1 - 1.4.3 (1.4.1 “Letter of authorization”, 1.4.2 “Statement of right of reference”, 1.4.3 “List of authorized persons to incorporate by reference”). If there are standards you will reference in the Performance Specifications which also meet these criteria, then please put them in module 1.4.4. The Performance Specifications section should link to this information.
5. All device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with 21 CFR Part 4 and the applicable 21 CFR part 820 regulations should be located in Section 3.2.P.3.
 - a. The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site involved with the device constituent part.
 - b. Suggestions on the types of documents to submit for review of required sections of 21 CFR Part 820 (based upon the combination product 21 CFR Part 4 GMP operating system at the facility) can be found in the guidance document titled “Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,” issued on February 3, 2003. The complete document may be found at [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Guidance Documents/ucm070897.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm).
6. We recommend that you provide an "Information to Reviewers” or “Reviewers Guide” document in Module 1.2 Cover letters. This document would be separate from the cover letter and placed after the cover letter and should provide a high level overview (with reference links) of the submission’s content and list where the information is located in the eCTD. For example, it should identify where drug, device and combination product is located.

Discussion: No discussion occurred.

Question 13: Given the insulin glargine drug substance is the same as in Lantus and LixiLan, Sanofi plans to cross-reference the drug substance section of the original paper Lantus NDA 021081 and all subsequent supplements and annual reports under Module 1.4.4 of the combination product NDA. The Lantus NDA 021081 will be the central repository for all insulin glargine drug substance information.

Additionally, the drug substance lixisenatide is the same as in single-active drug product currently under registration (NDA 208471) and the combination product. Sanofi plans to cross-reference the drug substance section of NDA 208471, under Module 1.4.4 of the combination product NDA. The NDA 208471 will be the central repository for all lixisenatide drug substance information.

Data required under 21 CFR 314.50(d)(1)(ii) (Drug Product) will be provided under Module 3.2.P in the NDA for the fixed-ratio combination of insulin glargine and lixisenatide.

Does the Agency agree with this approach?

FDA Response to Question 13: We agree with the proposal, provided that Form 356h of the new NDA includes up-to-date, detailed establishment information on all sites involved in the commercial manufacturing, testing, and packaging of the two drug substances (in addition to the information on the new drug product).

We also remind you that the new insulin glargine/lixisenatide drug product in the disposable pen injectors is a drug-device combination product and as such is subject to 21 CFR Part 4- Current Good Manufacturing Practice Requirements for Combination Products.

Discussion: No discussion occurred.

2.6 Labeling

Question 14: Proposed draft labeling for LixiLan will be provided in accordance with content and format requirements of the January 2006 Physicians Labeling Rule. Specific sections of the proposed USPI will be the same as those in the currently approved Lantus USPI or proposed for the Lixisenatide label currently under review. For such sections, the Sponsor plans to electronically annotate to the corresponding sections of the approved Lantus USPI and the submitted Lixisenatide USPI.

Does the Agency agree with this approach?

FDA Response to Question 14: Yes, your proposal is acceptable.

Discussion: No discussion occurred.

Question 15:

(b) (4)

Does the Agency agree with the Sponsor's proposal?

FDA Response to Question 15: It is premature to discuss labeling details at this point. This will be addressed during NDA review.

Discussion: No discussion occurred.

2.7 Financial Disclosure of Clinical Investigators

Question 16: *The Sponsor plans to submit financial certification and disclosure from clinical investigators who conducted the Phase 2 study (ACT12374) as well as the two global pivotal Phase 3 clinical studies (EFC12404 and EFC12405) in line with the FDA Financial Disclosure guidance dated February 2013.*

Does the Agency agree with the Sponsor's plan for submission of financial certifications and disclosures?

FDA Response to Question 16: The proposal is acceptable.

Discussion: No discussion occurred.

Additional FDA General Comments:

Statistical:

1. Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

Discussion: No discussion occurred.

2. The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the submission.

Discussion: No discussion occurred.

3. Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will be appearing in the label.

Discussion: No discussion occurred.

4. In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment)

Discussion: No discussion occurred.

3. DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed during the meeting and agreed upon in the preliminary comments conveyed prior to the meeting. These agreements are noted above.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- As stated in the preliminary comments, the sponsor plans to submit a similar REMS proposal for Lixilan as was submitted with the lixisenatide NDA (NDA 208471). The Agency found this proposal acceptable. See response to question 10.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

4. PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if

applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

5. PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

6. ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information

required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

7. **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Combination Product Manufacturing Facilities

Include all device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with 21 CFR Part 4 and the applicable 21 CFR Part 820 regulations in section 3.2.P.3. This includes the list of

manufacturing facilities provided on Form FDA 356h, or as an attachment to the form, and should explicitly describe the manufacturing, assembly, or testing processes taking place at each site with regards to the device constituent part.

- In this section, as applicable, identify whether facilities subject to 21 CFR Part 4 follow the combination product streamlined manufacturing approach and identify the base set of regulations (i.e., 21 CFR 211 or 820). Manufacturing documents that you submit for review of required sections of 21 CFR Part 820 should be placed in this section.
- Information on 21 CFR Part 4 “Current Good Manufacturing Practice Requirements for Combination Products” is accessible at:
<https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

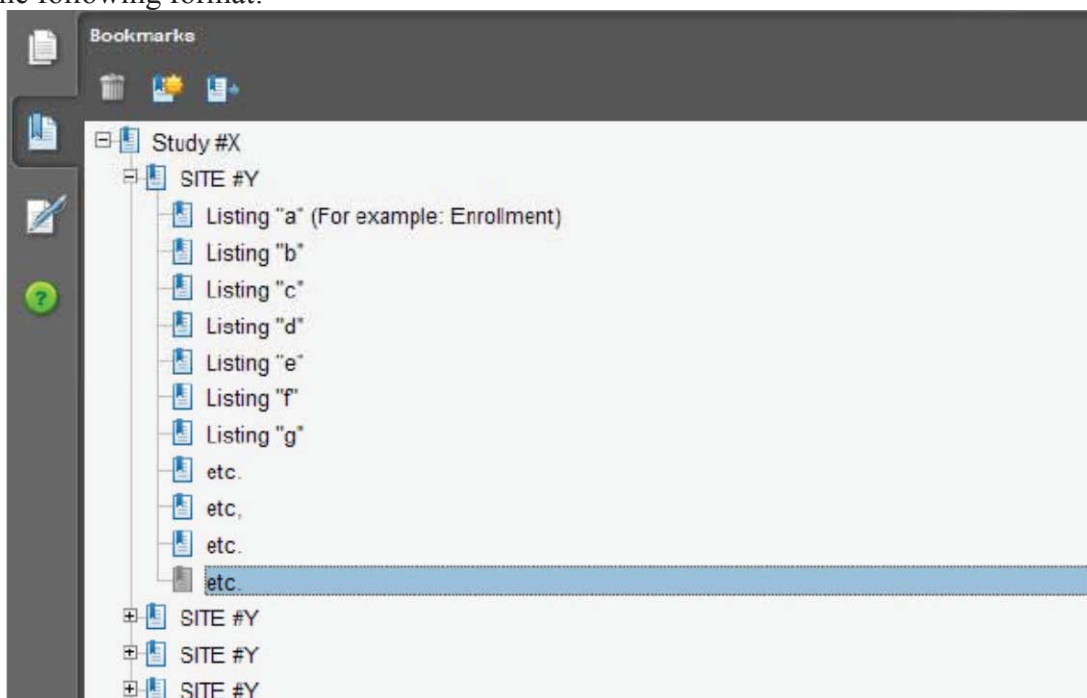
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator’s site address or contact information since the time of the clinical

- investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
 3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
 4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates

- g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

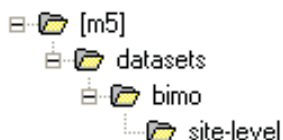
Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

8. ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

9. ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide additional questions based on sponsor response to question 2 above.	FDA	The FDA will provide the questions in the Official Meeting Minutes.
Provide Summary of what the (b) (4)	Sponsor	The sponsor will provide the summary as soon as possible.

10. ATTACHMENTS AND HANDOUTS

The attached slides were presented by Sanofi US Services Inc at the meeting.

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

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

/s/

JENNIFER R PIPPINS
10/28/2015



IND 105157

IND 062724

MEETING MINUTES

Sanofi-aventis U.S. Inc.
Attention: Pierre Mugnier, Ph.D., Pharm.D.
Associate Director, Regulatory Research and Development Portfolio
200 Crossing Boulevard, Mailstop: BX2-700B
Bridgewater, NJ 08807

Dear Dr. Mugnier:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for **insulin glargine and lixisenatide combination** and for **lixisenatide**.

We also refer to the meeting between representatives of your firm and the FDA on June 25, 2010. The purpose of the meeting was to discuss the drug development of 1) insulin glargine and lixisenatide combination and 2) lixisenatide.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

FDA version of Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2
Application Number: IND 105157
Product Name: insulin glargine + lixisenatide combination
Indication: adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide therapy is appropriate

Meeting Type: Type C
Meeting Category: Guidance
Application Number: IND 062724
Product Name: lixisenatide
Indication: metabolic control of type 2 diabetes mellitus

Meeting Date and Time: Friday, June 25, 2010 1:00 p.m. – 2:30 p.m.
Location: 10903 New Hampshire Avenue
White Oak Building 22
Silver Spring, Maryland 20903

Sponsor/Applicant Name: Sanofi-aventis U.S. Inc.

Meeting Chair: Ilan Irony, M.D.
Meeting Recorder: Pooja Dharia, Pharm.D.

FDA ATTENDEES

Office of Drug Evaluation II

Lina AlJuburi, Pharm.D. Chief, Project Management Staff, Division of Metabolism and Endocrinology Products (DMEP)
Pooja Dharia, Pharm.D. Regulatory Project Manager, DMEP
Ilan Irony, M.D. Diabetes Clinical Team Leader, DMEP
Robert Misbin, M.D. Clinical Reviewer, DMEP
Karen Davis-Bruno, Ph.D. Pharmacology/Toxicology Team Leader, DMEP
Tim Hummer, Ph.D. Pharmacology/Toxicology Reviewer, DMEP

Office of Biometrics

Wei Liu, Ph.D. Statistical Reviewer, Division of Biometrics II (DBII)

Office of Clinical Pharmacology

Sally Choe, Ph.D. Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2 (DCP2)

Office of New Drug and Quality Assessment

Olen Stephens, Ph.D. Chemistry Reviewer

Office of Surveillance and Epidemiology

Margarita Tossa, M.S. Safety Regulatory Project Manager, Review Management Staff (RMS)

Center for Devices and Radiological Health

Nikhil Thakur Reviewer, Office of Device Evaluation

SPONSOR ATTENDEES

Alasdair Mackellar, Ph.D.	Medical Devices Project Leader
Thomas Kissner, Ph.D.	Disposition, Safety and Animal Research, Preclinical Safety
Pam Algatt-Bergstrom, Pharm.D.	Projects
Reinhard Becker, M.D.	Clinical Pharmacology, Diabetes
Patrick Miossec, M.D.	Clinical Research Director, Diabetes
Pierre Mugnier, Ph.D., Pharm.D.	Regulatory Liaison, Diabetes
Rima Nassar, Ph.D.	Global Regulatory Affairs, Diabetes US head
Galina Hesse	Projects, Diabetes
Julie Doerr, B.S.	Regulatory CMC expert
Louise Silvestre, Head	Clinical Development Diabetes

1.0 BACKGROUND

Sanofi-aventis submitted IND 105157 for insulin glargine and lixisenatide injection on April 9, 2009 for the treatment of type 2 diabetes mellitus (T2DM).

Lixisenatide injection is currently in Phase 3 studies under IND 062724, which was submitted on June 8, 2001 for the treatment of T2DM.

Lantus (insulin glargine) injection was approved on April 20, 2000 and is indicated to improve glycemic control in adults and children with type 1 diabetes mellitus (T1DM) and in adults with T2DM.

This meeting combines an End-of-Phase 2 meeting for IND 105157 and an advice meeting for IND 062724. The purpose of this meeting was to discuss the nonclinical, clinical, chemistry and device issues relevant to the proposed (b) (4) combination product of insulin glargine and lixisenatide. Clarifying comments regarding the lixisenatide product alone were also provided.

2. DISCUSSION

2.1. IND 105157 Nonclinical

1. Does the Agency agree that the existing nonclinical data package for each of insulin glargine and lixisenatide, together with an additional cardiovascular dog safety study and the local tolerance study with the combination will be acceptable to support conduct of phase 3 studies and subsequent approval of the combination product?

Specifically,

- a) Does the Agency agree to grant a waiver for additional safety pharmacology studies with the combination?
- b) Does the Agency agree to grant a waiver for additional nonclinical general toxicity studies with the combination?
- c) Does the Agency agree to grant a waiver for additional nonclinical reproductive toxicology studies with the combination?
- d) Does the Agency agree to grant a waiver for additional nonclinical genotoxicity studies with the combination?

FDA Response: FDA agrees that the existing nonclinical databases for lixisenatide and for insulin glargine support the clinical use of the combination. However since the insulin glargine formulation (b) (4) used in the combination differs slightly from marketed Lantus (b) (4) there is a possibility that the impurity and degradant profiles of the to-be-marketed FDC may differ from that of the individual drug components. In that case, it may be necessary to qualify those differences in a subchronic, single species, combination toxicology study. If unforeseen safety concerns are observed in the clinic with the combination,

additional nonclinical studies could be warranted. The acceptability of the data to support the approval of the combination product is a review issue and cannot be commented on at this time.

Sponsor response: The combination product [REDACTED] (b) (4)

However, if different impurities/degradants are detected, the sponsor suggests to conduct a 4 week study in the rat for toxicological qualification.

Discussion: FDA agreed that, if needed, a 28-day study in the rat should be sufficient to qualify new impurities and degradation products. Dose level selection for the 28-day study should be based on the concentration of the impurities requiring qualification rather than based on establishment of a maximum tolerated dose as is typical in toxicology study design. The sponsor was reminded to refer to the ICH Q3 guidances regarding the impurity and degradation levels that would require qualification. Depending on the level of impurities, in vitro genetic toxicology studies would also be required.

2. Based on the results of the carcinogenicity studies with the individual agents, the difference in target receptors for each of the actives, and the planned mechanistic studies, does the Agency agree to grant a waiver for nonclinical carcinogenicity studies with the combination?

FDA Response: At this time a combination carcinogenicity assessment is not needed. However, the mechanistic studies described in the meeting package which include binding studies to assess a possible interaction of lixisenatide to bind target receptors for insulin glargine (insulin receptor and IGF-1 receptor) and the potential for insulin glargine to bind to the GLP-1 receptor will be needed with the NDA filing. Because indices of mitogenicity and relative IGF-1 receptor binding are reported as slightly higher for Lantus compared to human insulin it would be helpful to have similar assessments conducted with lixisenatide plus insulin glargine, particularly to assess mitogenicity of the combination. As with other GLP-1 receptor agonist products, additional studies regarding the effects on thyroid c-cells may be required as a post-marketing requirement.

Sponsor response: Mechanistic studies which include binding studies to assess a possible interaction of lixisenatide to bind target receptors for insulin glargine and the potential for insulin glargine to bind to the GLP-1 receptor will be included in the NDA.

An assessment of lixisenatide plus insulin glargine to assess mitogenicity of the combination will be conducted and included in the NDA.

The Sponsor requests further clarification as to what type of additional studies regarding the effects on thyroid c-cells may be required as a post-marketing requirement, and confirmation that these studies apply only to lixisenatide.

Discussion: The sponsor was encouraged to include cell lines that have functional GLP-1 and insulin/IGF-1 receptors. The sponsor confirmed that they plan to identify human cell lines with functional GLP-1/insulin/IGF-1 receptors for use in the mitogenicity assays.

Regarding studies that may be required post-marketing, FDA stated that specific studies could not be identified at this time and that any requested studies will be determined during the NDA review on a case-by-case basis and will depend on the specific data included in the NDA and on the extent of concern that still exists.

The sponsor stated that they plan to submit data as they become available, (b) (4)

2.2. IND 105157 Clinical

3. Does the Agency agree that the clinical development plan is adequate to support the target indication?

FDA Response: (b) (4)

You will need to show that the combination of lixisenatide plus insulin glargine is superior to either component alone. In addition, a clinical trial with coadministration of lixisenatide plus insulin glargine will be required. Such a trial is needed to evaluate safety of coadministration at the injection site. (b) (4) It is strongly recommended that the coadministration of lixisenatide and insulin glargine be accomplished with the to-be-marketed device. Alternatively, the applicant could compare coadministration to administration at separate subcutaneous sites.

Sponsor response: The sponsor proposes (b) (4)

To ensure that the injection site safety concerns the Agency has identified are addressed, the sponsor will use a device (b) (4) that provides the same delivery characteristics (e.g. to-be-marketed formulation and combined drug concentrations, rate of delivery, needle size) of the to-be-marketed device. All aspects of the to-be-marketed device will be fully validated in the final design validation study.

Discussion: FDA clarified that the sponsor needs to show that the combination of lixisenatide plus insulin glargine is statistically superior to both components alone. FDA questioned why the proposed (b) (4),

(b) (4)
In addition, FDA stated that (b) (4) of uncontrolled data is a risk taken by the sponsor. FDA prefers more robust, controlled data. 24 weeks of data are considered more standard, as this is the duration it takes for HbA_{1c} to reach baseline levels. The duration of the study must be long enough for HbA_{1c} levels to plateau. Sponsor asked if testing the free combination (i.e. injection of two drug components at separate sites, but simultaneously) versus combination (i.e. injection of both drug components in the device as one drug product) would be considered a controlled study. FDA agreed. FDA concluded discussion by stating that since lixisenatide/insulin glargine is a novel product (i.e. a combination of two different active peptides has not been approved), FDA will take a conservative approach in its evaluation, so data should be robust and controlled.

4.

- a) Does the Agency agree that study (b) (4) will support submission and approval of a combination product of insulin glargine and lixisenatide for use with the (b) (4)

FDA Response: Because of the unavailability of a reliable assay specific for insulin glargine, your proposal of assessing BE in patients with type 1 diabetes is acceptable. However, there have been recent attempts of a specific assay development for insulin glargine according to the literature survey and we recommend that you pursue the latest available specific assay method for insulin glargine, if possible (e.g., www.aapsj.org/abstracts/NBC_2008/NBC08-000483.PDF). In addition, you should include comparability assessment of PD parameters such as GIR-AUC and GIR-Cmax (b) (4).

Regarding the basis for approving the combination product, see the response to Question 3 (b) (4).

Discussion: No discussion occurred.

- b) Does the Agency concur with the acceptance criteria selected by the applicant for bioequivalence?

FDA Response: We do not concur with your proposal. The 90% confidence interval of 80-125% criteria for both AUC and Cmax should be used to demonstrate bioequivalence for each of the drug substances, lixisenatide and insulin glargine. You may consider exposure -response analysis to support the clinical significance of results which do not meet the bioequivalence criteria. However, the acceptability of the results is a review issue.

Discussion: No discussion occurred.

5.

- a) Does the Agency agree that the safety results to be included in the NDA would satisfy requirements for the submission and approval of the combination?

FDA Response: The exposure of 500 patients to both drugs for 24 weeks is probably adequate, (assuming that lixisenatide is approved and that no unexpected safety issues arise from the trial proposed). Added to this number will be the patients exposed to the combination product in the clinical trial requested by FDA.

Sponsor response: Please refer to response #3 above regarding patient exposure. The sponsor requests clarification on exposure requirements should the lixisenatide NDA still be under review.

Discussion: Please refer to post-meeting comment below for further clarification on this response.

Post-Meeting Comment: After the meeting, FDA clarified that, while the lixisenatide + glargine combination NDA can be submitted during the review cycle for lixisenatide alone, the required exposure for the combination will be determined by the review of the lixisenatide NDA and by any potential issues that may emerge during the review.

- b) Does the Agency agree that the cardiovascular risk assessment plan to be implemented in the development of lixisenatide, together with the experience accumulated with the use of insulin glargine will also support the approval of the lixisenatide-insulin glargine combination?

FDA Response: Yes.

Discussion: No discussion occurred.

6. Sanofi-aventis is requesting a waiver for the development of the lixisenatide and insulin glargine combination in the pediatric population.

Does the Agency agree with this proposal?

FDA Response: No, but discussion of a pediatric program can be deferred until the NDA is submitted.

Discussion: No discussion occurred.

Post-Meeting Comment: 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

In your initial NDA submission, please include (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indications proposed in this application.

A full pediatric waiver for this combination is not likely to be granted.

2.3. IND 105157 Chemistry, Manufacturing and Controls (CMC)

7.

- a) Does the Agency agree with the approach that sanofi-aventis proposes for the primary stability studies and the batch size of the [REDACTED] (b) (4) produced?

FDA Response: Your approach for primary stability studies and the batch size of the [REDACTED] (b) (4) is acceptable.

Discussion: No discussion occurred.

- b) Does the Agency agree that the manufacturing scale of the batches for the bioequivalence study will be acceptable for the NDA submission and approval?

FDA Response: Your manufacturing scale for the batches to be used in future bioequivalence studies is acceptable.

Discussion: No discussion occurred.

8. Does the agency agree that the combination product injection system [REDACTED] (b) (4) as described above?

FDA Response: You state that [REDACTED] (b) (4)

1) the premix approach in which lixisenatide and insulin glargine are mixed in a fixed ratio in one container and the administered dose of lixisenatide is proportional to the titrated dose of insulin glargine;

[REDACTED] (b) (4)

[REDACTED] (b) (4)

(b) (4)

You have provided a description of the device constituent within the section of the IND titled “Meeting Background materials – Chemistry and Manufacturing Controls.”

Questions to the sponsor:

1. [Redacted] (b) (4)

Please address the following concerns:

- a. [Redacted] (b) (4) **please provide performance data to demonstrate that [Redacted] (b) (4) device can safely and effectively deliver the requested dose.**
- b. [Redacted] (b) (4), **please provide performance data to demonstrate that the dosing algorithms for this device will result in a safe and effective delivery of the requested dose of lixisenatide and insulin glargine.**

Sponsor’s response: With regard to FDA questions 1 a. and b., the Sponsor confirms that it will generate performance data to cover both points during our device verification program. [Redacted] (b) (4)

Discussion: [Redacted] (b) (4) *from a clinical perspective. However, patient education is key.*

- 9. Does the Agency agree that the measures described above are appropriate to ensure the quality of the lixisenatide / insulin glargine in the [Redacted] (b) (4)

FDA Response: Your proposal [Redacted] (b) (4)

Additionally, long-term, accelerated, and in-use stability data will be required to demonstrate that this solution [Redacted] (b) (4) upon storage and use.

Discussion: No discussion occurred.

10. Does the Agency agree with the general approach to application of ISO11608 to assessment of dose accuracy for this multi-component device?

FDA Response: CDRH does not object to your use of standard, ISO11608, “Pen-Injectors for Medical Use - .” This standard is recognized by FDA in its entirety.

Questions to the sponsor:

2. **You referenced that your general approach for the assessment of dose accuracy for this multi-component device would be based on the standard ISO 11608, “Pen-Injectors for Medical Use.”** (b) (4)

This standard has been recognized by the FDA and is commonly referred to during our review process. (b) (4)

(b) (4)

[Redacted] (b) (4)

Discussion: A robust human factors study is an acceptable approach (please refer to guidance in response #12.). [Redacted] (b) (4)

3. [Redacted] (b) (4)

Sponsor response: [Redacted] (b) (4)

[Redacted] (b) (4)

Discussion: FDA stressed to the sponsor that they can refer to ISO 11608, however, ultimately the FDA will assess the safety and effectiveness of their device based on its ability to meet its pre-defined physical and performance specifications. [Redacted] (b) (4)

11. Does the Agency agree [redacted] (b) (4)

[redacted]

FDA Response: [redacted] (b) (4)

[redacted]

[redacted] (b) (4)

Sponsor response:

[redacted] (b) (4)

12. Does the Agency agree with the options to be evaluated during the usability validation process?

FDA Response: Based on the description provided regarding the usability validation, CDRH does not have enough information to provide a definitive response regarding the appropriateness of [REDACTED] (b) (4) CDRH is further concerned that this is a limited usability study that does not address the human factor study concerns identified in CDRH's guidance regarding Human Factors and Risk Assessment.

Questions to the sponsor:

5. Based on the description provided regarding the usability validation, CDRH does not have enough information to provide a definitive response regarding the appropriateness of [REDACTED] (b) (4) stated in your inquiry (i.e. declaring the quantitative amount of both drug substances in the labeling [REDACTED] (b) (4) [REDACTED] (b) (4). CDRH is also concerned that your usability study, as described in the submission does not address the human factor study concerns as identified in CDRH's guidance regarding Human Factors and Risk Assessment.

For this kind of device, FDA is concerned about the adequacy of the device user interface design. The device interface includes all device components with which the user handles, reads, manipulates etc. including the size shape and operation of hand-held devices and their accessories, labeling and user instructions. FDA requires that consideration of risk associated with unintentional errors arising from confusion or misinterpretation of the device user interface when users perform critical tasks be undertaken and that demonstration of successful control of these risks be demonstrated by validation testing involving simulated use of the device. For devices that involve critical user tasks, FDA will expect results of a validation study involving simulated use of the device, prioritization of user tasks, involving a minimum of 15 users that represent the population of intended users.

The intent of the a human factors validation study is to demonstrate that representative users can use the device under simulated conditions without exhibiting patterns of failures or difficulties that could result in clinical impact to patients (or in some cases, but likely not for your device, to users themselves).

To the extent that failures are found in a validation study, the study should collect sufficient and appropriate data such that the failures can be described in terms of their cause. The test report should present a summary of these results within a discussion with respect to whether or not and the extent to which failures found are due to aspects of the design of the device, its labeling or the content or proximity of training and whether modifications are indicated. FDA may agree or disagree with this determination and stated plans to modify design flaws in future versions of the device are generally unacceptable.

We recommend that you contact CDRH prior to beginning the human factors

assessment to discuss your approach to the studies.

Please review the Center Guidance on Human Factors and Risk Management available at:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf>

Please provide results of a Human Factors, or “Usability” evaluation for your device. In addition to the guidance document, the following points are emphasized:

- a. Relative priority of tasks. FDA needs to understand the relative priority of the user tasks you select for testing in terms of the potential results of inadequate performance on these tasks. Indeed, the tasks selected for testing should be selected on this basis. Please provide this information in the report of your HF/Usability validation study.**
- b. Comprehensiveness of task set. FDA needs to understand that the tasks you chose to test represent the extent of the tasks that could lead to use-related problems (as defined) for use of your device. Please provide this information in the report of your HF/Usability validation study.**
- c. Realism of simulated use. Please describe how the device was used by study participants during use scenarios the performance of critically important tasks.**
- d. Training. Please describe any training that is necessary for successful operation of your device. If you intend to provide training to users, the participants in your validation study should receive equivalent training.**
- e. Please contact FDA if you have any questions about how to perform Human Factors/Usability validation testing.**

Sponsor response: Please clarify what further information is needed to provide definitive response on the appropriateness of the (b) (4).

The sponsor acknowledges the feedback provided on an approach to User Validation Studies and Human Engineering considerations. We confirm that the approach described is in line with our intended approach to these considerations, and is much broader than the reference in the briefing package.

We would be pleased to follow the Agency’s recommendation to discuss this item and other aspects of the device and drug product development program in a future meeting.

Discussion: The sponsor will discuss these issues again with FDA in a future meeting.

3.1. IND 062724 Nonclinical

1. Does the Agency agree that the proposed mechanistic study strategy is appropriate to provide sufficient evidence that the rodent thyroid C-cell tumors observed in lifetime carcinogenicity studies with lixisenatide are not relevant to humans, and that no additional mechanistic studies are required?

FDA Response: The proposed mechanistic studies may provide useful information that could support the hypothesis that c-cell tumors induced by GLP-1 receptor agonists are rodent specific. However, the adequacy of the mechanistic data to alleviate concerns regarding human risk or a decision about whether additional mechanistic studies will be required cannot be determined until the study data have been submitted and reviewed. FDA has the following suggestions regarding the mechanistic studies:

- a. **For receptor mRNA expression in human thyroid c-cells, you should consider assessing c-cells from normal tissue, hyperplastic tissue, adenomas, and carcinomas to determine whether the GLP-1 receptor becomes upregulated during tumor progression. If available, assessing samples from MEN patients should also be considered. A sufficient number of thyroid samples should be assessed to account for heterogeneity in the human population.**

Sponsor response: The Sponsor would welcome advice from the Agency on the feasibility to conduct assessments in thyroid c-cells from patients with hyperplasia or adenomas, as well as obtaining samples from MEN patients.

Discussion: FDA prefers testing on human tissue over cell lines. The sponsor stated that identifying thyroid tissue with c-cell hyperplasia and/or adenomas could be challenging because patients are generally not diagnosed with these lesions, but rather, normal tissue and thyroids with c-cell carcinomas would be easier to acquire. FDA understands this limitation and suggests that some thyroid specimens could be examined microscopically to identify areas with c-cell hyperplasia and/or adenomas. However, given the potential limitation in identifying/acquiring tissues with these lesions, a comparison of GLP-1 receptor expression between normal tissue and c-cell carcinomas, especially from the same individual, could be very informative. Depending on the results of this testing, if there is an increase in mRNA, the sponsor should consider assessing whether the mRNA expression correlates with protein expression of the GLP-1 receptor.

- b. **Regarding the second set of proposed mechanistic studies, you are encouraged to study the effect of lixisenatide on c-cell proliferation in GLP-1 receptor knock-out mice even if significant calcitonin release is not evident in wild-type mice.**

Discussion: As a follow-up to this point, FDA stated that the primary endpoint for a study in knock-out mice should be c-cell proliferation rather than only calcitonin secretion, as the link between GLP-1-induced calcitonin secretion and c-cell hyperplasia has not been sufficiently established. It was emphasized that the key objective for the mechanistic studies is to determine whether the proliferative mechanism observed in rodents is relevant to humans.

Can the Agency also provide the Sponsor with an update of their thinking on the potential relevance of rodent tumors to human with some representatives of the class of GLP-1m receptor agonists?

FDA Response: Currently, there is still insufficient evidence to conclude that GLP- 1 receptor agonist-induced c-cell tumors in rodents are not relevant to human risk. FDA's view on human relevance will continue to be addressed as additional mechanistic data are received.

Discussion: No discussion occurred.

2. Does the Agency agree with the Sponsor's consideration that an additional rat carcinogenicity study with lixisenatide is not scientifically warranted?

FDA Response: Although a NOAEL for thyroid c-cell hyperplasia and c-cell adenomas was not determined for the rat carcinogenicity study, FDA does not feel that this study should be repeated to identify a NOAEL. However, as with other GLP-1 receptor agonist products, additional studies regarding the effects on thyroid c-cells may be required as a post-marketing requirement.

Discussion: No discussion occurred.

3. Does the Agency agree with the favorable risk profile of lixisenatide specifically regarding the thyroid C-cell carcinoma issue based on nonclinical data available to date, and that labeling for rodent thyroid tumors will be done on a case-by-case basis?

FDA Response: From a nonclinical perspective, the incidence of adenomas plus carcinomas is generally used for estimating human risk rather than focusing on the exposure margin at which only carcinomas were observed. The rat carcinogenicity study failed to identify a NOAEL for adenomas. Therefore, FDA cannot conclude that lixisenatide has a favorable risk profile compared to other approved GLP-1 receptor agonists because it is not known whether lixisenatide induces c-cell tumors in rats near clinical exposures. As you noted, there are differences in labeling for different approved GLP-1 receptor agonist products based on perceived human risk for thyroid c-cell tumors. Ultimately, labeling considerations for lixisenatide will be addressed during the NDA review process on a case by case basis.

Discussion: No discussion occurred.

4. Does the Agency agree that the nonclinical studies and mechanistic approaches conducted and planned, in conjunction with the human sperm assessment study, are adequate to address the Agency's concerns regarding a potential effect of lixisentide on the male reproductive system, and that no additional nonclinical studies are necessary?

FDA Response: Yes, FDA agrees that your proposal appears to be adequate to address the concerns regarding effects on spermatogenesis observed in dogs. However, a determination of the adequacy of the data and whether additional studies might be required is a review decision, which cannot be made until the study data are submitted.

Discussion: No discussion occurred.

3.2. **IND 062724 Chemistry, Manufacturing and Controls (CMC)**

5. Does the agency agree with the proposed bracketing concept to be used during process validation [REDACTED] (b) (4)

FDA Response: We have no objections to your proposed plan for validating the manufacturing process by using bracketing concept. However, FDA does not approve manufacturing process validation approaches or protocols. The process activities, including actual protocols, sampling plans and acceptance criteria, as well as study outcomes will be evaluated during a CGMP inspection. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product. A good understanding of the variables, both material attributes and processing parameters, in each unit operation that impact the drug product's specifications and quality attributes, will enable you to generate a sound protocol(s) for the commercial scale performance qualification. For example, your protocol(s) should address the process performance criteria against which you will judge the success of your process validation study(ies). Protocols should also address the data and measurements to be collected, sampling plans, comparisons to be made between individual commercial runs included in the study(ies), and the scientific data analyses, including any statistical analyses, to be performed on all the data collected. A scientific rationale for the protocol design should be available.

Discussion: No discussion occurred.

6. Does the agency agree with the sponsor's proposed stability plan to support the approval of the lixisenatide drug product, in particular,
 - a) Does the agency agree that - in addition to primary stability data on drug product [REDACTED] (b) (4) - initial submission of at least 6 months stability data per dosage strength obtained on one representative commercial scale batch [REDACTED] (b) (4)

(b) (4) is sufficient to confirm stability of the drug product in the pen injector presentation?

FDA Response: The bracketing strategy appears acceptable.

Sponsor response: The Sponsor would appreciate clarification if at least 6 months stability per dosage strength obtained on one representative commercial scale batch (b) (4) is sufficient to confirm the stability of the drug product in the pen injector presentation.

Discussion: FDA questioned whether the photostability study will be performed (b) (4)
This is still to be determined by the sponsor.

7. (b) (4)
?

FDA Response: (b) (4)

Discussion: No discussion occurred.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

1. Sponsor will arrange a follow-up meeting with FDA about questions regarding performing Human Factors/Usability validation testing. This meeting will involve the Center for Device and Radiological Health (CDRH).
2. The Office of Surveillance and Epidemiology (OSE) will be involved to assess issues with labeling of the combination product. The lixisenatide/insulin glargine product has a drug reservoir of the two drugs pre-mixed. Glargine is part of this pre-mix (b) (4)

(b) (4) The sponsor raised the following point: if (b) (4)
On the other hand, it may not be (b) (4) permissible (b) (4) One solution the sponsor proposed is to label the (b) (4) OSE will be

involved in future meetings to provide guidance on development of labels and a human factor study.

5.0 ATTACHMENTS AND HANDOUTS

1. Attachment 1: Illustration of primary and secondary packaging
2. Attachment 2: Proposed Strategy for Co-Stimulation

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-105157	GI-1	SANOFI AVENTIS US INC	lixisenatide and insulin glargine
IND-62724	GI-1	AVENTIS PHARMACEUTICA L PRODUCTS INC	lixisenatide

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

/s/

POOJA DHARIA
07/23/2010

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 208471

NDA 208673

LATE-CYCLE MEETING MINUTES

Sanofi US Services Inc.
Attention: David Faunce and Shefali Goyal
55 Corporate Drive
Mail Stop: 55D-215A
Bridgewater, NJ 08807

Dear Mr. Faunce and Ms. Goyal:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lixisenatide dated July 27, 2015, and insulin glargine/lixisenatide injection dated December 21, 2015.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on May 11, 2016.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

William Chong, M.D.
Clinical Team Leader
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: May 11, 2016, 2:00 – 4:00pm
Meeting Location: FDA White Oak, Building 22, Room 1313

Application Number: NDA 208471 and NDA 208673
Product Name: lixisenatide and insulin glargine/lixisenatide injection
Applicant Name: Sanofi US Services Inc.

Meeting Chair: William Chong, M.D.
Meeting Recorder: Martin White, M.S.

FDA ATTENDEES

Office of Drug Evaluation II

Mary Parks, M.D., Deputy Director

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D., Division Director
William Chong, M.D., Clinical Team Leader
Suchitra Balakrishnan, M.D. Ph.D., Clinical Reviewer
Lisa Yanoff, M.D., Clinical Team Leader
Feleke Eshete, Ph.D. Nonclinical Reviewer
Monika Houston, Pharm.D., Associate Director for Labeling
Pamela Lucarelli, Chief, Project Management Staff
Martin White, M.S. Regulatory Project Manager

Center for Devices and Radiological Health

John McMichael, General Hospital Devices Branch
Lana Shiu, M.D., General Hospital Devices Branch

Office of Clinical Pharmacology

Manoj Khurana, PhD, Clinical Pharmacology Team Leader
Suryanarayana Sista, PhD, Clinical Pharmacology Reviewer
Nitin Mehrotra, M.Pharm., PhD, Pharmacometrics Team Leader

Office of Biostatistics

Mark Rothmann PhD, Biometrics Team Leader
Jiwei He, Ph.D., Biometrics Reviewer

Office of Combination Products

Bindi Nikhar, M.D., Associate Clinical Director

Office of Surveillance and Epidemiology

Lubna Merchant, M.S. Pharm.D., Deputy Director, Division of Medication Error Prevention and Analysis (DMEPA)

Yelena Maslov, Pharm.D., Team Leader, DMEPA

Ariane Conrad, Pharm.D., BCACP, CDE, FASCP, Safety Evaluator, DMEPA

Sarah Vee, Pharm.D., Safety Evaluator, DMEPA

Christian Cao, MPAS, PA-C, Team Leader, Division of Pharmacovigilance I (DPV)

Ali Niak, M.D., Medical Officer, DPV

Christian Hampp, Ph.D., Reviewer, Division of Epidemiology I

Terrolyn Thomas, M.S., M.B.A., Safety Regulatory Project Manager

Office of Product Quality

Juhong Liu Ph.D., Team Leader, Office of Biotechnology Products (OBP)

Harold Dickensheets, Ph.D., Reviewer, OBP

Faruk Sheikh, Ph.D., Reviewer, OBP

Division of Pediatric and Maternal Health (DPMH)

Christos Mastroyannis, M.D., Medical Officer

Office of Prescription Drug Promotion (OPDP)

Ankur Kalola, Pharm.D., Regulatory Review Officer

Endocrinologic and Metabolic Drugs Advisory Committee

LaToya Bonner, Pharm.D., Designated Federal Officer

EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein, Independent Assessor

APPLICANT ATTENDEES

John Newton, Ph.D. Vice President, Head Metabolism and Pharmacokinetics

Elisabeth Niemoeller, M.D., Clinical Lead, Late Stage Clinical Development, Global Diabetes Division

Patrick Miossec, M.D., Clinical Lead, Late Stage Clinical Development, Global Diabetes Division

Rene Belder, M.D., Vice President, Deputy Head Clinical Development, Global Diabetes Division

Meehyung Cho, Ph.D., Director, Biostatistics

Peng-Liang Zhao, Ph.D. Associate Vice President, Biostatistics

Sandeep Kumar, M.D., Senior Director, Pharmacovigilance

Jean-Luc Delhay, M.D., Medical Safety Evaluation, Pharmacovigilance

Kirsten Sharma, MD., Vice President, Drug Safety, North America Medical Affairs

Anthony Watson, Ph.D., Head, Regulatory Devices

Dave Faunce, M.S., Director, Global Regulatory Affairs

Shefali Goyal, M.S., MSc., Director, Global Regulatory Affairs

Don Giesecker, Ph.D., Associate Vice President, Global Regulatory Affairs

Barry Sickels, Ph.D., Vice President, North America and Global, Global Regulatory Affairs

1.0 BACKGROUND

NDA 208471 was submitted on July 27, 2015, for lixisenatide.

NDA 208673 was submitted on December 21, 2015, for insulin glargine/lixisenatide injection.

Proposed indications:

Lixisenatide is proposed to be indicated as an adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus.

Insulin glargine/lixisenatide fixed ratio combination is proposed to be indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and lixisenatide is appropriate.

PDUFA goal date:

NDA 208471: July 27, 2016

NDA 208673: August 21, 2016

FDA issued a Background Package in preparation for this meeting on May 5, 2016.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

NDA 208471- Review issues with lixisenatide

The potential for anaphylaxis with lixisenatide (a component of insulin glargine and lixisenatide injection) remains under consideration. Based on their preliminary reviews, FDA pharmacovigilance and epidemiology reviewers have determined that the post-marketing analyses that you have submitted in your white paper dated February 26, 2016, have limitations, and do not advance our knowledge about this risk with lixisenatide, when compared to approved GLP-1 agonists. Our inferences will be primarily based on clinical trial data. We acknowledge that differences in the size of the development programs as well as the adjudication process could have contributed to these differences and makes across program comparisons difficult.

Discussion: The Agency's concerns with regard to anaphylaxis and hypersensitivity reactions were discussed. The Agency stated that this will be discussed at the Advisory Committee meeting.

NDA 208673 - Review issues identified with lixisenatide and insulin glargine fixed-ratio combination (FRC)

a. Interpretability of efficacy data due to study design issues and Insulin dosing

The Division has reservations about your conclusion of superiority of the FRC to insulin glargine. Insulin titration was based upon a pre-specified algorithm which limited dose titration to no more than 4 units per week. Despite having an algorithm in place, the overall proportion of subjects achieving fasting plasma glucose targets was less than 40% in study EFC12404, and only 30% achieved fasting plasma glucose targets in study EFC12405. Given the poor performance in achieving titration targets, there is uncertainty with regard to whether the achieved HbA1c accurately reflects the ability of treatment to improve glycemic control.

For both studies, the insulin glargine dose was capped at 60 units. This cap, together with the limitations of the insulin titration algorithm, raises concerns that the change in HbA1c for the insulin glargine arm is not reflective of the full effect of therapy.

Additionally, the subjects in study EFC12405 were already inadequately controlled on basal insulin therapy at baseline. Due to the design of the study, subjects randomized to the insulin glargine arm were essentially randomized to a therapy that was already known to be inadequate.

Discussion: The Agency's concerns with regard to the design of the trials and potential impact on unbiased conclusions of superiority were discussed. Sanofi inquired whether the White Paper submitted on April 15, 2016, addressed these concerns. The Agency stated that this was still under review, and that this would be discussed at the Advisory Committee meeting.

Sanofi stated that they believe the fixed ratio combination product is superior on improving HbA1c and that it also mitigated weight gain associated with insulin use. The Agency stated that the studies were not designed to demonstrate the benefit of weight differences.

b. Benefit of adding lixisenatide at low dose range

Due to the design of the studies, there were few subjects with data to support a benefit of adding lixisenatide at doses below 10 µg. We have considered your post-hoc analyses by dose category and this remains a residual concern.

Discussion: The residual concerns with regard to the benefit-risk of low doses of lixisenatide in the fixed ratio combination product were discussed. The Agency reiterated that this is a concern and that it will be discussed at the Advisory Committee meeting.

c. Medication errors/Usability and Clinical Utility of the device

(b) (4)
Despite the results of the Human Factors study, the Division has residual concerns with regard to the potential for errors. The simulated use conditions from this testing may not be reflective of the time prescribers have to review the available information regarding selecting the appropriate pen injector and initiating therapy.

While the FRC is recommended for use when insulin glargine doses of 10 to 60 units, the devices will allow for dosing as little as 1 unit of insulin glargine (b) (4). There is the potential for inadvertent administration of higher than studied doses of lixisenatide. The safety of lixisenatide above 20 µg has not been studied.

With the FRC, if a dose reduction is needed, patients will be forced to reduce the dose of two products when reducing the dose of one may be sufficient. The rationale for reducing two components when reducing one may be sufficient is unclear.

The proposal for two different pen injectors with two different dosage strengths raises further questions of practicality. A switch from Pen A to Pen B would result in a decrease in the amount of lixisenatide administered. For a patient requiring increased therapy to improve glycemic control, the rationale for decreasing the dose of one medication while increasing the other is unclear.

The proposed drug product places a limit on the amount of insulin that can be delivered. This limit may not be practical and, as seen in the clinical studies, could lead to exposure to higher doses of lixisenatide. We have considered your analyses of data from the (b) (4) Database and believe that these analyses have limitations. We remain uncertain on whether a majority of the target population will be included in the limited dose range of 10 and 60 units.

Discussion: Sanofi requested further clarification regarding the Agency's concern about the human factors study results. The Agency expressed continued concern about the amount of time that prescribers were allowed to review the prescribing information prior to completing the prescribing tasks and the risk for error due to the availability of two pen devices containing different ratios of the product. The Agency acknowledged that human factors studies could not address some of the concerns with this multi-ingredient product but expressed that the availability of the two pens increases the risk

of error with this product. The Agency stated that these issues will be discussed at the Advisory Committee meeting.

3. Additional Applicant Data

Discussion: Sanofi stated that there was data on subjects switching between the two different proposed pen injectors and that this data would be submitted to the Agency.

4. Information Requests

NDA 208471

Device:

The below information request (item a) is incomplete. You partially addressed the device performance issue by providing dose accuracy data for the pre-aged product and at 36 month of shelf-life in your February 05, 2016, submission. In your response, you specified the cap removal force, activation force and dispensing force specifications but you did not specify injection time. In order to complete our review, we need the performance reports and summary table for the injector's injection time, activation force, dispensing force before aging and after 36 month of aging as well as after shipping.

- a. You have provided the dose accuracy specifications and test results as your measure of the autoinjector's functional performance criteria but we do not have other basic specifications and test results for the subject autoinjector such as cover removal force, activation force, spring injection force, and injection time. The Agency would also like to know that your combination product can perform as specified (not only measured by dose accuracy) after shipping and right before the expiry of shelf life, so please provide the appropriate performance testing data after accelerate aging conditions and shipping.

Discussion: The Agency stated that the above request is still outstanding. Specifically can the combination product perform as specified (not only measured by dose accuracy) after shipping and right before the expiry of shelf life.

Sanofi agreed to provide this information in the May 18, 2016 submission.

The below information requests (items b) is incomplete. As noted in your response dated February, 05, 2016, you will provide a response to the Agency no later than May 18, 2016.

- b. In your response dated January 21, 2016, you clarified that the pen injectors proposed for use for injection of lixisenatide solution will be provided in green and burgundy colors, while the (b) (4) pen-injector is not part of this NDA application. You further clarified that a (b) (4) agent used in the patient contact device components was changed after your initial biocompatibility evaluation as indicated in Table 6.

In response to the biocompatibility deficiencies (Deficiencies #4-6), you stated that you would re-do the biocompatibility testing to address the issues identified by the FDA and provide new test reports for cytotoxicity, skin irritation or intracutaneous reactivity, and sensitization for each color type of the pen-injectors proposed. However, the response provided does not include any of the revised test reports for review. To proceed with our

review, please provide the indicated biocompatibility test reports for the final finished subject devices.

In addition, you stated “*Evaluation of leachables according to ISO 10993-18 and the cytotoxicity assays demonstrated no significant differences between the extracts of differently colored pens. To comply with animal welfare requirements in accordance with ISO 10993-2, biocompatibility tests concerning irritation and sensitization were conducted only for the green pen.*” Please be advised that, *in vitro* cytotoxicity testing cannot address the concerns for skin irritation and sensitization. Based on your test protocols and reports provided in Attachments #13, #16, and #17, the chemical extractable and leachable testing was limited only to analysis of organic substances by GC/MS Fingerprint, while chemical comparison of (b) (4) device extracts was not conducted. The justification for only performing the skin irritation and sensitization testing on the green pen-injector is considered inadequate. To support that biocompatibility testing based on one selected color type can adequately address the biocompatibility concerns for all color types of the pen-injectors proposed, please provide a clear and comprehensive comparison for both (b) (4) chemical extractables and leachables. Please clearly demonstrate that the various color types of the pen-injectors proposed have the same types and levels of the chemical extractables and leachables. Alternatively, please provide all required biocompatibility testing for each color type of the pen-injectors proposed. Please provide the testing using (b) (4) device extracts, both (b) (4), from the final finished green and burgundy pen-injectors intended for marketing. Please ensure all patient contact device components were included in the testing.

Discussion: Sanofi stated that the above information is still on track to be submitted no later than May 18, 2016.

Office of Biotechnology Products:

The below information requests (items c through e) are incomplete. As noted in your response dated April, 25, 2016, you will reevaluate cross-reactivity data using a newly determined specificity cut-point and submit to the Agency no later than May 4, 2016. The Agency issued an additional information request on May 2, 2016, and requested a response from Sanofi no later than May 4, 2016, for items c through e.

- c. Clarify which Biacore instrument (T100 vs. T200) was used for sample analysis for cross-reactivity of GLP-1 and glucagon.
- d. Include an additional column in the data table for cross-reactivity results from the new analysis as a percent inhibition of control for each sample.
- e. Submit data in Excel and pdf formats.

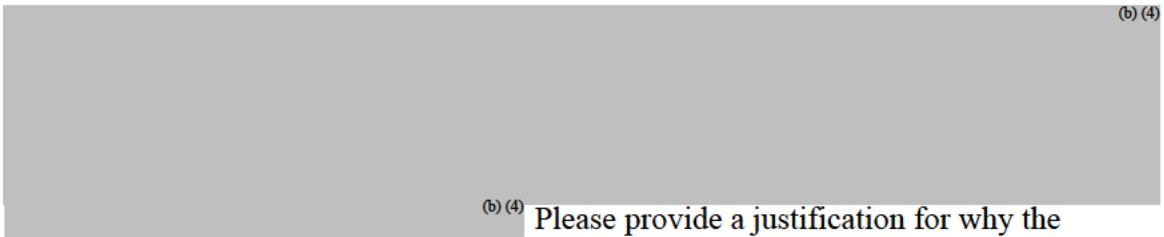
Discussion: The Agency received the response to the information request on May 4, 2016, and is currently reviewing this submission. Upon review, the Agency will inform Sanofi of any additional information requests regarding this topic.

NDA 208673

Device:

The Agency received responses to the below information requests on May 2, 2016. At this time, we have not completed our review of the response. If additional information is required, we will send notify you during the Late-Cycle Meeting.

a.



(b) (4) Please provide a justification for why the vehicles you have used are appropriate for this test. Alternatively, please provide a method validation demonstrating that the extracts from the chosen vehicles are able to detect potential sensitizers. For more information, please refer to ASTM F2148: standard practice for evaluation of delayed contact hypersensitivity using the murine local lymph node assay.

- b. In response to an information request dated March 2, 2016, you stated that the glargine/lixisenatide pen-injector is operated manually and therefore essential performance requirements associated with automated features do not apply. The Agency accepts this rationale for certain performance criteria, however the Agency notes that a specification should be developed for the injection time per unit dose so that the users have an expectation of how long it should take to inject given a maximum dispensing force of less than or equal to (b) (4) N. Please state the minimum time to inject (i.e. at a dispensing force of (b) (4) N) the minimum and maximum dose for both pen A and pen B. This minimum time to inject should be included in the labeling of the device to inform users the minimum time they must sustain the injection (independent of any audible/visual/tactile feedback for the end of injection). Alternatively, please provide a more detailed rationale for not including an estimated injection time for the minimum and maximum dose of the pen-injectors.
- c. The Agency notes that your pen-injectors include tactile/visual/audible feedback per ISO 11608-1. However, you have not provided any verification of this feedback. Please develop a specification for this feedback as a part of your essential performance requirements and provide verification that the feedback functions as intended.
- d. The Agency notes that of your essential performance requirements you have only included extractable volume as a test of dose accuracy within your current batch release (document QUA-FR-2014-23122). The Agency notes that all essential performance

requirements should be verified during batch release including dose selection, dispensing force, injection time (based on results of request for specification), audible/visual/tactile feedback, and dose accuracy. Please provide documentation as evidence that you have included dose selection, dispensing force, and audible/visual/tactile feedback within your batch release testing.

- e. In response to an information request dated March 2, 2016, you stated that the tests performed during in-use and long term stability studies are performed according to ISO 11608-1:2012 and require full functional assessment of the pen-injector, including steps to set up the pen for an injection and dispense the dose. However, you have not stated specifically what essential performance requirements were tested post-aging besides dose accuracy. It seems that you are asserting that a test for dose accuracy is a downstream effect of all functional characteristics of the pen-injector and therefore is representative of all other essential performance criteria. The Agency believes that certain essential performance requirements such as dispensing force, injection time, and visual/audible/tactile feedback should be verified after aging and preconditioning the device in order to establish that the device meets all essential performance requirements up to the labeled date of expiry for the device. Please provide this testing on a currently available batch within the long-term stability study in order to verify the essential performance requirements after aging. Alternatively, please provide greater detail regarding the full functional testing based on the instructions for use completed post-aging and if the functional testing included testing for the other essential performance requirements of your device besides dose accuracy.

Discussion: The Agency received responses to the below information requests on May 2, 2016. The responses provided are currently under review.

The Agency provided an additional information request prior to May 9, 2016. The information request is below:

In document QUA-FD-2015-19978 you executed a simulated shipping study and performed functional inspection and dose accuracy testing to confirm the pen-injectors maintained functionality after shipping. The Agency believes that certain essential performance requirements such as dispensing force, injection time, and visual/audible/tactile feedback should be verified after shipping in order to establish that the device continues to meet all essential performance requirements. Please provide this testing in order to verify the essential performance requirements after shipping. Alternatively, please provide greater detail regarding the ‘functional testing’ performed in accordance with ISO 11608-1 Section 10.1 d) and if the functional testing included testing for the other essential performance requirements of your device besides dose accuracy.

Sanofi agreed to provide a response in a May 12, 2016 submission.

5. Discussion of Upcoming Advisory Committee Meeting

FDA's preparations for the upcoming AC meeting are ongoing, and we have no further information to communicate at this time. The high level issues to be discussed at the AC meeting are noted above.

Discussion: No additional discussion occurred.

6. Review Plans

FDA will continue review of the NDA and, at this time, there appear to be no significant review issues that would prevent FDA from taking an action on or before the PDUFA goal date.

Discussion: No additional discussion occurred.

7. Wrap-up and Action Items

The AC meeting will be held on May 25, 2016. Please see above for Action items. This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

8. Additional Discussion:

a. Prior to the meeting, the Agency sent a request to Sanofi

(b) (4)

(b) (4)

Sanofi expressed their concerns

(b) (4)

Ultimately, Sanofi wanted to discuss this topic more internally and present another option to the Agency.

b. Prior to the meeting, Sanofi requested that the

(b) (4)

Sanofi felt that these data were not relevant since final data is available and has been provided for the NDA208471 under review. In addition, the interim analysis of the ELIXA trial was handled by a firewalled team at Sanofi and was never made available to the rest of the company or released to the Public.

The Agency acknowledged Sanofi's concern and but pointed to the fact that the study was complete and that the final data was public. In addition, the Agency felt that the interim data was an important part of the regulatory history for lixisenatide. The Agency stated that the interim data would not be emphasized during the Advisory Committee.

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/s/

WILLIAM H CHONG
06/22/2016

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: May 11, 2016, 2:00 – 4:00pm
Meeting Location: FDA White Oak, Building 22, Room 1313

Application Number: NDA 208471 and 208673
Product Name: lixisenatide and insulin glargine/lixisenatide injection
Indication: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant Name: Sanofi US Services Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review. These applications have not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the applications. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

NDA208471- Review issues with lixisenatide

The potential for anaphylaxis with lixisenatide (a component of insulin glargine and lixisenatide injection) remains under consideration. Based on their preliminary reviews, FDA pharmacovigilance and epidemiology reviewers have determined that the post-

marketing analyses that you have submitted in your white paper dated February 26, 2016, have limitations, and do not advance our knowledge about this risk with lixisenatide, when compared to approved GLP-1 agonists. Our inferences will be primarily based on clinical trial data. We acknowledge that differences in the size of the development programs as well as the adjudication process could have contributed to these differences and makes across program comparisons difficult.

NDA 208673 - Review issues identified with lixisenatide and insulin glargine fixed-ratio combination (FRC)

a. Interpretability of efficacy data due to study design issues and Insulin dosing

The Division has reservations about your conclusion of superiority of the FRC to insulin glargine. Insulin titration was based upon a pre-specified algorithm which limited dose titration to no more than 4 units per week. Despite having an algorithm in place, the overall proportion of subjects achieving fasting plasma glucose targets was less than 40% in study EFC12404, and only 30% achieved fasting plasma glucose targets in study EFC12405. Given the poor performance in achieving titration targets, there is uncertainty with regard to whether the achieved HbA1c accurately reflects the ability of treatment to improve glycemic control.

For both studies, the insulin glargine dose was capped at 60 units. This cap, together with the limitations of the insulin titration algorithm, raises concerns that the change in HbA1c for the insulin glargine arm is not reflective of the full effect of therapy.

Additionally, the subjects in study EFC12405 were already inadequately controlled on basal insulin therapy at baseline. Due to the design of the study, subjects randomized to the insulin glargine arm were essentially randomized to a therapy that was already known to be inadequate.

b. Benefit of adding lixisenatide at low dose range

Due to the design of the studies, there were few subjects with data to support a benefit of adding lixisenatide at doses below 10 µg. We have considered your post-hoc analyses by dose category and this remains a residual concern.

c. Medication errors/Usability and Clinical Utility of the device

(b) (4)
Despite the results of the Human Factors study, the Division has residual concerns with regard to the potential for errors. The simulated use conditions from this testing may not be reflective of the time prescribers have to review the available information regarding selecting the appropriate pen injector and initiating therapy.

While the FRC is recommended for use when insulin glargine doses of 10 to 60 units, the devices will allow for dosing as little as 1 unit of insulin glargine (b) (4). There is the potential for inadvertent administration of higher than studied doses of lixisenatide. The safety of lixisenatide above 20 µg has not been studied.

With the FRC, if a dose reduction is needed, patients will be forced to reduce the dose of two products when reducing the dose of one may be sufficient. The rationale for reducing two components when reducing one may be sufficient is unclear.

The proposal for two different pen injectors with two different dosage strengths raises further questions of practicality. A switch from Pen A to Pen B would result in a decrease in the amount of lixisenatide administered. For a patient requiring increased therapy to improve glycemic control, the rationale for decreasing the dose of one medication while increasing the other is unclear.

The proposed drug product places a limit on the amount of insulin that can be delivered. This limit may not be practical and, as seen in the clinical studies, could lead to exposure to higher doses of lixisenatide. We have considered your analyses of data from the (b) (4) Database and believe that these analyses have limitations. We remain uncertain on whether a majority of the target population will be included in the limited dose range of 10 and 60 units.

ADVISORY COMMITTEE MEETING

Date of AC meeting: May 25, 2016

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: To be determined

Potential questions and discussion topics for AC Meeting are as follows:

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM)
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues - 60 minutes
See above.
3. Additional Applicant Data – 15 minutes (Applicant)
Reserved for the Applicant to provide any additional data if necessary.
4. Information Requests – 15 minutes

NDA 208471

Device:

The below information request (item a) is incomplete. You partially addressed the device performance issue by providing dose accuracy data for the pre-aged product and at 36 month of shelf-life in your February 05, 2016, submission. In your response, you specified the cap removal force, activation force and dispensing force specifications but you did not specify injection time. In order to complete our review, we need the performance reports and summary table for the injector's injection time, activation force, dispensing force before aging and after 36 month of aging as well as after shipping.

- a) You have provided the dose accuracy specifications and test results as your measure of the autoinjector's functional performance criteria but we do not have other basic specifications and test results for the subject autoinjector such as cover removal force, activation force, spring injection force, and injection time. The Agency would also like to know that your combination product can perform as specified (not only measured by dose accuracy) after shipping and right before the expiry of shelf life, so please provide the appropriate performance testing data after accelerate aging conditions and shipping.

The below information requests (items b) is incomplete. As noted in your response dated February, 05, 2016, you will provide a response to the Agency no later than May 18, 2016.

- b) In your response dated January 21, 2016, you clarified that the pen injectors proposed for use for injection of lixisenatide solution will be provided in green and burgundy colors, while the (b) (4) pen-injector is not part of this NDA application. You further

clarified that a (b) (4) agent used in the patient contact device components was changed after your initial biocompatibility evaluation as indicated in Table 6.

In response to the biocompatibility deficiencies (Deficiencies #4-6), you stated that you would re-do the biocompatibility testing to address the issues identified by the FDA and provide new test reports for cytotoxicity, skin irritation or intracutaneous reactivity, and sensitization for each color type of the pen-injectors proposed. However, the response provided does not include any of the revised test reports for review. To proceed with our review, please provide the indicated biocompatibility test reports for the final finished subject devices.

In addition, you stated "*Evaluation of leachables according to ISO 10993-18 and the cytotoxicity assays demonstrated no significant differences between the extracts of differently colored pens. To comply with animal welfare requirements in accordance with ISO 10993-2, biocompatibility tests concerning irritation and sensitization were conducted only for the green pen.*" Please be advised that, *in vitro* cytotoxicity testing cannot address the concerns for skin irritation and sensitization. Based on your test protocols and reports provided in Attachments #13, #16, and #17, the chemical extractable and leachable testing was limited only to analysis of organic substances by GC/MS Fingerprint, while chemical comparison of (b) (4) device extracts was not conducted. The justification for only performing the skin irritation and sensitization testing on the green pen-injector is considered inadequate. To support that biocompatibility testing based on one selected color type can adequately address the biocompatibility concerns for all color types of the pen-injectors proposed, please provide a clear and comprehensive comparison for both (b) (4) (b) (4) chemical extractables and leachables. Please clearly demonstrate that the various color types of the pen-injectors proposed have the same types and levels of the chemical extractables and leachables. Alternatively, please provide all required biocompatibility testing for each color type of the pen-injectors proposed. Please provide the testing using (b) (4) device extracts, both (b) (4), from the final finished green and burgundy pen-injectors intended for marketing. Please ensure all patient contact device components were included in the testing.

Office of Biotechnology Products:

The below information requests (items c through e) are incomplete. As noted in your response dated April, 25, 2016, you will reevaluate cross-reactivity data using a newly determined specificity cut-point and submit to the Agency no later than May 4, 2016. The Agency issued an additional information request on May 2, 2016, and requested a response from Sanofi no later than May 4, 2016, for items c through e.

- c) Clarify which Biacore instrument (T100 vs. T200) was used for sample analysis for cross-reactivity of GLP-1 and glucagon.
- d) Include an additional column in the data table for cross-reactivity results from the new analysis as a percent inhibition of control for each sample.
- e) Submit data in Excel and pdf formats.

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Device:

The Agency received responses to the below information requests on May 2, 2016. At this time, we have not completed our review of the response. If additional information is required, we will send notify you during the Late-Cycle Meeting.

- a)  (b) (4)
- (b) (4). Please provide a justification for why the vehicles you have used are appropriate for this test. Alternatively, please provide a method validation demonstrating that the extracts from the chosen vehicles are able to detect potential sensitizers. For more information, please refer to ASTM F2148: standard practice for evaluation of delayed contact hypersensitivity using the murine local lymph node assay.
- b) In response to an information request dated March 2, 2016, you stated that the glargine/lixisenatide pen-injector is operated manually and therefore essential performance requirements associated with automated features do not apply. The Agency accepts this rationale for certain performance criteria, however the Agency notes that a specification should be developed for the injection time per unit dose so that the users have an expectation of how long it should take to inject given a maximum dispensing force of less than or equal to (b) (4) N. Please state the minimum time to inject (i.e. at a dispensing force of (b) (4) N) the minimum and maximum dose for both pen A and pen B. This minimum time to inject should be included in the labeling of the device to inform users the minimum time they must sustain the injection (independent of any audible/visual/tactile feedback for the end of injection). Alternatively, please provide a more detailed rationale for not including an estimated injection time for the minimum and maximum dose of the pen-injectors.
- c) The Agency notes that your pen-injectors include tactile/visual/audible feedback per ISO 11608-1. However, you have not provided any verification of this feedback. Please develop a specification for this feedback as a part of your essential performance requirements and provide verification that the feedback functions as intended.
- d) The Agency notes that of your essential performance requirements you have only included extractable volume as a test of dose accuracy within your current batch release (document QUA-FR-2014-23122). The Agency notes that all essential performance requirements should be verified during batch release including dose selection, dispensing force, injection time (based on results of request for specification), audible/visual/tactile feedback, and dose accuracy. Please provide documentation as evidence that you have

included dose selection, dispensing force, and audible/visual/tactile feedback within your batch release testing.

- e) In response to an information request dated March 2, 2016, you stated that the tests performed during in-use and long term stability studies are performed according to ISO 11608-1:2012 and require full functional assessment of the pen-injector, including steps to set up the pen for an injection and dispense the dose. However, you have not stated specifically what essential performance requirements were tested post-aging besides dose accuracy. It seems that you are asserting that a test for dose accuracy is a downstream effect of all functional characteristics of the pen-injector and therefore is representative of all other essential performance criteria. The Agency believes that certain essential performance requirements such as dispensing force, injection time, and visual/audible/tactile feedback should be verified after aging and preconditioning the device in order to establish that the device meets all essential performance requirements up to the labeled date of expiry for the device. Please provide this testing on a currently available batch within the long-term stability study in order to verify the essential performance requirements after aging. Alternatively, please provide greater detail regarding the full functional testing based on the instructions for use completed post-aging and if the functional testing included testing for the other essential performance requirements of your device besides dose accuracy.

5. Discussion of Upcoming Advisory Committee Meeting – 15 minutes

FDA's preparations for the upcoming AC meeting are ongoing, and we have no further information to communicate at this time. The high level issues to be discussed at the AC meeting are noted above.

6. Review Plans – 5 minutes

FDA will continue review of the NDA and, at this time, there appear to be no significant review issues that would prevent FDA from taking an action on or before the PDUFA goal date.

7. Wrap-up and Action Items – 5 minutes

The AC meeting will be held on May 25, 2016.

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/s/

JEAN-MARC P GUETTIER
05/05/2016