

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208471Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208471	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Adlyxin Established/Proper Name: lixisenatide injection Dosage Form: injection		Applicant: Sanofi Agent for Applicant (if applicable):
RPM: Martin White		Division: Division of Metabolism and Endocrinology Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> • 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) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: </p> <p><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></p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>July 27, 2016</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> 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 _____		<input type="checkbox"/> 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)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> 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
<input type="checkbox"/> Accelerated approval (21 CFR 314.510)
<input type="checkbox"/> Restricted distribution (21 CFR 314.520)
Subpart I
<input type="checkbox"/> Approval based on animal studies

<input type="checkbox"/> Submitted in response to a PMR
<input type="checkbox"/> Submitted in response to a PMC
<input type="checkbox"/> Submitted in response to a Pediatric Written Request | BLAs: Subpart E
<input type="checkbox"/> Accelerated approval (21 CFR 601.41)
<input type="checkbox"/> Restricted distribution (21 CFR 601.42)
Subpart H
<input type="checkbox"/> Approval based on animal studies

REMS: <input type="checkbox"/> MedGuide
<input type="checkbox"/> Communication Plan
<input type="checkbox"/> ETASU
<input type="checkbox"/> MedGuide w/o REMS
<input type="checkbox"/> REMS not required |
|---|--|

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes (7/8/2016) <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information were issued 	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? If so, specify the type 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> 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>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) AP: 7/27/2016
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included See Final Package insert in approval letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> 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>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included See final Medication Guide in approval letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included See final Carton/Container labels in approval letter
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	6/23/2016(2), 2/17/2016, 10/29/2015 6/14/2016, 2/9/2016, 10/26/2015
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 10/17/2016 DMEPA: 3/23/2016 DMPP/PLT (DRISK): 7/25/2016 OPDP: <input type="checkbox"/> None 7/25/2016 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: DPMH 4/7/2016
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	10/07/2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included 7/29/2016
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ 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>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>06/29/2016</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • 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>) 	
<ul style="list-style-type: none"> ❖ 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>) 	7/27/2016 (2), 7/25/2016, 7/22/2016, 7/21/2016, 7/15/2016, 7/7/2016, 7/5/2016, 6/23/2016, 6/10/2016, 6/6/2016 (2), 5/20/2016, 5/3/2016, 4/26/2016, 4/20/2016, 4/11/2016, 3/31/2016, 3/29/2016, 3/25/2016, 3/22/2016, 3/17/2016, 3/16/2016, 2/26/2016, 12/17/2015, 12/8/2015 (2), 12/7/2015, 10/8/2015, 8/6/2015
<ul style="list-style-type: none"> ❖ 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
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>date of Meeting 11/28/2012</i>) 	Date of Minutes: 6/8/2015 (WRO); 12/11/2012
<ul style="list-style-type: none"> • EOP2 meeting (<i>12/19/2007</i>) 	Date of Minutes: 9/9/2008
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>1/14/2016</i>) 	Date of Minutes: 1/21/2016
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>5/11/2016</i>) 	Date of Minutes: 6/22/2016, 5/5/2016
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	

❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	05/25/2016
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	7/27/2016
Division Director Summary Review (<i>indicate date for each review</i>)	7/27/2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	7/25/2016
PMR/PMC Development Templates (<i>indicate total number</i>) 3	7/27/2016
• PMR-01- PREA PK-PD	
• PMR-02 PREA S-E	
• PMR-03 PRE OBP-Immuno	
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	see CDTL review dated 7/25/2016
• Clinical review(s) (<i>indicate date for each review</i>)	07/01/2016; 09/17/2015
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	see clinical review dated 07/01/2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	N/A
• 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>)	<input type="checkbox"/> None 7/19/2016
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 6/6/2016, 5/12/2016, 5/9/2016, 4/4/2016 (2)
❖ Clinical Consults: OSE DEPI, OBP, OSE DEPI, DPARP, Statistical (Division of Biometrics VII)	7/22/2016, 6/21/2016, 4/7/2016 (2), 4/6/2016, 4/4/2016, 9/21/2015
❖ Withdrawn NDA (NDA 204961): DPARP, Statistical (Division of Biometrics II), CMC, Microbiology	DPARP review from NDA 204961(8-26-2013); Statistical Review from NDA 204961 (8-19-2013); OPQ Reviews from NDA 204961 (5-31-13, 7-25-13 and 9-13-13) microbiology from NDA 204961 (9-4-13)

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 Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	See Product Quality Summary dated 4/11/2016
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	3/21/2016; 9/24/2015
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	4/8/2016; 11/12/2015
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	7/18/2016; 4/8/2016
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	4/8/2016 ;9/18/2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 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>	4/11/2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input type="checkbox"/> None

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

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(all original applications and all efficacy supplements that could increase the patient population)	4/11/2016
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes N/A <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done N/A
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> 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> <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done 7/27/2016
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done 7/27/2016
❖ 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	<input checked="" type="checkbox"/> Done 7/27/2016
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done 7/27/2016
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done 7/27/2016

EXCLUSIVITY SUMMARY

NDA # 208471

SUPPL # N/A

HFD # 510

Trade Name Adlyxin

Generic Name lixisenatide injection

Applicant Name Sanofi

Approval Date, If Known 5/27/2016

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?

5 years

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#

NDA#

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:

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

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

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"):

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 #

YES

!
!

! NO

! Explain:

Investigation #2

IND #

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 ! NO
Explain: ! 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
Title: Regulatory Project Manager
Date: 7/18/2016

Name of Office/Division Director signing form: Jean-Marc Guettier, 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
07/29/2016

JEAN-MARC P GUETTIER
07/29/2016

From: White, Martin
To: ["David.Faunce@sanofi.com"](mailto:David.Faunce@sanofi.com)
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 6_7-27-2016
Date: Wednesday, July 27, 2016 4:50:00 PM
Attachments: [image001.png](#)

David,

We note your agreement to the IFUs dated July 27, 2016.

Thanks
Martin

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

From: David.Faunce@sanofi.com [mailto:David.Faunce@sanofi.com]
Sent: Wednesday, July 27, 2016 4:27 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 6_7-27-2016

Martin,

Attached are the three IFUs. We accepted all FDA changes in these documents and made the requested revisions. We have no revisions.

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Wednesday, July 27, 2016 2:43 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 6_7-27-2016

David

Attached are the 3 IFUs and the Medguide for the above referenced NDA.

We request that you accept all proposed changes and return the IFUs and the Medguide no later than today, Wednesday, July 27, 2016 by 3:30PM.

At this time we do not have comments for the PI. If there are additional comments for the PI, we will forward them to you within the next hour.

Please confirm receipt of this email.

Regards,
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Wednesday, July 27, 2016 12:44 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

Martin,

Attached are the 3 IFUs with all pictures included.

Thanks,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Wednesday, July 27, 2016 9:34 AM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

Good Morning David,

Just following up to check on the status of the IFUs. What is the estimated time of delivery?

Thanks
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Tuesday, July 26, 2016 11:13 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

Martin,

Attached are the IFU for the green (10 ug) and burgundy (20 ug) pens. The situation with these two is the same as the with the starter pack in that some of the pictures need to be replaced, and those

that do are so indicated. I will send the final versions with the pictures replaced tomorrow morning. As with the previous IFU for the starter pack these version are able to show where most of the FDA comments have been addressed. Again, early tomorrow morning I will email the final revised versions with the new pictures and then submit them to the NDA shortly thereafter.

Thanks and regards,

Dave

From: Faunce, David R&D/US
Sent: Tuesday, July 26, 2016 8:50 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

Martin,

We encountered several problems with making the requested modifications to some of the pictures in the IFUs. Some of the pictures will need to be sourced from our Sanofi colleagues in Europe, and they will have them to us very early tomorrow morning, likely well before we all arrive to the office. For now I have attached to this email the IFU for the starter pack, which is missing some of the modified pictures, and those that are missing are indicated in the comments. This version can be used to show where most all of the FDA comments have been addressed for this particular IFU (starter pack), and these revisions will be indicative of the changes in the other 2 IFUs since they are essentially the same. Please note that sometimes it is difficult to read in in the MSWord "Final: Show Markup" view, and we suggest reading it in the MSWord "Final" view, as the pictures tend to move around due to all of the mark-ups.

I can email you the 3 completed IFUs early tomorrow morning, and we will formally submit them to the NDA tomorrow morning as well.

For now we have provided the revised PI and Medguide via email, and they have also been submitted to the NDA. Note that the submission cover letter indicates that IFUs are included, but as you will see in the submission Table of Contents they have not.

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Tuesday, July 26, 2016 4:57 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

David,

Emailing what you have finished now and the rest later would be great.

Thanks
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Tuesday, July 26, 2016 4:55 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

Martin,

I'm planning on emailing the labeling to you first, and then making the submission later. We are working on all of it now, but I believe we have the PI finished, possibly the Medguide as well. The IFUs are taking longer because changes in photographic images were requested and new images had to be constructed. I can email to you the parts we have finished now, and the rest later, if you would like.

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Tuesday, July 26, 2016 4:43 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

David,

Do you have an estimate time of delivery of the label?

Thanks
Martin

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

From: White, Martin
Sent: Tuesday, July 26, 2016 2:47 PM
To: 'David.Faunce@sanofi.com'
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

David,

After internal discussion, this was an oversight on our behalf. We do not need additional clarifications for use of BOCF.

Regards,
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Tuesday, July 26, 2016 2:38 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016
Importance: High

Martin,

I wanted to acknowledge receipt of your email attached below and say that we will add the p-value to the active control studies as requested. However, regarding the reasoning for use of BOCF and not jump to placebo method, we want to be sure that there may be something being implied here that we are not getting. Simply put, if you have an active control only study, i.e. no placebo in the study, then a jump to placebo analysis cannot be implemented. In the case of these two studies there was no placebo arm. Additionally, we used the BOCF method based on comments from the 14 July version (v3) package insert revisions we received from the Division that stated the following in the balloon comments in the margin at the beginning of the clinical studies section: "...For active-controlled studies, we would allow a less conservative "return to baseline" analysis that does not have an additional 0.4% margin added to imputed values in the experimental arm." Do we need to formally provide the reasoning for use of BOCF, and not using jump to placebo, in the active controlled studies comments in the PI revisions we are returning to you, or is this something that requires explanation in the PI itself? I was not clear on this point.

Thanks and regards,

Dave

David Faunce

Director

Lixisenatide Global Regulatory Affairs

Sanofi Services US, Inc.

55 Corporate Drive

Bridgewater, NJ 08807

Tel: 908-981-3538 - Mobile: [REDACTED] (b) (6)

david.faunce@sanofi.com



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Tuesday, July 26, 2016 12:16 PM

To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

David,

Thank you for confirming receipt.

We would also like for you to add the p-values for the two HbA1c comparisons where Adlyxin lost to Exenatide BID and Glulisine TID in the text and table before you return the label. Provide a reason why in your active comparator studies you use BOCF for multiple imputations and not jump to PBO. Please use the same methods to handle missing data across all studies or provide a reason why.

Regards,
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Monday, July 25, 2016 10:38 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

Martin,

I confirm receipt of your email below. We'll have these back to you tomorrow afternoon.

Thanks,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Monday, July 25, 2016 7:09 PM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016
Importance: High

Good Afternoon David,

FDA has compiled the attached comments for your draft labeling submitted for the above-mentioned NDA on July 27, 2015. We are providing a tracked-change version of the PI along with the clean version of the PI (both contain FDA Comments). In addition to the comments included in the PI, please also update the highlights section to be consistent with the Full Prescribing Information.

Also, we are providing the marked IFUs (starterpack-10 and 20 mcg, 10 mcg and 20 mcg) and the

Medguide with comments for this application.

For the PI, we request that you make additional revisions to the clean copy and fix any of the formatting that needs fixing (i.e., remove all footnotes). For all other labeling, (i.e, IFUs and Medguide) accept all proposed changes that you agree with, make additional revisions as requested.

Please return all revised labeling to me no later than **Tuesday, July 26, 2016.**

Again, All of your proposed changes from these versions 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

32 Page(s) of Draft Labeling have 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/

MARTIN L WHITE
07/27/2016

From: White, Martin
To: ["David.Faunce@sanofi.com"](mailto:David.Faunce@sanofi.com)
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 6_7-27-2016
Date: Wednesday, July 27, 2016 4:10:00 PM
Attachments: [image001.png](#)

David,

We note your agreement to the PI and the medguide dated July 27, 2016.

Regards,

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

From: David.Faunce@sanofi.com [mailto:David.Faunce@sanofi.com]
Sent: Wednesday, July 27, 2016 3:48 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 6_7-27-2016

Martin,

Attached are the PI and Medguide. We accepted all FDA revisions in these document and have no revisions. Regarding the PI, the SRPI checklist was used to ensure that the final agreed upon label conforms with format items in regulations and guidances.

The IFUs will follow in about 10 – 15 minutes. They are being given a final proofread as I'm writing this. In those document as well, we accepted all FDA revisions and have no revisions.

Should we formally submit all these labeling document to the NDA today?

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Wednesday, July 27, 2016 3:13 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 6_7-27-2016

David,

Attached is the PI for the above referenced NDA. There were minor edits section 11 and 14. Finally, use SRPI checklist to ensure that the final agreed upon label conforms with format items in regulations and guidances.

We request that you accept all proposed changes and return PI no later than today, Wednesday, July 27, 2016 by 3:45PM.

Please 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, July 27, 2016 2:40 PM
To: 'David.Faunce@sanofi.com'
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 6_7-27-2016

David

Attached are the 3 IFUs and the Medguide for the above referenced NDA.

We request that you accept all proposed changes and return the IFUs and the Medguide no later than today, Wednesday, July 27, 2016 by 3:30PM.

At this time we do not have comments for the PI. If there are additional comments for the PI, we will forward them to you within the next hour.

Please confirm receipt of this email.

Regards,
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Wednesday, July 27, 2016 12:44 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

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Attached are the 3 IFUs with all pictures included.

Thanks,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
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To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

Good Morning David,

Just following up to check on the status of the IFUs. What is the estimated time of delivery?

Thanks
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Tuesday, July 26, 2016 11:13 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

Martin,

Attached are the IFU for the green (10 ug) and burgundy (20 ug) pens. The situation with these two is the same as the with the starter pack in that some of the pictures need to be replaced, and those that do are so indicated. I will send the final versions with the pictures replaced tomorrow morning. As with the previous IFU for the starter pack these version are able to show where most of the FDA comments have been addressed. Again, early tomorrow morning I will email the final revised versions with the new pictures and then submit them to the NDA shortly thereafter.

Thanks and regards,

Dave

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To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

Martin,

We encountered several problems with making the requested modifications to some of the pictures in the IFUs. Some of the pictures will need to be sourced from our Sanofi colleagues in Europe, and they will have them to us very early tomorrow morning, likely well before we all arrive to the office. For now I have attached to this email the IFU for the starter pack, which is missing some of the

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I can email you the 3 completed IFUs early tomorrow morning, and we will formally submit them to the NDA tomorrow morning as well.

For now we have provided the revised PI and Medguide via email, and they have also been submitted to the NDA. Note that the submission cover letter indicates that IFUs are included, but as you will see in the submission Table of Contents they have not.

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Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

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Martin.White@fda.hhs.gov

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
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To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

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Thanks and regards,

Dave

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To: Faunce, David R&D/US
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Thanks
Martin

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

From: White, Martin
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To: 'David.Faunce@sanofi.com'
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

David,

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Tuesday, July 26, 2016 2:38 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016
Importance: High

Martin,

I wanted to acknowledge receipt of your email attached below and say that we will add the p-value to the active control studies as requested. However, regarding the reasoning for use of BOCF and not jump to placebo method, we want to be sure that there may be something being implied here

that we are not getting. Simply put, if you have an active control only study, i.e. no placebo in the study, then a jump to placebo analysis cannot be implemented. In the case of these two studies there was no placebo arm. Additionally, we used the BOCF method based on comments from the 14 July version (v3) package insert revisions we received from the Division that stated the following in the balloon comments in the margin at the beginning of the clinical studies section: "...For active-controlled studies, we would allow a less conservative "return to baseline" analysis that does not have an additional 0.4% margin added to imputed values in the experimental arm." Do we need to formally provide the reasoning for use of BOCF, and not using jump to placebo, in the active controlled studies comments in the PI revisions we are returning to you, or is this something that requires explanation in the PI itself? I was not clear on this point.

Thanks and regards,

Dave

David Faunce

Director

Lixisenatide Global Regulatory Affairs

Sanofi Services US, Inc.

55 Corporate Drive

Bridgewater, NJ 08807

Tel: 908-981-3538 - Mobile: [REDACTED] (b) (6)

david.faunce@sanofi.com



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

Sent: Tuesday, July 26, 2016 12:16 PM

To: Faunce, David R&D/US

Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

David,

Thank you for confirming receipt.

We would also like for you to add the p-values for the two HbA1c comparisons where Adlyxin lost to Exenatide BID and Glulisine TID in the text and table before you return the label. Provide a reason why in your active comparator studies you use BOCF for multiple imputations and not jump to PBO. Please use the same methods to handle missing data across all studies or provide a reason why.

Regards,

Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]

Sent: Monday, July 25, 2016 10:38 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016

Martin,

I confirm receipt of your email below. We'll have these back to you tomorrow afternoon.

Thanks,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Monday, July 25, 2016 7:09 PM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 5_7-25-2016
Importance: High

Good Afternoon David,

FDA has compiled the attached comments for your draft labeling submitted for the above-mentioned NDA on July 27, 2015. We are providing a tracked-change version of the PI along with the clean version of the PI (both contain FDA Comments). In addition to the comments included in the PI, please also update the highlights section to be consistent with the Full Prescribing Information.

Also, we are providing the marked IFUs (starterpack-10 and 20 mcg, 10 mcg and 20 mcg) and the Medguide with comments for this application.

For the PI, we request that you make additional revisions to the clean copy and fix any of the formatting that needs fixing (i.e., remove all footnotes). For all other labeling, (i.e, IFUs and Medguide) accept all proposed changes that you agree with, make additional revisions as requested.

Please return all revised labeling to me no later than **Tuesday, July 26, 2016.**

Again, All of your proposed changes from these versions 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

33 Page(s) of Draft Labeling have 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/

MARTIN L WHITE
07/27/2016

From: White, Martin
To: ["David.Faunce@sanofi.com"](mailto:David.Faunce@sanofi.com)
Subject: RE: NDA 208471 - Response to draft PMR List request of July 1, 2016
Date: Monday, July 25, 2016 1:27:00 PM
Attachments: [image001.png](#)

David,

We note your agreement to the PMR list for NDA 208471 dated July 21, 2016.

Regards,
Martin

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

From: David.Faunce@sanofi.com [mailto:David.Faunce@sanofi.com]
Sent: Monday, July 25, 2016 12:07 PM
To: White, Martin
Subject: RE: NDA 208471 - Response to draft PMR List request of July 1, 2016

Martin,

We concur with all the revisions to the PMR list as provided in the document in your email below. In the document attached to this email, all changes have been accepted. Does this document need to be submitted to the NDA? At this point I'm assuming that we can consider this as final.

Thanks and regards,

Dave

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Thursday, July 21, 2016 4:31 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471 - Response to draft PMR List request of July 1, 2016

David

Attached is the revised Adlyxin PMR-PMC list. Please review and send your concurrence by COB tomorrow.

Regards,
Martin

Martin White, M.S.
Phone 240.402.6018

Martin.White@fda.hhs.gov

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Thursday, July 14, 2016 4:36 PM
To: White, Martin
Subject: RE: NDA 208471 - Response to draft PMR List request of July 1, 2016

Martin,

We have some additional changes to some of the dates based upon the FDA edits provided in the document from your email attached immediately below. Note that in this document all FDA proposed changes, via MSWord track changes mode, have been accepted and the Sanofi proposed changes are indicated in track changes mode.

For PMR 2, Study Completion and Final Report Submission dates have been moved forward 3 months based on the revised FDA date for Final Protocol Submission date. In addition, for PMR 3, studies EFC12404 and EFC12405, month was inadvertently provided incorrectly in our initial proposal. The 3 months added are for sample analysis and were not taken into consideration in the previous proposal.

Submission of this attached document to the NDA is planned for tomorrow or Monday.

Thanks and regards,

Dave

David Faunce

Director

Lixisenatide Global Regulatory Affairs

Sanofi Services US, Inc.

55 Corporate Drive

Bridgewater, NJ 08807

Tel: 908-981-3538 - Mobile: [REDACTED] (b) (6)

david.faunce@sanofi.com



From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Friday, July 08, 2016 11:50 AM
To: Gieseke, Don PH/US
Cc: Faunce, David R&D/US
Subject: RE: Response to draft PMR List request of July 1, 2016

Don,

We have reviewed your responses and our edits are included in the attached document. Please send your final concurrence by COB Friday, July 15, 2016.

Thanks

Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: Don.Gieseke@sanofi.com [<mailto:Don.Gieseke@sanofi.com>]

Sent: Thursday, July 07, 2016 11:36 AM

To: White, Martin

Cc: David.Faunce@sanofi.com

Subject: RE: Response to draft PMR List request of July 1, 2016

Martin,

We have provided a revised response. We hope this clarifies for the team. I assume we should formally submit the revised information?

Don

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

Sent: Wednesday, July 06, 2016 3:18 PM

To: Gieseke, Don PH/US

Cc: Faunce, David R&D/US

Subject: RE: Response to draft PMR List request of July 1, 2016

Don,

Thank you for your response.

After review of your response, the review team would like for you to provide the Final Protocol Submission and Study Completion milestones for PMR #3 or a justification for not including them?

Thanks

Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: Don.Gieseke@sanofi.com [<mailto:Don.Gieseke@sanofi.com>]

Sent: Wednesday, July 06, 2016 2:47 PM

To: White, Martin

Cc: David.Faunce@sanofi.com

Subject: Response to draft PMR List request of July 1, 2016

Martin,

Here is the response by email. The formal submission is expected to go as well today.

Don

Don Gieseke
Global Regulatory
908 981 4822

PMR list for NDA 208471
ADLYXIN (lixisenatide) injection

While review of your application continues, we are sending you a draft list of PMRs 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 PMR studies to us with milestone dates, which include **Final Protocol Submission, Study Completion and 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.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA; you should plan on submitting your initial draft protocol at least 6 months prior to this date.

Postmarketing Requirements

- 1) Conduct a repeat dose, pharmacokinetic/pharmacodynamics (PK/PD) study evaluating Adlyxin (lixisenatide) in patients with type 2 diabetes ages 10 to 17 years (inclusive) that are insufficiently controlled with metformin and/or basal insulin. Subjects will be randomized to lixisenatide or placebo. Titration will occur every 2 weeks increasing the dose from 5 mcg to 10 mcg then to 20 mcg.

Study Completion: **March 2018**

Final Report Submission: **September 2018**

- 2) Conduct a 24-week, randomized, controlled efficacy and safety study comparing Adlyxin (lixisenatide) with placebo in patients with type 2 diabetes ages 10 to 17 years (inclusive), followed by a 28-week double-blind controlled extension. Subjects will be on a background of metformin and/or basal insulin at a stable dose. This trial should not be initiated until the results of the pediatric PK/PD study (PMR #1) have been submitted to and reviewed by the Agency.

Final Protocol Submission: **March 2019**

Study Completion: **March 2024**

Final Report Submission: **September 2024**

- 3) Perform immunogenicity testing on anti-drug antibody (ADA)-positive samples from clinical studies of type 2 diabetes subjects treated with lixisenatide for determination of the incidence of neutralizing antibodies (NAb) and anti-lixisenatide antibodies that are cross-reactive with endogenous GLP-1 and glucagon peptides and are capable of neutralizing these endogenous peptides. Assessments should be performed using assays

demonstrated to be suitable for their intended purposes through formal validation studies that have been reviewed by the Agency prior to their use in clinical sample analysis. Samples used for these assessments should be archived under suitable conditions until testing, and should include sufficient quantity to allow for completion of required immunogenicity assessments. Study report(s) submitted to the Agency will include evaluation of the impact of NAb and cross-reactive antibodies on patient safety as well as PK, PD, and efficacy of lixisenatide.

Interim Milestone 1 (Final Report Submission - Assay Validation): **September 2017**

Interim Milestone 2 (Studies EFC12404 and EFC12405 Completion): **June 2018**

Interim Milestone 3 (Studies EFC12404 and EFC12405 Final Report Submission):
December 2018

Study Completion (EFC13794): **January 2019**

Final Study Report Submission (EFC13794): **June 2019**

The dates are based on all immunogenicity assay validation reports submitted by September 2017 and that the review period by the agency is 6 months. Study completion is defined as the date when all immunogenicity samples have been collected and analyzed.

Additional Information

We would also like to inform you of our intention to include the following request in the action letter for this product, if approved:

We request that for a period of two years, you submit all cases of serious hypersensitivity reactions reported with Adlyxin (lixisenatide) injection as 15-day alert reports, and that you provide detailed analyses of clinical study and post-marketing reports of serious hypersensitivity reactions as adverse events of special interest in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to the date of approval of Adlyxin (lixisenatide) injection as well as relative to the prior periodic safety report. Medical literature reviews for case reports/case series of serious hypersensitivity reactions reported with Adlyxin (lixisenatide) injection should also be provided in the periodic safety report.

Please provide a proposal for data lock dates and frequency of reporting in relation to this request, ensuring that your proposal does not result in any gaps in reporting. Please note that if your product is approved, you will need to submit a waiver request to CDER's Office of Surveillance and Epidemiology to submit PBRERs instead of PADERs.

Sanofi Response:

The Sponsor acknowledges the request to submit all serious hypersensitivity reactions as 15-Day alert reports in the 2 years after US approval, and will plan to provide these as expedites as requested.

Concerning the aggregate report requirements outlined in 21 CFR 314.80, the Sponsor proposes to provide reports in the Periodic Benefit-Risk Evaluation Report [PBRER] format, as described in the Draft Guidance for Industry on this topic dated April 2013, synchronizing with the International Birth date for the product and prepared utilizing the timelines outlined in ICH E2C (R2). As lixisenatide has been approved outside of the US since January 2013 and is currently on an annual cycle for submission in the EU (b)(4)

(b)(4) the Sponsor proposes to submit an annual PBRER to FDA (consistent with the globally prepared report), and will *in addition*, prepare a 6-monthly report for the interim period between annual reports, the latter to be submitted only to the FDA in order to meet local reporting requirements for this new US product. The Sponsor believes this represents an optimized aggregate report for the Agency as compared to the PADER, in that it will provide analyses of benefit-risk in excess of those presented within the PADER, and will moreover provide the Agency with an assessment that is harmonized with the rest of world. The content of the report will include a detailed analysis of serious hypersensitivity reports, as requested in the current communication.

In the coming weeks, the Sponsor will prepare and submit a formal waiver request, outlining the details of this plan, to CDER's Office of Surveillance and Epidemiology.

FDA Response: Your response appears acceptable, but our final response will be pending review of the formal PADER waiver request to be submitted to OSE.

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
07/25/2016

From: White, Martin
To: ["David.Faunce@sanofi.com"](mailto:David.Faunce@sanofi.com)
Subject: RE: NDA 208471 - Response to draft PMR List request of July 1, 2016
Date: Thursday, July 21, 2016 4:31:00 PM
Attachments: [Adlyxin PMR-PMC list - Final v2 0-FDA comments 21Jul2016.doc](#)
[image001.png](#)

David

Attached is the revised Adlyxin PMR-PMC list. Please review and send your concurrence by COB tomorrow.

Regards,
Martin

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

From: David.Faunce@sanofi.com [mailto:David.Faunce@sanofi.com]
Sent: Thursday, July 14, 2016 4:36 PM
To: White, Martin
Subject: RE: NDA 208471 - Response to draft PMR List request of July 1, 2016

Martin,

We have some additional changes to some of the dates based upon the FDA edits provided in the document from your email attached immediately below. Note that in this document all FDA proposed changes, via MSWord track changes mode, have been accepted and the Sanofi proposed changes are indicated in track changes mode.

For PMR 2, Study Completion and Final Report Submission dates have been moved forward 3 months based on the revised FDA date for Final Protocol Submission date. In addition, for PMR 3, studies EFC12404 and EFC12405, month was inadvertently provided incorrectly in our initial proposal. The 3 months added are for sample analysis and were not taken into consideration in the previous proposal.

Submission of this attached document to the NDA is planned for tomorrow or Monday.

Thanks and regards,

Dave

David Faunce

Director

Lixisenatide Global Regulatory Affairs

Sanofi Services US, Inc.

55 Corporate Drive

Bridgewater, NJ 08807

Tel: 908-981-3538 - Mobile: (b) (6)

david.faunce@sanofi.com



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

Don Gieseke
Global Regulatory
908 981 4822

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Please provide a proposal for data lock dates and frequency of reporting in relation to this request, ensuring that your proposal does not result in any gaps in reporting. Please note that if your product is approved, you will need to submit a waiver request to CDER's Office of Surveillance and Epidemiology to submit PBRERs instead of PADERs.

Sanofi Response:

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(b) (4) the Sponsor proposes to submit an annual PBRER to FDA (consistent with the globally prepared report), and will *in addition*, prepare a 6-monthly report for the interim period between annual reports, the latter to be submitted only to the FDA in order to meet local reporting requirements for this new US product. The Sponsor believes this represents an optimized aggregate report for the Agency as compared to the PADER, in that it will provide analyses of benefit-risk in excess of those presented within the PADER, and will moreover provide the Agency with an assessment that is harmonized with the rest of world. The content of the report will include a detailed analysis of serious hypersensitivity reports, as requested in the current communication.

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FDA Response: Your response appears acceptable, but our final response will be pending review of the formal PADER waiver request to be submitted to OSE.

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/s/

MARTIN L WHITE
07/22/2016

From: David.Faunce@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 4_7-21-2016
Date: Thursday, July 21, 2016 1:41:06 PM

Martin,

I confirm receipt of your email below.

One question: are there any pending comments on the container (pen) labels? Yesterday, we submitted revised carton labels with the revised NDC numbers, but the pen labels were not changed.

Thanks and regards,

Dave

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Thursday, July 21, 2016 11:48 AM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 4_7-21-2016

Good Morning David,

FDA has compiled the attached comments for your draft labeling submitted for the above-mentioned NDA on July 27, 2015. We are providing a tracked-change version of the label along with the clean version of the label (both contain FDA Comments). We request that you make additional revisions to the clean copy of the label, and return a revised label no later than **9:00 AM Monday, July 25, 2016**. All of your proposed changes from this version should be marked via tracked changes.

In addition to the comments included in the label, please also update the highlights section to be consistent with the Full Prescribing Information.

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

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

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/s/

MARTIN L WHITE
07/21/2016

From: David.Faunce@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 3_7-14-2016
Date: Friday, July 15, 2016 2:06:14 PM
Attachments: [image001.png](#)

Martin,

Specifically, we would like to better understand how the FDA will be moving forward with some of the proposed changes in the lixi label, body weight for example, for other diabetes products, with the concern being about parity in our label.

Thanks and regards,

Dave

David Faunce

Director

Lixisenatide Global Regulatory Affairs

Sanofi Services US, Inc.

55 Corporate Drive

Bridgewater, NJ 08807

Tel: 908-981-3538 - Mobile: [REDACTED] (b) (6)

david.faunce@sanofi.com

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Friday, July 15, 2016 2:00 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 3_7-14-2016

David,

I will communicate this request to the review team. In the meantime, are you able to provide me with a list of the specific comments in the clinical studies section you would like to discuss?

Thanks

Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: David.Faunce@sanofi.com [mailto:David.Faunce@sanofi.com]
Sent: Friday, July 15, 2016 1:38 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 3_7-14-2016

Martin,

We would like to suggest a short teleconference with the Division either on this coming Monday afternoon or Tuesday morning to discuss the lixisenatide package insert, mainly the clinical studies section and the Division's proposed changes. Please let me know if the Division would be agreeable to this.

Thanks and regards,

Dave

David Faunce

Director

Lixisenatide Global Regulatory Affairs

Sanofi Services US, Inc.

55 Corporate Drive

Bridgewater, NJ 08807

Tel: 908-981-3538 - Mobile: [REDACTED] (b) (6)

david.faunce@sanofi.com



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

Sent: Thursday, July 14, 2016 4:27 PM

To: Faunce, David R&D/US

Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 3_7-14-2016

Good Afternoon David,

FDA has compiled the attached comments for your draft labeling submitted for the above-mentioned NDA on July 27, 2015. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised label no later than **10:00 AM Monday, July 18, 2016**. All of your proposed changes from this version should be marked via tracked changes.

In addition, we have the following comment related to the product code and NDC number:

As currently presented, the product code in the NDC number for 20 mcg strength (-5740-) is the same as the product code in the NDC number for the starter pack (-5740-). This can lead to wrong strength errors because barcode scanners may only read the first 10 digits of the NDC codes (i.e. "0024-5740") and pharmacists may rely on the middle portion as a manual check. Therefore, revise the product code in the NDC numbers to ensure that the middle 4 digits (XXXX) are different between the strengths/packages.

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

Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Wednesday, June 22, 2016 3:49 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 2_6-22-2016

Martin,

I confirm receipt of your email below with the labeling revisions.

I must say we are complete surprised based upon your email from yesterday.

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Wednesday, June 22, 2016 2:43 PM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 2_6-22-2016

Good Afternoon David,

FDA has compiled the attached comments for your draft labeling submitted for the above-mentioned NDA on July 27, 2015. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised label no later than **Wednesday, June 29, 2016**. All of your proposed changes from this version should be marked via tracked changes.

In addition to the comments included in the PI, we recommend the following comments for the Instructions for USE (IFU), Pen Label and the Carton and labels :

1. Instructions for Use (IFU)

- a. Section 2 - Getting Started
 - i. In step 5, revise the statement (b)(4) to a simpler statement such as "The pen is now ready to use" to better communicate this information to end user. This may prevent end users to activate the pen before each use, as observed during the validation study.
- b. Section 3 – Daily use of pen
 - i. Relocate the "Injection sites" section to Section 3 under Step C. This should be a separate Step "Choosing Injection Sites". This information is more appropriate in Section 3 to remind end users, especially first time users, of the appropriate injection sites prior to injecting.
 - ii. In Step D increase the prominence by bolding the statement "You may feel or hear a click". Participants in the validation study did not understand whether they had

already injected themselves.

2. Pen Label

- a. We recommend adding the route of administration, “For subcutaneous use only.” per 21 CFR 201.100(b)(3) as this device will be used by patients and caregivers at home. If additional space is needed to add that information, consider removing one of the “SANOFI” statements from the label.
- b. Provide NDC numbers of pen labels and carton labeling for Agency review.

3. Carton Labels

- a. Corrected acceptable proprietary name should be used.
- b. The established name and dosage form should be changed to “(lixisenatide) injection”.

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
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/s/

MARTIN L WHITE
07/15/2016

**PeRC Meeting Minutes
June 29, 2016**

PeRC Members Attending:

Robert “Skip” Nelson (acting chair)
Jacqueline Yancy
Hari Cheryl Sachs
Meshاون Payne
Shrikant Pagay
Adrienne Hornatko-Munoz
Gil Burkhart
Gerri Bauer
Lisa Faulcon
Lily Mulugeta
Freda Cooner
Dionna Greene
Gerri Bauer
Raquel Tapia
Belinda Hayes
Barbara Buch

Agenda

9:00	Non-Responsive				
9:30					
9:40					
9:55					
10:15					
10:30					
10:45					
11:05					
11:15					
11:35	NDA 208471	ADLYXIN (lixisenatide injection) Partial Waiver/Deferral/Plan (with Agreed iPSP)	DMEP	Martin White	Indicated as an adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus.
11:45	Non-Responsive				

					suspected ventilation defects
11:55	Non-Responsive				

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Non-Responsive

ADLYXIN (lixisenatide injection) Partial Waiver/Deferral/Plan (with Agreed iPSP)

- Indication: An adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus.
- PREA Trigger: new active ingredient, new indication, new dosage form, new dosing regimen
- Waiver request in children less than 10yrs of age with T2DM because studies are impossible or highly impractical.
- Deferral request in children ages 10-17 years.
- The Division states Lixisenatide has provided sufficient data to conclude that it is efficacious in improving glycemic control in adults with T2DM.

- *PeRC Recommendations:*
 - The PeRC concurred with the plan for partial waiver/deferral.

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/s/

JACQUILINE A YANCY
07/12/2016

From: White, Martin
To: ["Don.Gieseke@sanofi.com"](mailto:Don.Gieseke@sanofi.com)
Subject: RE: NDA 208471_PMR list_7.1.2016
Date: Wednesday, July 06, 2016 10:27:00 AM

Don,

You can send it via email and follow-up with an official submission through the gateway.

Thanks
Martin

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

From: Don.Gieseke@sanofi.com [mailto:Don.Gieseke@sanofi.com]
Sent: Wednesday, July 06, 2016 10:19 AM
To: White, Martin
Subject: RE: NDA 208471_PMR list_7.1.2016

Martin,

I note in your original email that you ask for this by email – do you not want it as a formal submission?

Don

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Wednesday, July 06, 2016 9:16 AM
To: Gieseke, Don PH/US
Cc: Faunce, David R&D/US
Subject: RE: NDA 208471_PMR list_7.1.2016

Don,

The responses to your questions are below.

Just a point of clarification. [REDACTED] (b) (4)

[REDACTED]
[REDACTED] *Therefore we would provide dates for each of those.*
Just want to check to make sure that is consistent with the expectation on your side.

FDA Response: [REDACTED] (b) (4)
[REDACTED] **however, FDA intends to review all results concurrently, and therefore only a single final report submission date is expected for your trackable milestones.**

I have another clarification to the document provided. Our reading is that you are looking for us to submit PBRERs following approval in place of PADERs. The Prior EU PBRER (b) (4) (b) (4) would be used as the reference for the first report. (b) (4) (b) (4). Can you confirm we have the correct expectation?

FDA Response: Yes, our intention is that PBRERs would be submitted instead of PADERs, although a formal waiver request will need to be submitted to OSE following approval, as directed in the document. Please include your proposal for frequency of reporting with your response document.

Regards,
Martin

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

From: Don.Gieseke@sanofi.com [<mailto:Don.Gieseke@sanofi.com>]
Sent: Tuesday, July 05, 2016 1:54 PM
To: White, Martin
Subject: RE: NDA 208471_PMR list_7.1.2016

Martin,

I have another clarification to the document provided. Our reading is that you are looking for us to submit PBRERs following approval in place of PADERs. The Prior EU PBRER (b) (4) (b) (4) would be used as the reference for the first report. (b) (4) (b) (4). Can you confirm we have the correct expectation?

Don

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Friday, July 01, 2016 4:07 PM
To: Faunce, David R&D/US
Cc: Gieseke, Don PH/US
Subject: NDA 208471_PMR list_7.1.2016
Importance: High

Good Afternoon David and Don,

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

Please submit by email a copy of the PMR studies to us with milestone dates, which include **Final Protocol Submission, Study Completion** and **Final Report Submission**.

We would like to request that this be returned by COB Tues 7/5, 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
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- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA; you should plan on submitting your initial draft protocol at least 6 months prior to this date.

Postmarketing Requirements

- 1) Conduct a repeat dose, pharmacokinetic/pharmacodynamics (PK/PD) study evaluating Adlyxin (lixisenatide) in patients with type 2 diabetes ages 10 to 17 years (inclusive) that are insufficiently controlled with metformin and/or basal insulin. Subjects will be randomized to lixisenatide or placebo. Titration will occur every 2 weeks increasing the dose from 5 mcg to 10 mcg then to 20 mcg.

Study Completion:

Final Report Submission:

- 2) Conduct a 24-week, randomized, controlled efficacy and safety study comparing Adlyxin (lixisenatide) with placebo in patients with type 2 diabetes ages 10 to 17 years (inclusive), followed by a 28-week double-blind controlled extension. Subjects will be on a background of metformin and/or basal insulin at a stable dose. This trial should not be initiated until the results of the pediatric PK/PD study (PMR #1) have been submitted to and reviewed by the Agency.

Final Protocol Submission:

Study Completion:

Final Report Submission:

- 3) Perform immunogenicity testing on anti-drug antibody (ADA)-positive samples from clinical studies of type 2 diabetes subjects treated with lixisenatide for determination of

the incidence of neutralizing antibodies (NAb) and anti-lixisenatide antibodies that are cross-reactive with endogenous GLP-1 and glucagon peptides and are capable of neutralizing these endogenous peptides. (b) (4)

Assessments should be performed using assays demonstrated to be suitable for their intended purposes through formal validation studies that have been reviewed by the Agency prior to their use in clinical sample analysis. Samples used for these assessments should be archived under suitable conditions until testing, and should include sufficient quantity to allow for completion of required immunogenicity assessments. Study report(s) submitted to the Agency will include evaluation of the impact of NAb and cross-reactive antibodies on patient safety as well as PK, PD, and efficacy of lixisenatide.

Final Protocol Submission :
Study Completion :
Final Report Submission :

Additional Information

We would also like to inform you of our intention to include the following request in the action letter for this product, if approved:

We request that for a period of two years, you submit all cases of serious hypersensitivity reactions reported with Adlyxin (lixisenatide) injection as 15-day alert reports, and that you provide detailed analyses of clinical study and post-marketing reports of serious hypersensitivity reactions as adverse events of special interest in your Periodic Benefit-Risk Evaluation Report (PBRER). These analyses should show cumulative data relative to the date of approval of Adlyxin (lixisenatide) injection as well as relative to the prior PBRER. Medical literature reviews for case reports/case series of serious hypersensitivity reactions reported with Adlyxin (lixisenatide) injection should also be provided in the PBRER.

Please provide a proposal for data lock dates and frequency of reporting in relation to this request, ensuring that your proposal does not result in any gaps in reporting. Please note that if your product is approved, you will need to submit a waiver request to CDER's Office of Surveillance and Epidemiology to submit PBRERs instead of PADERs.

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/s/

MARTIN L WHITE
07/07/2016

From: Don.Gieseke@sanofi.com
To: [White, Martin](mailto:White.Martin); David.Faunce@sanofi.com
Subject: RE: NDA 208471_PMR list_7.1.2016
Date: Sunday, July 03, 2016 9:42:10 PM

Thanks Martin. We will try to send the request to you by Tuesday but it may be Wednesday.

Don

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Friday, July 01, 2016 4:07 PM
To: Faunce, David R&D/US
Cc: Gieseke, Don PH/US
Subject: NDA 208471_PMR list_7.1.2016
Importance: High

Good Afternoon David and Don,

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

Please submit by email a copy of the PMR studies to us with milestone dates, which include **Final Protocol Submission, Study Completion** and **Final Report Submission**.

We would like to request that this be returned by COB Tues 7/5, 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 list for NDA 208471
ADLYXIN (lixisenatide) injection

While review of your application continues, we are sending you a draft list of PMRs 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 PMR studies to us with milestone dates, which include **Final Protocol Submission, Study Completion and 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.
- Note that the "Final Protocol Submission" date is the date by which you have submitted a complete protocol that has already received full concurrence by FDA; you should plan on submitting your initial draft protocol at least 6 months prior to this date.

Postmarketing Requirements

- 1) Conduct a repeat dose, pharmacokinetic/pharmacodynamics (PK/PD) study evaluating Adlyxin (lixisenatide) in patients with type 2 diabetes ages 10 to 17 years (inclusive) that are insufficiently controlled with metformin and/or basal insulin. Subjects will be randomized to lixisenatide or placebo. Titration will occur every 2 weeks increasing the dose from 5 mcg to 10 mcg then to 20 mcg.

Study Completion:

Final Report Submission:

- 2) Conduct a 24-week, randomized, controlled efficacy and safety study comparing Adlyxin (lixisenatide) with placebo in patients with type 2 diabetes ages 10 to 17 years (inclusive), followed by a 28-week double-blind controlled extension. Subjects will be on a background of metformin and/or basal insulin at a stable dose. This trial should not be initiated until the results of the pediatric PK/PD study (PMR #1) have been submitted to and reviewed by the Agency.

Final Protocol Submission:

Study Completion:

Final Report Submission:

- 3) Perform immunogenicity testing on anti-drug antibody (ADA)-positive samples from clinical studies of type 2 diabetes subjects treated with lixisenatide for determination of

the incidence of neutralizing antibodies (NAb) and anti-lixisenatide antibodies that are cross-reactive with endogenous GLP-1 and glucagon peptides and are capable of neutralizing these endogenous peptides. (b) (4)

Assessments should be performed using assays demonstrated to be suitable for their intended purposes through formal validation studies that have been reviewed by the Agency prior to their use in clinical sample analysis. Samples used for these assessments should be archived under suitable conditions until testing, and should include sufficient quantity to allow for completion of required immunogenicity assessments. Study report(s) submitted to the Agency will include evaluation of the impact of NAb and cross-reactive antibodies on patient safety as well as PK, PD, and efficacy of lixisenatide.

Final Protocol Submission :

Study Completion :

Final Report Submission :

Additional Information

We would also like to inform you of our intention to include the following request in the action letter for this product, if approved:

We request that for a period of two years, you submit all cases of serious hypersensitivity reactions reported with Adlyxin (lixisenatide) injection as 15-day alert reports, and that you provide detailed analyses of clinical study and post-marketing reports of serious hypersensitivity reactions as adverse events of special interest in your Periodic Benefit-Risk Evaluation Report (PBRER). These analyses should show cumulative data relative to the date of approval of Adlyxin (lixisenatide) injection as well as relative to the prior PBRER. Medical literature reviews for case reports/case series of serious hypersensitivity reactions reported with Adlyxin (lixisenatide) injection should also be provided in the PBRER.

Please provide a proposal for data lock dates and frequency of reporting in relation to this request, ensuring that your proposal does not result in any gaps in reporting. Please note that if your product is approved, you will need to submit a waiver request to CDER's Office of Surveillance and Epidemiology to submit PBRERs instead of PADERs.

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/s/

MARTIN L WHITE
07/05/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208471

**PROPRIETARY NAME REQUEST
ACKNOWLEDGEMENT/WITHDRAWAL**

Sanofi-Aventis U.S. LLC
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

ATTENTION: David Faunce
Director, Global Regulatory Affairs

Dear Mr. Faunce:

Please refer to your New Drug Application (NDA) dated July 27, 2015, received July 27, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lixisenatide Injection, 150 mcg/3 mL (50 mcg/mL) and 300 mcg/3 mL (100 mcg/mL).

We also refer to your June 9, 2016, correspondence, received on June 9, 2016, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4). Therefore, (b) (4) is considered withdrawn as of June 9, 2016.

Finally, we refer to your June 3, 2016, correspondence, received June 3, 2016, requesting reconsideration of your proposed proprietary name, Adlyxin. 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 September 1, 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
06/23/2016

From: David.Faunce@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 2_6-22-2016
Date: Wednesday, June 22, 2016 3:49:07 PM

Martin,

I confirm receipt of your email below with the labeling revisions.

I must say we are complete surprised based upon your email from yesterday.

Thanks and regards,

Dave

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Wednesday, June 22, 2016 2:43 PM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_FDA Comments for Labeling_Round 2_6-22-2016

Good Afternoon David,

FDA has compiled the attached comments for your draft labeling submitted for the above-mentioned NDA on July 27, 2015. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised label no later than **Wednesday, June 29, 2016**. All of your proposed changes from this version should be marked via tracked changes.

In addition to the comments included in the PI, we recommend the following comments for the Instructions for USE (IFU), Pen Label and the Carton and labels :

1. Instructions for Use (IFU)

- a. Section 2 - Getting Started
 - i. In step 5, revise the statement (b) (4) to a simpler statement such as "The pen is now ready to use" to better communicate this information to end user. This may prevent end users to activate the pen before each use, as observed during the validation study.
- b. Section 3 – Daily use of pen
 - i. Relocate the "Injection sites" section to Section 3 under Step C. This should be a separate Step "Choosing Injection Sites". This information is more appropriate in Section 3 to remind end users, especially first time users, of the appropriate injection sites prior to injecting.
 - ii. In Step D increase the prominence by bolding the statement "You may feel or hear a click". Participants in the validation study did not understand whether they had

already injected themselves.

2. Pen Label

- a. We recommend adding the route of administration, “For subcutaneous use only.” per 21 CFR 201.100(b)(3) as this device will be used by patients and caregivers at home. If additional space is needed to add that information, consider removing one of the “SANOFI” statements from the label.
- b. Provide NDC numbers of pen labels and carton labeling for Agency review.

3. Carton Labels

- a. Corrected acceptable proprietary name should be used.
- b. The established name and dosage form should be changed to “(lixisenatide) injection”.

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

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

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/s/

MARTIN L WHITE
06/23/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208471

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Sanofi-Aventis U.S. LLC
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

ATTENTION: David Faunce
Director, Global Regulatory Affairs

Dear Mr. Faunce:

Please refer to your New Drug Application (NDA) dated July 27, 2015, received July 27, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lixisenatide Injection, 150 mcg/3 mL (50 mcg/mL) and 300 mcg/3 mL (100 mcg/mL).

We also refer to your June 3, 2016, correspondence, received June 3, 2016, requesting reconsideration of your proposed proprietary name, Adlyxin.

We have completed our review of the proposed proprietary name, Adlyxin and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your June 3, 2016 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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/

TODD D BRIDGES
06/23/2016

From: David.Faunce@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208471_lixisenatide_Information Request_6-9-2016
Date: Friday, June 10, 2016 9:00:49 AM

Martin,

I confirm receipt of the information request below.

On another topic, the Mid-Cycle Communication letter mentioned that the Division was targeting 15 June to provide labeling comments. Can we expect comments on or about that date.

Thanks and regards,

Dave

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Thursday, June 09, 2016 4:18 PM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_Information Request_6-9-2016

David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following information request:

1. At the Advisory Committee meeting, there was mention of a post-marketing observational study to further evaluate hypersensitivity and anaphylaxis. Please provide details on the objectives and the type of post-marketing observational study that you are planning to conduct.
2. Please indicate whether you have sufficient banked patient serum samples from various time points in the completed lixisenatide phase 3 studies to assess for neutralizing and cross-reactive antibodies. These additional studies would be performed after the Agency has reviewed the validation of the assays. Provide a summary of the number of available ADA-positive samples from each pivotal study together with the sample collection time points available that could be used for the additional testing.

Please provide your responses by Thursday, June 16, 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
06/10/2016

From: David.Faunce@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208471_lixisenatide_Information Request_6-2-2016
Date: Thursday, June 02, 2016 1:57:29 PM

Martin,

I acknowledge receipt of the information request in your email below.

The data and information to support the information request below have been provided in our 18 May 2016 submission to NDA 2018471 (SN0029). Please note that there were two device-related information responses submitted on 18 May and that Sequence Number 0029 provides the data and information that responds to the request below.

The original request for this information was made in the 21 January 2016 Mid Cycle communication. Within this request was the following statement: "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." To support the biocompatibility sensitization testing for the green pen, the comparison testing strategy as given in the statement above was employed, and both the summary information as well as the report for this comparison testing are provided in the 18 May (SN0029) submission.

Please let me know today if a formal submission is required to respond to this requested received today. If yes, then most likely it will simply be a cover letter with reference to the 18 May submission.

Thanks and regards,

Dave

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Thursday, June 02, 2016 8:42 AM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_Information Request_6-2-2016

David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following information request:

In your response dated 21 JAN 2016, you clarified that the pen-injectors proposed for use for injection of the lixisenatide solution will be provided in green and burgundy colors, while the (b) (4) pen-injector is not part of this NDA application. In response to the biocompatibility deficiencies identified for the NDA 208471 IR response, you provided the cytotoxicity testing and intracutaneous reactivity testing for the green, burgundy, and (b) (4) colors of the pen-injectors. However, you only provided the sensitization testing for the burgundy and (b) (4) colors of the pen-injectors, while testing for the green pen-injector was not provided. As the green pen-injector is also intended to be used for injection of the lixisenatide solution, testing of delayed type hypersensitivity for the surface contact device is considered

necessary. To demonstrate that the green pen-injector is not a sensitizer, please provide a sensitization test report, based on both [REDACTED] (b) (4) test extracts. Alternatively, you may remove the green pen-injector from the submission.

Please provide your responses by COB Friday, 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
06/06/2016

From: David.Faunce@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208471_lixisenatide_Device Information Request_6-3-2016
Date: Monday, June 06, 2016 11:46:09 AM
Attachments: [image001.png](#)
[image002.png](#)

Martin,

I confirm receipt of your email below. We will provide response tomorrow as requested.

Thanks and regards,

Dave

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Friday, June 03, 2016 2:30 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_Device Information Request_6-3-2016

David,

Thank you for providing the correct source of the comment regarding a previous device information request. Please see the clarification below from our device reviewers:

The chemical analytical test report provided in Document 11162193 4.1 of your May 18 2016, response does not include adequate information to demonstrate that the green pen-injectors has the same types and levels of the chemical extractables and leachables as the (b) (4) and burgundy pen-injectors.

By GC/MS Fingerprint Investigation, you identified one organic chemical – (b) (4) in both the (b) (4) and the green auto-injectors.

Retention Time [min]	Detected Compounds	Semi-Quantitative Amount [mg per device] Using a Detector Response of			
		11162193 4.1-01 Lyxumia Pen – Bauteil (b) (4)		11162193 4.1-03: Lyxumia Pen – Bauteil grün	
		33 % ("worst-case")	100 %	33 % ("worst-case")	100 %
(b) (4)					

Table 1: Semi-quantitative Analyses of Detected Compounds in (b) (4) Extracts

However, based on your comparison above, the (b) (4) and the green auto-injectors showed a different level of the chemical compound detected.

By ICP investigation, you identified several (b) (4) ions in the chemical extractables and leachables, as shown below. However, you did not clarify from which auto-injector the inorganic (b) (4) were detected. You did not provide any comparison between the different color types of the auto-injectors proposed.

Inorganic Ions	Amount [µg per Device]				
	LOQ	Negative Control,	11162193 4 1-01: Sample Extract,	11162193 4 1-02: Sample Extract,	11162193 4.1-03: Sample Extract,
(b) (4)					

Table 3: Results of the ICP Quantification

In addition, while GC/MS is indicated for analysis of (b) (4) organic compounds and the ICP-OES is indicated for (b) (4) ions, it is unclear that GC/MS and ICP-OES can adequately detect the other chemical residues that may also leach out from the auto-injectors, such as the (b) (4) inorganic compounds, and other residues.

Therefore the chemical analytical testing provided is inadequate to address the sensitization concerns for the green pen-injector. As we have previously requested, please provide a sensitization test report based on both (b) (4) test extracts of the green pen-injector. Alternatively, you may remove the green pen-injector from the submission.

Please provide responses by COB, Tuesday, June 7, 2016.

Confirm receipt of this email.

Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Thursday, June 02, 2016 5:47 PM
To: White, Martin
Subject: FW: NDA 208471_lixisenatide_Device Information Request_3-25-2016

Martin,

Apologies for the confusion regarding the information cited in my email to you earlier today, and for

the difficulties in our phone conversation. I was not in the office most of this afternoon and had to rely on memory on where the initial citation of the information in question came from. The statements in question were not from the Mid-Cycle communication, but rather the email from you attached below containing a device-related information request. This information request was a follow-up to the original information request which originally came from the Mid-Cycle communication. I have highlighted the relevant statements in yellow.

I would note that for all of the biocompatibility testing performed on the green and burgundy pens, only the sensitization test for the green pen relies on the testing strategy as described below. For all other tests, both the green and the burgundy pens were tested and the reports submitted.

As we discussed, we will formally submit a response early next week, either Monday or Tuesday, making the correct reference to the information request below and to the 18 May submission (SN0029).

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Friday, March 25, 2016 8:43 AM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_Device Information Request_3-25-2016

David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following device information request:

In the NDA 208471 IR 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 NDA 208471 IR 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 the NDA 208471 IR response, 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) (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.

Please provide responses by COB, Thursday, March 31, 2016.

Confirm receipt of this email.

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
06/06/2016



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)

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 glycemic 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,”

(b) (4)

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):

(b) (4)

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 ~~the~~ **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 SOCs (primary and one or more secondary SOCs) 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 SOCs, ie, primary SOC and/or 1 or more secondary SOCs. Some PTs/HLTs appeared more than once under different SOCs. For example, HLT” Hypoglycaemic conditions NEC” and its PTs “Hypoglycaemia,” “Hypoglycaemic seizure,” “Hypoglycaemic unconsciousness” appeared twice under SOCs “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: missing (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 ≤ 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 “374” 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.

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

From: David.Faunce@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208471_lixisenatide_Information Request_5-2-2016_Additional Information
Date: Monday, May 02, 2016 6:08:15 PM

Martin,

I confirm receipt of your email below.

Thanks,

Dave

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Monday, May 02, 2016 4:35 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_Information Request_5-2-2016_Additional Information

David,

Please include the following requests below with your cut-point reevaluation data to be submitted on May 4th, 2016.

- Clarify which Biacore instrument (T100 vs. T200) was used for sample analysis for cross-reactivity of GLP-1 and glucagon.
- 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.
- Submit data in Excel and pdf formats as previously done.

Confirm receipt of this email.

Regards,
Martin

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

From: White, Martin
Sent: Tuesday, April 19, 2016 8:31 AM
To: 'David.Faunce@sanofi.com'
Subject: RE: NDA 208471_lixisenatide_Information Request_4-15-2016

Hi David,

April 22, 2016 is acceptable.

Thanks
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Monday, April 18, 2016 12:44 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_Information Request_4-15-2016

Martin,

I have just now been informed that the persons who would be responsible within Sanofi, both the primary and their back-ups, are all currently traveling from Germany to the US for a scientific congress in Orlando, which starts tomorrow. As such, they will not be able to start to address the information requests in your email below until tomorrow. Consequently, we would like to request postponing the response at least 2 days, until Friday 22 April. Please let me know if this is acceptable.

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Friday, April 15, 2016 4:41 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_Information Request_4-15-2016

David,

We acknowledge your March 29, 2016, responses to our request for additional immunogenicity information. You submitted anti-lixisenatide antibody cross-reactivity results to endogenous GLP-1 and native glucagon, which you classified as negative in 212 ADA-positive subjects from three Phase 3 studies (EFC10781, EFC11321 and EFC6015). You did not provide sufficient information for the agency to verify your claim. Provide the following information:

- Submit primary cross-reactivity data for all ADA-positive subjects evaluated for cross-reactivity in these studies. Data should be submitted both in Excel and pdf formats, and should include the ADA level measured for all samples and the timing of sample collection.
- Submit a description of the cross-reactivity method validation and data to demonstrate the suitability of the cross-reactivity method for its intended purpose.

Please provide your responses by Wednesday, April 20, 2016.

Confirm receipt of this email.

Regards,
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Wednesday, March 23, 2016 10:49 AM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Martin,

Good morning to you as well. Tuesday it is.

Thanks,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Wednesday, March 23, 2016 10:34 AM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Good Morning David,

All of the responses can be sent to us Tuesday, March 29, 2016.

Thanks
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Wednesday, March 23, 2016 10:17 AM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Martin,

Apologies to respond only this morning, but I was out of the office yesterday afternoon.

Would it be possible to split the response? I may have the response to questions 1 and 2 by the

requested date (this coming Friday), or at the latest next Monday. However, for questions 3 and 4 it may take until next Tuesday, possibly Wednesday. Would this scenario be acceptable? I should be able to firm up the dates when I meet with my team tomorrow. I apologize again for our delay and not being able to provide a definitive answer to your question. We do sincerely appreciate the Division being flexible with this request.

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Tuesday, March 22, 2016 4:11 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

David,

Is it possible for you to get the response back to us by Tuesday, March 29, 2016?

Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Monday, March 21, 2016 4:44 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Hi Martin,

I can give you my best guess for now since most all of the team members I need to speak with are in France and Germany and are gone for the day. I will speaking with them tomorrow morning. I would estimate that Tuesday of next week could work, but I'd rather give you a firmer estimate tomorrow morning after speaking with them. Can I can get back to you later tomorrow morning on this?

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Monday, March 21, 2016 4:23 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

David,

Thank you for confirming receipt. Please provide an estimate on how much time you will need to respond to the information request.

Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Monday, March 21, 2016 3:55 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Martin,

I confirm receipt of your email. Given the extent of the request, I am not certain we will be able to provide a response in four days. Is there any chance this timeline can be extended?

Thanks and regards,

David

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Monday, March 21, 2016 3:36 PM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_Information Request_3-21-2016

David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following information request:

Your 24 week meta-analysis of change in HbA1c (Table 23, Summary of Clinical Efficacy) indicates that a small group of the lixisenatide treated population (n=45, 2.4%) with anti-lixisenatide antibody concentrations >100nmol/L exhibits a significantly different response in HbA1c when compared to patients with low levels or no antibodies. Patients who were total anti-lixisenatide antibody negative or concentrations <LLOQ had a numerically greater decline in HbA1c compared to patients with antibody concentrations ≥ LLOQ [-0.86 (-0.930 to -0.795) vs. -0.63 (-0.732 to -0.534)].

The trend was also present at week 76 (Table 24) based on long-term data from the five pivotal phase 3 studies (EFC6014, EFC6015, EFC6016, EFC6017 and EFC10743): the change in HbA1c in patients who were antibody negative or had antibody concentrations <LLOQ was -0.91 [95% CI(-1.002 to -0.827)] while the change in HbA1c in patients who had

concentrations \geq the LLOQ was -0.5[95% CI (-0.617 to -0.380)].

Since lixisenatide and human GLP-1/glucagon share considerable amino acid sequence homology in the first 12 amino acids, the potential exists that exposure to lixisenatide may lead to the development of anti-drug antibodies (ADA) that cross-react with endogenous GLP-1 and or glucagon. In order to determine whether the HbA1c response difference could be related to changes in endogenous GLP-1 or glucagon activity anti-lixisenatide, antibody cross-reactivity data for these patients are needed. We could not find these data in your submission. Therefore, we request the following information for clarification:

- 1) Submit cross-reactivity testing data for the 45 patients with anti-lixisenatide antibody concentration $>100\text{nmol/L}$ (Table 23) and 279 patients with ADA concentration \geq LLOQ at Week 76 (Table 24) with endogenous GLP-1 and glucagon. Data should include tabular summary of these results organized by patient across the study timeline, if anti-lixisenatide cross-reactivity has been assessed at multiple time points.
- 2) Please include anti-lixisenatide antibody titers for each of these samples expressed both as a dilution ratio and as the mass units previously provided.
- 3) To better understand the clinical impact of the observed anti-lixisenatide antibodies, in the absence of information regarding the presence of anti-lixisenatide neutralizing antibodies (NAb), please submit an assessment for correlations between PK and PD effects observed with the relative abundance of ADA in lixisenatide-treated subjects.
- 4) If anti-lixisenatide antibodies from your clinical trial samples correlate with observed adverse clinical effects, or demonstrate cross-reactivity with endogenous GLP-1 and/or glucagon, you may be required to test for the presence of NAb using a validated NAb assay. Further, if cross-reactivity with endogenous GLP-1 or glucagon is demonstrated in samples from extended lixisenatide administration (76 weeks or later), the potential for development of a deficiency in one or both of these cross-reactive endogenous targets should be evaluated. Provide a plan to develop a NAb assay in the event that such studies are required.

Please provide your 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
05/03/2016

From: David.Faunce@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208471_lixisenatide_Information Request_4-26-2016
Date: Tuesday, April 26, 2016 11:50:21 AM

Martin,

I confirm receipt of the request below.

We have a couple of questions regarding this request:

- Where do you want these pen samples shipped? Is this a formal NDA submission with cover letter and submission form, sent to the usual address, or is this coming to your desk, or other?
- We are assuming these pen device samples are for demonstration purposes and not for analytical purposes. ***Can you please confirm this.*** Otherwise, if they are for analytical purposes shipping would need to be under controlled conditions.

Also, regarding last Friday's (22 April) submission to NDA 208471, which was a response to a clinical information request for anti-drug antibody cross-reactivity, there were a few errors in the variable description table appended to the response document. This table provided a description of the variable column headings in the Excel spreadsheet, which was also included in this submission. We will be submitting today a replacement response document with a new variable description table.

Thanks and regards,

Dave

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Tuesday, April 26, 2016 8:22 AM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_Information Request_4-26-2016

David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following clinical information request:

Please send lixisenatide injection devices: **6 - 10 microgram (mcg) pen and 6 - 20 microgram (mcg) pen** sample pen devices, to aid in our review of your application. We request that you submit these pens to us no later than close of business on May 5, 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: White, Martin
To: ["David.Faunce@sanofi.com"](mailto:David.Faunce@sanofi.com)
Subject: RE: NDA 208471_lixisenatide_Information Request_4-15-2016
Date: Tuesday, April 19, 2016 8:31:00 AM

Hi David,

April 22, 2016 is acceptable.

Thanks
Martin

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

From: David.Faunce@sanofi.com [mailto:David.Faunce@sanofi.com]
Sent: Monday, April 18, 2016 12:44 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_Information Request_4-15-2016

Martin,

I have just now been informed that the persons who would be responsible within Sanofi, both the primary and their back-ups, are all currently traveling from Germany to the US for a scientific congress in Orlando, which starts tomorrow. As such, they will not be able to start to address the information requests in your email below until tomorrow. Consequently, we would like to request postponing the response at least 2 days, until Friday 22 April. Please let me know if this is acceptable.

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Friday, April 15, 2016 4:41 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_Information Request_4-15-2016

David,

We acknowledge your March 29, 2016, responses to our request for additional immunogenicity information. You submitted anti-lixisenatide antibody cross-reactivity results to endogenous GLP-1 and native glucagon, which you classified as negative in 212 ADA-positive subjects from three Phase 3 studies (EFC10781, EFC11321 and EFC6015). You did not provide sufficient information for the agency to verify your claim. Provide the following information:

- Submit primary cross-reactivity data for all ADA-positive subjects evaluated for cross-reactivity in these studies. Data should be submitted both in Excel and pdf formats, and should include the ADA level measured for all samples and the timing of sample collection.
- Submit a description of the cross-reactivity method validation and data to demonstrate the suitability of the cross-reactivity method for its intended purpose.

Please provide your responses by Wednesday, April 20, 2016.

Confirm receipt of this email.

Regards,
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Wednesday, March 23, 2016 10:49 AM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Martin,

Good morning to you as well. Tuesday it is.

Thanks,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Wednesday, March 23, 2016 10:34 AM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Good Morning David,

All of the responses can be sent to us Tuesday, March 29, 2016.

Thanks
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]

Sent: Wednesday, March 23, 2016 10:17 AM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Martin,

Apologies to respond only this morning, but I was out of the office yesterday afternoon.

Would it be possible to split the response? I may have the response to questions 1 and 2 by the requested date (this coming Friday), or at the latest next Monday. However, for questions 3 and 4 it may take until next Tuesday, possibly Wednesday. Would this scenario be acceptable? I should be able to firm up the dates when I meet with my team tomorrow. I apologize again for our delay and not being able to provide a definitive answer to your question. We do sincerely appreciate the Division being flexible with this request.

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Tuesday, March 22, 2016 4:11 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

David,

Is it possible for you to get the response back to us by Tuesday, March 29, 2016?

Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Monday, March 21, 2016 4:44 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Hi Martin,

I can give you my best guess for now since most all of the team members I need to speak with are in France and Germany and are gone for the day. I will speaking with them tomorrow morning. I would estimate that Tuesday of next week could work, but I'd rather give you a firmer estimate tomorrow morning after speaking with them. Can I can get back to you later tomorrow morning on this?

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Monday, March 21, 2016 4:23 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

David,

Thank you for confirming receipt. Please provide an estimate on how much time you will need to respond to the information request.

Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Monday, March 21, 2016 3:55 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Martin,

I confirm receipt of your email. Given the extent of the request, I am not certain we will be able to provide a response in four days. Is there any chance this timeline can be extended?

Thanks and regards,

David

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Monday, March 21, 2016 3:36 PM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_Information Request_3-21-2016

David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following information request:

Your 24 week meta-analysis of change in HbA1c (Table 23, Summary of Clinical Efficacy) indicates that a small group of the lixisenatide treated population (n=45, 2.4%) with anti-lixisenatide antibody concentrations >100nmol/L exhibits a significantly different response in HbA1c when compared to patients with low levels or no antibodies. Patients who were

total anti-lixisenatide antibody negative or concentrations <LLOQ had a numerically greater decline in HbA1c compared to patients with antibody concentrations \geq LLOQ [-0.86 (-0.930 to -0.795) vs. -0.63 (-0.732 to -0.534)].

The trend was also present at week 76 (Table 24) based on long-term data from the five pivotal phase 3 studies (EFC6014, EFC6015, EFC6016, EFC6017 and EFC10743): the change in HbA1c in patients who were antibody negative or had antibody concentrations <LLOQ was -0.91 [95% CI(-1.002 to -0.827)] while the change in HbA1c in patients who had concentrations \geq the LLOQ was -0.5[95% CI (-0.617 to -0.380)].

Since lixisenatide and human GLP-1/glucagon share considerable amino acid sequence homology in the first 12 amino acids, the potential exists that exposure to lixisenatide may lead to the development of anti-drug antibodies (ADA) that cross-react with endogenous GLP-1 and or glucagon. In order to determine whether the HbA1c response difference could be related to changes in endogenous GLP-1 or glucagon activity anti-lixisenatide, antibody cross-reactivity data for these patients are needed. We could not find these data in your submission. Therefore, we request the following information for clarification:

- 1) Submit cross-reactivity testing data for the 45 patients with anti-lixisenatide antibody concentration >100nmol/L (Table 23) and 279 patients with ADA concentration \geq LLOQ at Week 76 (Table 24) with endogenous GLP-1 and glucagon. Data should include tabular summary of these results organized by patient across the study timeline, if anti-lixisenatide cross-reactivity has been assessed at multiple time points.
- 2) Please include anti-lixisenatide antibody titers for each of these samples expressed both as a dilution ratio and as the mass units previously provided.
- 3) To better understand the clinical impact of the observed anti-lixisenatide antibodies, in the absence of information regarding the presence of anti-lixisenatide neutralizing antibodies (NAb), please submit an assessment for correlations between PK and PD effects observed with the relative abundance of ADA in lixisenatide-treated subjects.
- 4) If anti-lixisenatide antibodies from your clinical trial samples correlate with observed adverse clinical effects, or demonstrate cross-reactivity with endogenous GLP-1 and/or glucagon, you may be required to test for the presence of NAb using a validated NAb assay. Further, if cross-reactivity with endogenous GLP-1 or glucagon is demonstrated in samples from extended lixisenatide administration (76 weeks or later), the potential for development of a deficiency in one or both of these cross-reactive endogenous targets should be evaluated. Provide a plan to develop a NAB assay in the event that such studies are required.

Please provide your 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
04/20/2016

From: David.Faunce@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208471_lixisenatide injection_ Clinical Information Request 4-8-2016
Date: Friday, April 08, 2016 5:27:42 PM

Hi Martin,

I confirm receipt of your email below.

Thanks,

Dave

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Friday, April 08, 2016 4:04 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide injection_ Clinical Information Request 4-8-2016

David,

Please refer to your submission dated March 18, 2016, for NDA 208471. We are having a problem in generating this pool of subjects on basal insulin. After reviewing ADSLBINS, we noted that there are only 270 subjects with uncorrupted data. In addition, there are over 7,400 rows of corrupted data or other errors in creating the datasets. Will you please resubmit the datasets as soon as possible but no later than April 13, 2016?

Please confirm receipt of this email.

Regards,
Martin

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

From: David.Faunce@sanofi.com [mailto:David.Faunce@sanofi.com]
Sent: Friday, March 18, 2016 12:25 PM
To: White, Martin
Subject: RE: NDA 208471_ (b) (4) ixisenatide injection_ Clinical Information Request 3-15-2016

Martin,

Regarding the clinical information request in your email below for datasets, we are having some significant technical issues with these datasets, and in order to meet the requested timeline we will likely be submitting the two dataset files as single files, both approximately 2.8 gigabytes in size. As you may know, generally FDA requests that there be a size limit of 1 gigabyte before splitting such

files. However, at this point, in order to make the requested timelines, we will need to submit the files through the gateway later today as two separate files, each approximately 2.8 gig. We have had experience with submitting such files previously through the gateway without issue, but I wanted to alert you in case you need to inform anyone on your end, or in case there might be an alternative.

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Tuesday, March 15, 2016 1:41 PM
To: Goyal, Shefali R&D/US; Faunce, David R&D/US
Subject: RE: NDA 208471_ (b) (4) ixisenatide injection_ Clinical Information Request 3-15-2016

Shefali and David,

(b) (4)

Please provide the datasets as an amendment to the lixisenatide NDA (208471) 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: Thursday, March 10, 2016 9:39 AM
To: 'Shefali.Goyal@sanofi.com'
Subject: NDA (b) (4) Clinical Information Request 3-10-2016

(b) (4)

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
04/11/2016

From: White, Martin
To: ["David.Faunce@sanofi.com"](mailto:David.Faunce@sanofi.com)
Subject: RE: NDA 208471_lixisenatide_ Clinical Information Request_ additional items requested on 3-30-2016
Date: Wednesday, March 30, 2016 4:03:00 PM

David,

The following questions pertain to your March 28, 2016, response to FDA's information request:

- Tables 9 and 11 (pp.64 and 66) include angioedema cases but the numbers seem to reflect hypersensitivity events, as included in the Results section, for instance, in Table 2 (p. 12). Please explain whether the terms angioedema and hypersensitivity were used interchangeably.
- Please provide a listing of the exact MedDRA SMQ terms that were applied to the investigator reported terms for:
 - anaphylactic reaction by narrow SMQ search
 - hypersensitivity by narrow SMQ search
 - angioedema by narrow SMQ search

Please provide a response to this request as soon as possible but no later than Friday, April 1, 2016.

Regards,
Martin

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

From: White, Martin
Sent: Monday, March 21, 2016 3:45 PM
To: 'David.Faunce@sanofi.com'
Subject: RE: NDA 208471_lixisenatide_ Clinical Information Request_ additional items requested on 3-21-2016

David,

In addition to previous questions pertaining to Item D below, Section 3.2.2 of the document titled "Evaluation of hypersensitivity in the lixisenatide development program" dated February 26, 2016?

5. Provide locations of data tables, such as in the Integrated Summary of Safety, that allow us to verify the following numbers used in the analyses reported in Section 3.2.2 (Incidence in a Reference Population):
 - a. Incidence of anaphylactic reaction/anaphylactic shock identified (SMQ analysis) for lixisenatide patients in the clinical trials: 0.07/ 100 PY
 - b. Incidence of hypersensitivity for lixisenatide patients in the clinical trials: 0.58/ 100 PY
 - c. 11,275.6 PY exposure in lixisenatide treated patients

- d. 9,287.9 PY exposure in all controls
 - e. Anaphylaxis events observed in clinical trials: n=8 (lixisenatide), n=2 (controls)
 - f. Hypersensitivity events observed in clinical trials: n=65 (lixisenatide), n=50 (controls)
6. Provide a definition or algorithm that was used to ascertain anaphylactic reaction/anaphylactic shock (SMQ analysis) and hypersensitivity events in the clinical trial population.

As stated below, we request that you respond to this information request no later than the close of business on **Monday, March 28, 2016**.

Confirm receipt of this email.

Regards,
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Thursday, March 17, 2016 3:46 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_ Clinical Information Request 3-17-2016

Martin,

I confirm receipt of your email below.

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Thursday, March 17, 2016 3:30 PM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_ Clinical Information Request 3-17-2016

David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following clinical information request:

- A. Provide report counts and aggregate summary for all postmarketing cases in the Sanofi global pharmacovigilance safety database retrieved using the MedDRA SMQ "Hypersensitivity" (narrow) for lixisenatide.

- B. Please summarize the following data by reports with serious outcomes and non-serious outcomes: hypersensitivity event by MedDRA PT, age, sex, reporter, reporting country, co-suspect or concomitant medications, re-challenge, previous allergy to a GLP-1 product, action taken toward lixisenatide, treatment for the reported hypersensitivity event, and the outcomes by the coded PT.
- C. In addition to the report counts and aggregate summary, please provide a case-level analysis for the following specific hypersensitivity reactions:
1. Stevens-Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN)
 2. Drug reaction with eosinophilia and systemic symptoms
 3. Immune-Complex Reactions (e.g., Acute glomerulonephritis, Serum Sickness)
 4. Type II Hypersensitivity reactions (e.g., autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura)
- D. Please respond to the following questions regarding Section 3.2.2 of the document titled "Evaluation of hypersensitivity in the lixisenatide development program" dated February 26, 2016:
1. Please explain whether patients who used GLP-1 analogs in the (b) (4) database included only new users (treatment naïve) or also prevalent users of the respective drugs. If the sample was restricted to new users, please provide how new use was operationalized. If the sample included both new and prevalent users, please estimate the proportion of new users among all patients who used a GLP-1 analog in your analysis.
 2. Please provide the coding algorithm that was used to ascertain anaphylaxis and hypersensitivity events, and state whether events included those detected during inpatient, outpatient, or emergency department visits. If possible, provide information on sensitivity and positive predictive values based on published validation studies.
 3. Please provide the age categories used in the calculation of observed vs. expected cases.
 4. If available, please provide a study protocol that details the analyses conducted using the (b) (4) data.

We request that you respond to this information request no later than the close of business on **Monday, March 28, 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
03/31/2016

From: White, Martin
To: ["David.Faunce@sanofi.com"](mailto:David.Faunce@sanofi.com)
Subject: NDA 208471_FDA Comments for Labeling_Round 1_3-25-2016
Date: Friday, March 25, 2016 10:37:00 AM
Attachments: [NDA 208471_Lixi_PI_to_applicant_on_3-25.2016.doc](#)

Good Morning David,

FDA has compiled the attached comments for your draft labeling submitted for the above-mentioned NDA on July 27, 2015. Please note that these comments are high level comments compiled by the review team and we have not yet considered the details of label. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised label no later than **Friday, April 8, 2016**. All of your proposed changes from this version should be marked via tracked changes.

The following comment below is also included in the label; however, I am including it below for your convenience:

Comment 8: For use in considering the presentation of safety, we request the following:

Generate tables with **pooled data** of the nine phase 3 placebo-controlled efficacy and safety studies that includes **all** (regardless of investigator causality assessment) adverse events that occurred in at least 5% of patients treated with TRADENAME and occurred more frequently on TRADENAME than on placebo. These tables should include total number and percentage of AEs that occurred in the main treatment period and the entire treatment period. Organize these adverse events by System Organ Class/ Preferred Term and in order of their frequency: the most commonly occurred AEs on TRADENAME should be followed by the least commonly occurred AEs. Placebo should appear in the first column and TRADENAME in the second column. Please provide the proportions of patients experiencing each adverse event between lixisenatide and placebo groups using an analysis stratified by study. For example, the proportions of patients in each treatment group experiencing a given adverse event can be estimated by a weighted average of the study-specific proportions for that treatment using Cochran-Mantel-Haenszel weights.

The example of this table is below:

Table. Adverse Reactions from pool of nine placebo-controlled studies reported in ≥5% of TRADENAME-treated patients- main treatment period.

Adverse reactions	Placebo Number of patients (N)	TRADENAME, Number of patients (N)
nausea	% (n)	%(n)
vomiting		

Provide a description of the study population for all pools (datapool 1, datapool2 and the ELIXA study) as follows: Mean age, mean duration of diabetes, % male, % caucasian, % Black

or African American, % American Indian, % Hispanic, mean eGFR, % of patients with eGFR>90, mean BMI, HbA1c at baseline. A sentence stating the exposure of the # patients for a mean exposure duration of _#_ weeks.

Please 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
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Martin.White@fda.hhs.gov

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

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/s/

MARTIN L WHITE
03/29/2016

From: David.Faunce@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016
Date: Wednesday, March 23, 2016 10:49:02 AM

Martin,

Good morning to you as well. Tuesday it is.

Thanks,

Dave

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Wednesday, March 23, 2016 10:34 AM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Good Morning David,

All of the responses can be sent to us Tuesday, March 29, 2016.

Thanks
Martin

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

From: David.Faunce@sanofi.com [mailto:David.Faunce@sanofi.com]
Sent: Wednesday, March 23, 2016 10:17 AM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Martin,

Apologies to respond only this morning, but I was out of the office yesterday afternoon.

Would it be possible to split the response? I may have the response to questions 1 and 2 by the requested date (this coming Friday), or at the latest next Monday. However, for questions 3 and 4 it may take until next Tuesday, possibly Wednesday. Would this scenario be acceptable? I should be able to firm up the dates when I meet with my team tomorrow. I apologize again for our delay and not being able to provide a definitive answer to your question. We do sincerely appreciate the Division being flexible with this request.

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Tuesday, March 22, 2016 4:11 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

David,

Is it possible for you to get the response back to us by Tuesday, March 29, 2016?

Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Monday, March 21, 2016 4:44 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Hi Martin,

I can give you my best guess for now since most all of the team members I need to speak with are in France and Germany and are gone for the day. I will speaking with them tomorrow morning. I would estimate that Tuesday of next week could work, but I'd rather give you a firmer estimate tomorrow morning after speaking with them. Can I can get back to you later tomorrow morning on this?

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Monday, March 21, 2016 4:23 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

David,

Thank your for confirming receipt. Please provide an estimate on how much time you will need to respond to the information request.

Martin

Martin White, M.S.

Phone 240.402.6018

Martin.White@fda.hhs.gov

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Monday, March 21, 2016 3:55 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_Information Request_3-21-2016

Martin,

I confirm receipt of your email. Given the extent of the request, I am not certain we will be able provide a response in four days. Is there any chance this timeline can be extended?

Thanks and regards,

David

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Monday, March 21, 2016 3:36 PM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_Information Request_3-21-2016

David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following information request:

Your 24 week meta-analysis of change in HbA1c (Table 23, Summary of Clinical Efficacy) indicates that a small group of the lixisenatide treated population (n=45, 2.4%) with anti-lixisenatide antibody concentrations >100nmol/L exhibits a significantly different response in HbA1c when compared to patients with low levels or no antibodies. Patients who were total anti-lixisenatide antibody negative or concentrations <LLOQ had a numerically greater decline in HbA1c compared to patients with antibody concentrations \geq LLOQ [-0.86 (-0.930 to -0.795) vs. -0.63 (-0.732 to -0.534)].

The trend was also present at week 76 (Table 24) based on long-term data from the five pivotal phase 3 studies (EFC6014, EFC6015, EFC6016, EFC6017 and EFC10743): the change in HbA1c in patients who were antibody negative or had antibody concentrations <LLOQ was -0.91 [95% CI(-1.002 to -0.827)] while the change in HbA1c in patients who had concentrations \geq the LLOQ was -0.5[95% CI (-0.617 to -0.380)].

Since lixisenatide and human GLP-1/glucagon share considerable amino acid sequence homology in the first 12 amino acids, the potential exists that exposure to lixisenatide may lead to the development of anti-drug antibodies (ADA) that cross-react with endogenous GLP-1 and or glucagon. In order to determine whether the HbA1c response difference could be related to changes in endogenous GLP-1 or glucagon activity anti-lixisenatide, antibody cross-reactivity data for these patients are needed. We could not find these data in your

submission. Therefore, we request the following information for clarification:

- 1) Submit cross-reactivity testing data for the 45 patients with anti-lixisenatide antibody concentration >100nmol/L (Table 23) and 279 patients with ADA concentration ³LLOQ at Week 76 (Table 24) with endogenous GLP-1 and glucagon. Data should include tabular summary of these results organized by patient across the study timeline, if anti-lixisenatide cross-reactivity has been assessed at multiple time points.
- 2) Please include anti-lixisenatide antibody titers for each of these samples expressed both as a dilution ratio and as the mass units previously provided.
- 3) To better understand the clinical impact of the observed anti-lixisenatide antibodies, in the absence of information regarding the presence of anti-lixisenatide neutralizing antibodies (NAb), please submit an assessment for correlations between PK and PD effects observed with the relative abundance of ADA in lixisenatide-treated subjects.
- 4) If anti-lixisenatide antibodies from your clinical trial samples correlate with observed adverse clinical effects, or demonstrate cross-reactivity with endogenous GLP-1 and/or glucagon, you may be required to test for the presence of NAb using a validated NAb assay. Further, if cross-reactivity with endogenous GLP-1 or glucagon is demonstrated in samples from extended lixisenatide administration (76 weeks or later), the potential for development of a deficiency in one or both of these cross-reactive endogenous targets should be evaluated. Provide a plan to develop a NAb assay in the event that such studies are required.

Please provide your 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
03/25/2016

From: David.Faunce@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208471_lixisenatide_ Clinical Information Request_ additional items requested on 3-21-2016
Date: Monday, March 21, 2016 3:59:01 PM

Martin,

I confirm receipt of your email below.

Thanks and regards,

David

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Monday, March 21, 2016 3:45 PM
To: Faunce, David R&D/US
Subject: RE: NDA 208471_lixisenatide_ Clinical Information Request_ additional items requested on 3-21-2016

David,

In addition to previous questions pertaining to Item D below, Section 3.2.2 of the document titled "Evaluation of hypersensitivity in the lixisenatide development program" dated February 26, 2016?

5. Provide locations of data tables, such as in the Integrated Summary of Safety, that allow us to verify the following numbers used in the analyses reported in Section 3.2.2 (Incidence in a Reference Population):
 - a. Incidence of anaphylactic reaction/anaphylactic shock identified (SMQ analysis) for lixisenatide patients in the clinical trials: 0.07/ 100 PY
 - b. Incidence of hypersensitivity for lixisenatide patients in the clinical trials: 0.58/ 100 PY
 - c. 11,275.6 PY exposure in lixisenatide treated patients
 - d. 9,287.9 PY exposure in all controls
 - e. Anaphylaxis events observed in clinical trials: n=8 (lixisenatide), n=2 (controls)
 - f. Hypersensitivity events observed in clinical trials: n=65 (lixisenatide), n=50 (controls)

6. Provide a definition or algorithm that was used to ascertain anaphylactic reaction/anaphylactic shock (SMQ analysis) and hypersensitivity events in the clinical trial population.

As stated below, we request that you respond to this information request no later than the close of business on **Monday, March 28, 2016**.

Confirm receipt of this email.

Regards,
Martin

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

From: David.Faunce@sanofi.com [<mailto:David.Faunce@sanofi.com>]
Sent: Thursday, March 17, 2016 3:46 PM
To: White, Martin
Subject: RE: NDA 208471_lixisenatide_ Clinical Information Request 3-17-2016

Martin,

I confirm receipt of your email below.

Thanks and regards,

Dave

From: White, Martin [<mailto:Martin.White@fda.hhs.gov>]
Sent: Thursday, March 17, 2016 3:30 PM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_ Clinical Information Request 3-17-2016

David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following clinical information request:

- A. Provide report counts and aggregate summary for all postmarketing cases in the Sanofi global pharmacovigilance safety database retrieved using the MedDRA SMQ "Hypersensitivity" (narrow) for lixisenatide.
- B. Please summarize the following data by reports with serious outcomes and non-serious outcomes: hypersensitivity event by MedDRA PT, age, sex, reporter, reporting country, co-suspect or concomitant medications, re-challenge, previous allergy to a GLP-1 product, action taken toward lixisenatide, treatment for the reported hypersensitivity event, and the outcomes by the coded PT.
- C. In addition to the report counts and aggregate summary, please provide a case-level analysis for the following specific hypersensitivity reactions:
 1. Stevens-Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN)
 2. Drug reaction with eosinophilia and systemic symptoms
 3. Immune-Complex Reactions (e.g., Acute glomerulonephritis, Serum Sickness)
 4. Type II Hypersensitivity reactions (e.g., autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura)
- D. Please respond to the following questions regarding Section 3.2.2 of the document

titled "Evaluation of hypersensitivity in the lixisenatide development program" dated February 26, 2016:

1. Please explain whether patients who used GLP-1 analogs in the (b) (4) database included only new users (treatment naïve) or also prevalent users of the respective drugs. If the sample was restricted to new users, please provide how new use was operationalized. If the sample included both new and prevalent users, please estimate the proportion of new users among all patients who used a GLP-1 analog in your analysis.
2. Please provide the coding algorithm that was used to ascertain anaphylaxis and hypersensitivity events, and state whether events included those detected during inpatient, outpatient, or emergency department visits. If possible, provide information on sensitivity and positive predictive values based on published validation studies.
3. Please provide the age categories used in the calculation of observed vs. expected cases.
4. If available, please provide a study protocol that details the analyses conducted using the (b) (4) data.

We request that you respond to this information request no later than the close of business on **Monday, March 28, 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
03/22/2016

From: David.Faunce@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208471_lixisenatide_ Clinical Information Request 3-17-2016
Date: Thursday, March 17, 2016 3:47:04 PM

Martin,

I confirm receipt of your email below.

Thanks and regards,

Dave

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Thursday, March 17, 2016 3:30 PM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_ Clinical Information Request 3-17-2016

David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following clinical information request:

- A. Provide report counts and aggregate summary for all postmarketing cases in the Sanofi global pharmacovigilance safety database retrieved using the MedDRA SMQ "Hypersensitivity" (narrow) for lixisenatide.
- B. Please summarize the following data by reports with serious outcomes and non-serious outcomes: hypersensitivity event by MedDRA PT, age, sex, reporter, reporting country, co-suspect or concomitant medications, re-challenge, previous allergy to a GLP-1 product, action taken toward lixisenatide, treatment for the reported hypersensitivity event, and the outcomes by the coded PT.
- C. In addition to the report counts and aggregate summary, please provide a case-level analysis for the following specific hypersensitivity reactions:
 1. Stevens-Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN)
 2. Drug reaction with eosinophilia and systemic symptoms
 3. Immune-Complex Reactions (e.g., Acute glomerulonephritis, Serum Sickness)
 4. Type II Hypersensitivity reactions (e.g., autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura)
- D. Please respond to the following questions regarding Section 3.2.2 of the document titled "Evaluation of hypersensitivity in the lixisenatide development program" dated February 26, 2016:
 1. Please explain whether patients who used GLP-1 analogs in the (b) (4)

database included only new users (treatment naïve) or also prevalent users of the respective drugs. If the sample was restricted to new users, please provide how new use was operationalized. If the sample included both new and prevalent users, please estimate the proportion of new users among all patients who used a GLP-1 analog in your analysis.

2. Please provide the coding algorithm that was used to ascertain anaphylaxis and hypersensitivity events, and state whether events included those detected during inpatient, outpatient, or emergency department visits. If possible, provide information on sensitivity and positive predictive values based on published validation studies.
3. Please provide the age categories used in the calculation of observed vs. expected cases.
4. If available, please provide a study protocol that details the analyses conducted using the (b) (4) data.

We request that you respond to this information request no later than the close of business on **Monday, March 28, 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
03/17/2016

From: Shefali.Goyal@sanofi.com
To: [White, Martin](#)
Cc: David.Faunce@sanofi.com
Subject: RE: NDA 208471_ (b) (4) ixisenatide injection_ Clinical Information Request 3-15-2016
Date: Tuesday, March 15, 2016 1:41:46 PM

Received, thanks.

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Tuesday, March 15, 2016 1:41 PM
To: Goyal, Shefali R&D/US; Faunce, David R&D/US
Subject: RE: NDA 208471_ (b) (4) ixisenatide injection_ Clinical Information Request 3-15-2016

Shefali and David,

(b) (4)

Please provide the datasets as an amendment to the lixisenatide NDA (208471) 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: Thursday, March 10, 2016 9:39 AM
To: 'Shefali.Goyal@sanofi.com'
Subject: NDA (b) (4) Clinical Information Request 3-10-2016

(b) (4)

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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MARTIN L WHITE
03/16/2016

From: David.Faunce@sanofi.com
To: [White, Martin](#)
Subject: RE: NDA 208471_lixisenatide_Clinical and CDRH Information Request_2-26-2016
Date: Friday, February 26, 2016 3:03:19 PM

Martin,

I'm confirming receipt of your email below with the clinical and device information request.

Please note that the white paper on hypersensitivity reactions and anaphylaxis, discussed during the mid-cycle teleconference, is being submitted today. It should be sent through the gateway within the next 20 minutes or so if it has not already.

Thanks and regards,

Dave

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Friday, February 26, 2016 1:06 PM
To: Faunce, David R&D/US
Subject: NDA 208471_lixisenatide_Clinical and CDRH Information Request_2-26-2016

Hi David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following clinical and device information request:

1. Provide an analyses of the following events for the sub-group of patients in ELIXA on background insulin therapy during the on-treatment period (safety population)"
 - deaths,
 - SAEs,
 - discontinuations due to AEs ,
 - common AEs, and
 - Adverse events of special interest
2. In your application, you provided the device specification for the actuation force and dispensing/firing force. The Agency would like to review the test data to demonstrate that specified actuation force and dispensing/firing force did not change after aging/shipping. If this information is already in your application, please provide the location.

Please provide your responses by Thursday, March 10, 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
02/26/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208471

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Sanofi-Aventis U.S. LLC
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

ATTENTION: David Faunce
Director, Global Regulatory Affairs

Dear Mr. Faunce:

Please refer to your New Drug Application (NDA) dated and received, July 27, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lixisenatide Injection, 50 mcg/mL and 100 mcg/mL.

We also refer to your correspondence, dated and received December 11, 2015, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your December 11, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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/

TODD D BRIDGES
02/17/2016



NDA 208471

MID-CYCLE COMMUNICATION

Sanofi US Services Inc.
Attention: David Faunce
Director, Global Regulatory Affairs
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

Dear Mr. Faunce:

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

We also refer to the teleconference between representatives of your firm and the FDA on January 14, 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: January 14, 2016 – 9:00AM to 10:00AM

Application Number: 208471
Product Name: lixisenatide
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
Michael White, Ph.D.	Regulatory Project Manager
Marissa Petruccelli, M.S.	Regulatory Project Manager

APPLICANT ATTENDEES

Rene Belder	Deputy Head Sanofi Diabetes
Christopher Morabito	Global Project Head
Christine Soltys-Robitaille	Global Project Manager
Barry Sickels	North American Regulatory Affairs Head
Anthony Watson	Global Regulatory Affairs, Head of Devices
Amy Jennings	Global Regulatory Affairs, Diabetes
David Faunce	Global Regulatory Affairs, Diabetes
Molly Story	Device Development Unit, Head of Usability Engineering and Risk Management, iCMC New Product Program
Verena Siefke-Henzler	Device Development
Kristian Horvat	Device Development
Udo Stauder	Device Development
Malte Kock	Regulatory Compliance, Devices
Francesca Lawson	Clinical Development
Jean-Luc Delhay	Global Pharmacovigilance and Epidemiology

Zoran Doder	Global Pharmacovigilance and Epidemiology
Sandeep Kumar	Global Pharmacovigilance and Epidemiology
Heather Schiappacasse	US Risk Management
Meehyung Cho	Biostatistics
Martin Lorenz	Clinical Pharmacology
Roland Wesch	Drug Disposition
Thomas Kissner	Preclinical Drug Safety
Philippe Detilleux	Preclinical Drug Safety

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

CLINICAL

Risk of anaphylaxis

CDRH

Testing information provided in the application is incomplete for the device

3.0 INFORMATION REQUESTS

CLINICAL

1. Anaphylaxis and hypersensitivity reactions remain a safety issue under consideration. In the safety update, you report that there were 47 cases of systemic hypersensitivity reactions. Provide narrative summaries of these cases.

CDRH

2. 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.

3. Please detail device failures or malfunctions from your clinical trials. The Agency is interested in knowing how many occurrences out of the total devices used, description of the circumstances/adverse events related to the failure/malfunction, final root cause analysis and any future improvement plans to prevent similar device failures/malfunctions.
4. In NDA 208471, you only provided a brief summary report for the testing of cytotoxicity, intracutaneous reactivity, and sensitization. Complete biocompatibility test reports from the testing laboratory were not provided for review. To determine if the testing provided is adequate to support the biocompatibility of the auto-injectors proposed in NDA 208471, please provide complete biocompatibility test reports from the testing laboratory, dated and signed, for each of the testing referenced above. To proceed with our review, please include the following information in the test reports: a clear and detailed description of the test devices, description of the sample preparation, the test systems (animals or cells), test procedures, test standards followed, appropriate controls, summary of the test results including the control test data, test criteria, and conclusions. Please provide the testing based on the final finished subject devices, including all patient contact device components. If the test devices were not the final finished subject devices, please provide a valid scientific justification to explain how the devices tested represented a worst case condition for the subject devices. Based on your Table 1 - Parts of the pen-injector with body contact, it appears that you have used various color additives in the patient contact device components. Please be advised that FDA considers that addition of a color additive to a medical device is a significant change. If the auto-injectors proposed in NDA 208471 will be provided in various colors, biocompatibility testing for each color type of the patient contact device components is considered necessary.
5. It appears that the test extracts used in the *in vitro* cytotoxicity testing were (b) (4) is generally considered inappropriate and not acceptable by the FDA. Please provide chemical analytical testing data to support that (b) (4). Alternatively please provide the cytotoxicity testing using the neat test extracts (b) (4).
6. The intracutaneous reactivity testing was based only (b) (4) test extracts, while (b) (4) test extracts were not tested. Since both (b) (4) residues may leach out from the subject devices during the use, to support your claim that the auto-injectors proposed are not an irritant, we believe that testing of both (b) (4) device extracts is necessary. Please provide the intracutaneous reactivity or skin irritation testing based on both (b) (4) test extracts.

7. The performance testing documents (Performance testing per ISO 11608-3 Appendix 1 and 2) located in Module 3.2.P.2 are currently in German with English subtitles. For ease of reading, please provide the documents in English only.

STATISTICAL

8. Please justify the non-inferiority margin for EFC12261 mealtime study (0.4%) based on the effect on HbA1c change at 6 months of lixisenatide given at breakfast with a background of metformin versus metformin alone. Please also provide a justification for the non-inferiority margin for study EFC6019 (0.4%) based on the effect on HbA1c change at 6 months of exenatide with a background of metformin versus metformin alone. Please refer to the draft FDA Non-inferiority guidance when providing your justifications.
9. We are requesting a sensitivity analysis that uses multiple imputation, where the imputation is under the null hypothesis and all observed cases of HbA1c change from baseline at the endpoint are treated as non-missing. For a placebo-controlled study, the multiple imputation analyses should consider a washout of any lixisenatide effect for those subjects known or believed to have discontinued protocol therapy who do not have HbA1c measurements at the endpoint. A “washout analysis” would have the distribution for the HbA1c measurement at the endpoint centered at the mean for a subject in the placebo group that had the same baseline HbA1c value. For an active-controlled study, the multiple imputation analyses should consider a return to baseline for those subjects known or believed to have discontinued protocol therapy who do not have HbA1c measurements at the endpoint. A “return to baseline analysis” would have the distribution for the HbA1c measurement at the endpoint centered at their baseline HbA1c value. More specifically:
 - For placebo-controlled studies, impute missing Week 24 HbA1c measurements (except Week 12 in Study EFC6018) in the placebo arm based on the missing at random assumption. Impute missing Week 24 HbA1c measurements (except Week 12 in Study EC6018) in the experimental arm based on baseline HbA1c and the imputation model for placebo plus an error.
 - For active-controlled studies, impute missing Week 24 HbA1c measurements (except Week 26 in Study EFC12626) in the control arm equal to their baseline plus an error. Impute missing Week 24 HbA1c measurements (except Week 26 in Study EFC12626) in the experimental arm equal to their baseline plus 0.4% 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).

Please perform such an analysis using the same ANCOVA model used in the primary analysis, provide the SAS program code and any new dataset that have not been provided to the FDA.

10. Please perform MMRM with all available post-baseline observations for all the key secondary endpoints that may appear in the label and conduct sensitivity analyses for missing data in these analyses as well.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

The new trial data submitted with the application 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 lixisenatide 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 a need to discuss benefits and risks of lixisenatide at an Advisory Committee meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

At this time, the Late Cycle Meeting will occur on April 27, 2016. The format of this meeting will be face-to-face unless the applicant decides to change the format to a teleconference. The Agency will inform the applicant should this date change.

The projected date that the proposed labeling for this application will be sent to the Applicant is June 15, 2016.

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/s/

MARTIN L WHITE
01/21/2016

From: White, Martin
To: ["David.Faunce@sanofi.com"](mailto:David.Faunce@sanofi.com)
Subject: NDA 208471_lixisenatide_Clinical Information Request_12-17-2015
Date: Thursday, December 17, 2015 5:23:00 PM

David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following clinical information request:

Please submit a copy of the DMC meeting minutes for the ELIXA study. If already submitted, please identify the location in the eCTD folder.

Provide your response by Tuesday, December 22, 2015.

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
12/17/2015

- b. [REDACTED] (b) (4)
- c. [REDACTED] (b) (4)

Please provide your responses by December 24, 2015.

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
12/08/2015

From: White, Martin
To: ["David.Faunce@sanofi.com"](mailto:David.Faunce@sanofi.com)
Subject: NDA 208471_lixisenatide_Clinical Information Request_12-8-2015
Date: Tuesday, December 08, 2015 6:14:00 PM

David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following clinical information request:

In order to facilitate the review of your application, provide the information requested in the table below for each of the following groups of studies:

- Group 1: Oral antidiabetic background (studies 11321, 6015, 6017, 10743)
- Group 2: Basal insulin background (studies 10781, 10887, 6016)
- Group 3: Different timing of administration (studies 6014, 12261)
- Group 4: Active comparator (studies 12626, 6019, 10780)

We ask that you compare and contrast the categories listed below for each of the studies in a group. Within each group of studies do not just list the items by study, but rather contrast the similarities and differences between studies. A separate table should be provided for each of the groups of studies.

Category	Description
Location	Number of centers and countries
Trial design	i.e. Open/blinded label, centrally randomized, comparator, etc
Blinding	If blinding was performed, how was it accomplished?
Dose selection and lixisenatide titration strategy	
Comparator	
Randomization ratio	
Stratification of randomization	i.e. by screening HbA1c (<8.0% versus ≥8.0%), other
Study duration, dates initiated and completed	
Primary objective	
Primary efficacy variable	
Define the efficacy population used in the primary analysis	

Define the safety population	
Primary efficacy endpoints	
Secondary efficacy endpoints	
Inclusion and exclusion criteria	
Concomitant antidiabetic medications allowed, and not allowed by protocol	
Rescue medication	If rescue medications were planned in the trial, describe the schedule, type, and doses permitted in the trial. Discuss any restrictions or limitations for use of rescue medications.
Subject completion, discontinuation, or withdrawal	Describe the definitions that were used to consider patients as trial completers. Discuss how subjects who discontinued or withdrew from the study were handled. Discuss whether subjects withdrawn from the study were replaced or not, regardless of the reason for withdrawal. Discuss whether any follow-up (procedures and/or assessments) were provided for subjects who discontinued or were withdrawn from the study.
Statistical methodology for primary endpoint	
Statistical methodology for secondary endpoints	
Administrative structure and safety monitoring committees	
Pre-specified safety endpoints	

Please provide your responses by December 22, 2015.

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
12/08/2015

From: White, Martin
To: ["David.Faunce@sanofi.com"](mailto:David.Faunce@sanofi.com)
Subject: NDA 208471_lixisenatide_Stats Information Request_12-7-2015
Date: Monday, December 07, 2015 9:58:00 AM

David,

With reference to your above-mentioned NDA submitted on July 27, 2015, we have the following information request:

Please provide SAS code for the supportive analyses for the primary endpoints, including MMRM using on-treatment values and MMRM using all post-baseline observations regardless of adherence to assigned treatment. If you have already done so, please state where the code is located. Please also state the location of the corresponding results more clearly. Based on our understanding, the results from MMRM using on-treatment values are presented in the Appendix of CSR, whereas the results from MMRM using all post-baseline observations are presented in the ISE.

Please provide your response by December 14, 2015.

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
12/07/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208471

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Sanofi-Aventis U.S. LLC.
55 Corporate Drive
Mail Stop: 55D-2225A
Bridgewater, NJ 08807

ATTENTION: David Faunce
Director, Global Regulatory Affairs

Dear Mr. Faunce:

Please refer to your New Drug Application (NDA) dated and received July 27, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lixisenatide Injection, 150 mcg/3 mL and 300 mcg/3 mL.

We also refer to your correspondence, dated and received, August 20, 2015, requesting review of your proposed proprietary name, Adlyxin.

We have completed our review of the proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

Your proposed proprietary name, Adlyxin, could result in medication errors (b) (4)

(b) (4)

We note that you have proposed an alternate proprietary name in your submission dated August 20, 2015. In order to initiate review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

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) 402-5146.

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
10/29/2015



NDA 208471

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Sanofi US Services Inc.
Attention: David Faunce
Director, Global Regulatory Affairs
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

Dear Mr. Faunce:

Please refer to your New Drug Application (NDA) dated and received July 27, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), lixisenatide injection.

We also refer to your amendments dated August 17, 20, and 26, 2015.

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 **Standard**. Therefore, the user fee goal date is July 27, 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 commitment requests by April 8, 2016.

In addition, the planned date for our internal mid-cycle review meeting is January 14, 2016. We have not determined if an advisory committee meeting is needed to discuss this application.

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

1. 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 Lixisenatide use in pregnant and lactating women by November 20, 2015:

- a) A review and summary of all available published literature regarding [drug name];
- b) A review and summary from your pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable);
- c) A 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.

2. We note that there were 103 investigators with relevant financial disclosures. To assist in our consideration of the impact of these investigators on study conduct and findings, submit tables for each of the individual pivotal phase 3 studies as well as for your cardiovascular outcomes study containing the following:
 - 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.

We are providing the above comments 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.

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 [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 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 42 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 instructions for use. 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 package insert (PI), Medication Guide, and instructions for use, 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 partial waiver and partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver and partial deferral request are denied.

We note that you have submitted pediatric studies with this application for pediatric patients 10 to 17. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Martin White, M.S., Regulatory Project Manager, at (240) 4020-6018.

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
10/08/2015



NDA 208471

NDA ACKNOWLEDGMENT

Sanofi US Services Inc.
Attention: David Faunce
Director, Global Regulatory Affairs
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

Dear Mr. Faunce:

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: lixisenatide injection

Date of Application: July 27, 2015

Date of Receipt: July 27, 2015

Our Reference Number: NDA 208471

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 **September 25, 2015**, 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 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
08/06/2015



IND 062724

**MEETING REQUEST-
WRITTEN RESPONSES**

Sanofi US Services Inc.
Attention: David Faunce
Director, Global Regulatory Affairs
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

Dear Mr. Faunce:

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

We also refer to your submission dated April 9, 2015, containing a Type B meeting request. The purpose of the requested meeting was to discuss questions related to the cardiovascular outcomes trial, EFC11319 (ELIXA), submission of stability data within 30 days of the NDA submission, and the REMS requirements for new GLP-1 receptor agonists, such as lixisenatide.

Further reference is made to our Meeting Granted letter dated April 29, 2015, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your April 8, 2015, background package.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-NDA

Application Number: 062724
Product Name: lixisenatide injection
Indication: treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Sanofi Services US, Inc.
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

The purpose of the requested meeting was to discuss questions related to the cardiovascular outcomes trial, EFC11319 (ELIXA – Evaluation of LIXisenatide in Acute coronary syndrome), submission of stability data within 30 days after the NDA re-submission, and the Risk Evaluation and Mitigation Strategy (REMS) requirements for new GLP-1 receptor agonists, such as lixisenatide.

Lixisenatide is glucagon-like-peptide-1 (GLP-1) receptor agonist that reduces blood glucose by glucose-dependent stimulation of insulin release and inhibition of glucagon secretion, which decreases prandial blood glucose excursion and hepatic glucose production. It is being developed for the treatment of adults with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise to improve glycemic control. The initial IND was submitted to the FDA on June 8, 2001.

The End-of-Phase 2 (EOP2) meeting was held on December 19, 2007, during which the Phase 3 clinical development plan was presented and discussed with the Agency.

On November 6, 2008, FDA informed Sanofi that the development of lixisenatide should address the new cardiovascular (CV) requirements that were later incorporated in a guidance issued on December 17, 2008, and entitled “Guidance for Industry Diabetes Mellitus —Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes”.

The sponsor submitted the protocol for the cardiovascular outcome study, ELIXA, and proposal for the submission of results of the interim analyses on April 7, 2010. The Agency provided advice on June 28, 2010.

On June 25, 2010, a Type C meeting (combined with EOP2 meeting for IND (b) (4)), was held with the Agency to discuss nonclinical and CMC aspects of the lixisenatide drug product development program.

The Agency provided Type C written responses on September 20, 2011. In the responses, the Agency proposed that Sanofi use a fire-walled group for submission of interim data.

On March 21, 2012, the sponsor submitted a Type-B Pre-NDA meeting to discuss the data within and the format of the planned NDA, and to obtain concurrence that the data currently available is adequate to support NDA submission and review by FDA. The Agency responded that the sponsor's request was premature and suggested delaying the pre-NDA meeting until the sponsor was certain that the requirements of the FDA Guidance for Industry: "Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" were met.

On July 30, 2012, the Agency provided Type C written responses, in response to a request to gain written feedback on NDA submission-related clinical, CMC and regulatory questions.

The pre-NDA meeting was held on November 28, 2012. The NDA for lixisenatide was submitted on December 20, 2012, followed by the submission of the interim analysis data from the ELIXA CV trial by the fire-walled group at Sanofi on the same day.

The NDA was accepted for filing. The review was classified as Standard and the application was subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V.

The user fee goal date was set for December 20, 2013, and the Agency indicated their plans to hold an Advisory Committee meeting to discuss the application.

The mid-cycle review meeting was held between Sanofi and the Agency on May 20, 2013. During this meeting, it was discussed that the Agency would hold the Advisory Committee meeting on October 15, 2013. Sanofi was informed that they should plan for the possibility of a closed/open session and prepare two briefing documents.

On September 10, 2013, Sanofi withdrew the lixisenatide NDA following discussions with the Agency regarding the proposed process for the review of the interim CV ELIXA data. Following the NDA withdrawal, Sanofi requested a Type A meeting, held on October 15, 2013. The purpose of this meeting was to obtain the Agency's feedback on major deficiencies and review issues identified during the NDA review.

2.0 QUESTIONS AND RESPONSES

Question 1: *Does the Division agree that the EFC11319 (ELIXA) study results, together with the previously submitted preclinical and clinical package, can support the evaluation of the lixisenatide NDA for the proposed indication?*

FDA Response to Question 1:

We agree that the ELIXA study results along with the previously submitted pre-clinical and clinical package can support evaluation of the lixisenatide for the

proposed indication. However, if there are changes in formulation from the previous submission dated December 20, 2012, additional nonclinical studies may be required.

To allow for an efficient and thorough review of the lixisenatide NDA, please submit with your application subject-level datasets for the ELIXA trial, including but not limited to: baseline characteristics (e.g. demographics, risk factors, concomitant medications), drug exposure, subject compliance, subject disposition, adverse events and time to event data. Among other variables planned for inclusion in your time to event dataset, please include variables for key dates: dates of randomization, treatment initiation and discontinuation, events (if applicable), and study completion. In addition, please include variables for identifying the following outcomes:

- **primary endpoint comprising cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for unstable angina,**
- **individual components of the primary endpoint,**
- **composite endpoint comprising CV death, non-fatal MI, or non-fatal stroke,**
- **secondary CV composite outcomes as defined in the protocol,**
- **all-cause mortality.**

For each of these outcomes, include variables for censoring and for time to first event/censoring in order to facilitate on-study analyses (i.e. the primary analysis method) as well as on-treatment analyses. For on-treatment analyses, please include outcomes occurring while subject is on treatment or within 30 days of end of treatment. Submit all datasets in SAS System XPORT transport format. Also for each dataset, submit detailed data definition files including a brief description of the data structure (one record per subject or multi-record per subject) and definitions for all variables along with specification of any derivation rules.

Question 2: For the drug product batches manufactured according to manufacturing process

(b) (4)

the sponsor intends to provide 3-month stability data in the NDA submission and will provide a simple stability update (6-month stability data) within the 30-day period following NDA receipt.

Does the Agency agree to review the updated 6-month stability data if they are submitted, as a minor application component under the provision of the PDUFA V, during 30-day period?

FDA Response to Question 2:

Yes, we agree to review the updated 6-month stability data if submitted during the 30-day period after the initial NDA submission. The adequacy of the data will be determined during our review of the NDA.

Question 3: While the Sponsor acknowledges that definitive feedback concerning pancreatic adverse events and the need for risk mitigation will require full review of all new and previously submitted data within the upcoming lixisenatide dossier, the sponsor is interested in the Agency's general views on REMS requirements for any new GLP-1 receptor agonists, including lixisenatide, in the context of its ongoing review of the class; and whether, in light of its current understanding of pancreatic and other potential risks which have been widely communicated for the class, these risks might today be adequately mitigated within product prescribing information.

FDA Response to Question 3:

Our position is unchanged from that communicated at the pre-NDA meeting held on November 28, 2012, and we refer you to the minutes of that meeting dated December 11, 2012. At that time you asked if the Agency concurred with your plan for voluntary risk management activities in place of a REMS. In our response we noted that, "Since other glucagon-like peptide-1 (GLP-1) receptor agonists have been approved with REMS communication plans because they share the same key risks of medullary carcinoma of the thyroid and pancreatitis, we cannot rule out the possibility that your product will require a REMS, if approved. Therefore, we encourage you to submit a proposed REMS with your application. A complete review of the REMS, in conjunction with the full clinical review of the NDA, will be necessary to determine that the REMS adequately addresses the safety risks and meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act." We also note that the meeting minutes document your intent to submit a REMS.

(b) (4)

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 29, 2015, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG

will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

4.0 PREA REQUIREMENTS

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.

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>.

5.0 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.

6.0 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.				

7.0 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).

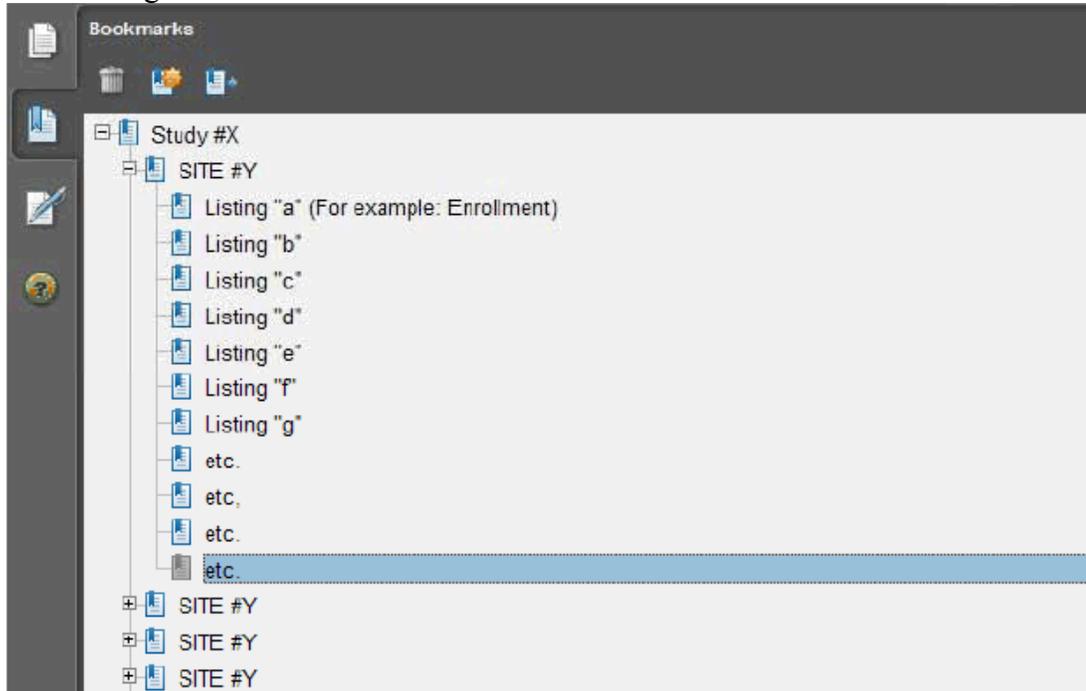
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - 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.

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
06/08/2015



IND 062724

MEETING MINUTES

Sanofi U.S. Services Inc.
Attention: Ayse Baker, Ph.D., M.B.A.
Director, Diabetes
55 Corporate Drive, Mailstop: 55D-215A
Bridgewater, NJ 08807

Dear Dr. Baker:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lixisenatide (AVE0010).

We also refer to the meeting between representatives of your firm and the FDA on November 28, 2012. The purpose of the meeting was to discuss the submission and contents of the NDA for lixisenatide.

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 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:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Wednesday November 28, 2012, 3:00 - 4:00 PM, EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: IND 062724
Product Name: lixisenatide solution for subcutaneous injection
Indication: Adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Sanofi U.S. Services Inc.

FDA ATTENDEES

Office of Drug Evaluation II

Mary H. Parks, M.D. Director, Division of Metabolism and Endocrinology Products (DMEP)
Amy Egan, M.D., MPH Deputy Director Safety, DMEP
Julie Marchick Chief, Project Management Staff, DMEP
Pooja Dharia, Pharm.D. Regulatory Project Manager, DMEP
Jean-Marc Guettier, M.D. Clinical Team Leader, DMEP
Suchitra Balakrishnan, M.D. Clinical Reviewer, DMEP
Karen Davis-Bruno, Ph.D. Pharmacology/Toxicology Team Leader, DMEP
Tim Hummer, Ph.D. Pharmacology/Toxicology Reviewer, DMEP
Leah Ripper Associate Director for Regulatory Affairs, ODE II

Office of Clinical Pharmacology

Lokesh Jain, Ph.D. Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2
Jaya Vaidyanathan, Ph.D. Clinical Pharmacology Reviewer

Office of Biometrics

J. Todd Sahlroot, Ph.D. Deputy Director, Division of Biometrics II (DBII)
Wei Liu, Ph.D. Biostatistics Reviewer

Office of Surveillance and Epidemiology

Cynthia LaCivita	Team Leader, Division of Risk Management (DRISK)
Yelena Maslov	Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)
Sarah Vee	Safety Evaluator, DMEPA

Office of Scientific Investigations

Cynthia Kleppinger, M.D.	Senior Medical Officer, Division of Good Clinical Practice Compliance
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CDRH

QuynhNhu Nguyen	Human Factors Reviewer
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SPONSOR ATTENDEES

Hugo Fry	Diabetes Division, Lixisenatide Family Global Project Leader
Ayse Baker, Ph.D., MBA	Diabetes Division, Director Lixisenatide Family Global Regulatory Affairs
Riccardo Perfetti M.D. Ph.D.	Head of Diabetes Division, Clinical Development
Richard Gural, Ph.D.	Corporate Head of Global Regulatory Affairs
Patrick Miossec, M.D.	Diabetes Division, Clinical Development
Stephen Lin, M.D.	Diabetes Division Pharmacovigilance
Rima Nassar, Ph.D.	Head Diabetes Division, US Regulatory Affairs
Meehyung Cho, Ph.D.	Biostatistics
Thomas Kissner, DVM, Ph.D.	Toxicologist
Anke Liewald	Device usability and risk management

1.0 BACKGROUND

Lixisenatide is glucagon-like-peptide-1 (GLP-1) receptor agonist that reduces blood glucose by glucose-dependent stimulation of insulin release and inhibition of glucagon secretion, which decreases prandial blood glucose excursion and hepatic glucose production. It is being developed for the treatment of adults with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise to improve glycemic control. The efficacy of lixisenatide was evaluated in the target population either as monotherapy or in combination with metformin, sulfonylureas, pioglitazone, and basal insulin. Lixisenatide is subcutaneously administered once daily, within the hour prior to the first meal of the day (b)(4). Two disposable fixed-dose pen injectors will be available (10 µg for dose initiation; 20 µg for maintenance dose).

As of June 1, 2012, 40 clinical studies have been completed, including 12 phase 3 studies. Overall, 4,046 subjects have been exposed to lixisenatide in completed phase 2/3 studies.

A pre-NDA meeting was requested by Sanofi to discuss aspects of the lixisenatide NDA related to presentation of data. Specifically, concurrence is sought with respect to questions related to clinical, nonclinical, device, and regulatory topics.

2. DISCUSSION

Your questions are repeated below, followed by our responses in **bold** print:

1. Does the Agency agree with the proposed content and format of the 120-Day Safety Update Report?

FDA Response: The proposed content and format of the 120 day safety update seems acceptable. We may request additional information based on our preliminary review of the submission

We also have the following additional comments:

- a. **You mentioned that the completed study report for the (b)(4) will be submitted with the 120-day safety update. With the limited information provided in the briefing document, the objectives of this study were not clear. If you intend to submit this study to the NDA, as per the regulations stipulated in PDUFA V, you should submit the final study report at the time of initial submission of the NDA. If this study is a bioequivalence study, you are expected to submit it at the time of initial submission (see comment 1b).**

Sanofi response dated 11/28/12: (b)(4)

(b)(4) The bioequivalence study BEQ 11094 (see 1b) will be included in the NDA. (b)(4)

(b) (4)

Discussion: No discussion occurred.

- b. Your initial submission should have adequate bridging data between the to-be-marketed formulation and the clinical formulation, if they are different. Pivotal bioavailability/bioequivalence study(ies) are expected to be submitted at the time of initial submission.**

Sanofi response dated 11/28/12: The 100µg/mL formulation was used for the clinical studies and is the to-be-marketed formulation for the maintenance dose of 20µg. A 50µg/mL formulation is the to-be-marketed formulation for the 10µg starting dose (to be used during the initial 2 weeks of treatment). Study BEQ11094 evaluated the bioequivalence between the 50 µg/mL and the 100 µg/mL lixisenatide formulations. The final study report will be submitted in the initial submission package.

Appendix 1 – Correspondence from the Agency [05/04/2011]

Discussion: No discussion occurred.

- c. You plan to submit** (b) (4), (b) (4)
(b) (4). **As per**
PDUFA V, the NDA application should be complete at the time of initial submission.

Sanofi response dated 11/28/12: We will not submit (b) (4)
(b) (4)

Discussion: No discussion occurred.

- d. To facilitate the review, in addition to the planned clinical pharmacology information in the NDA, we encourage you to submit the exposure/dose-response analysis for plasma calcitonin data obtained from the Phase 2-3 trials.**

Sanofi response dated 11/28/12: We will explore the data from approximately 300 patients for whom same day plasma levels of calcitonin and lixisenatide at 24 weeks from our phase 3 studies are available.

In accordance with PDUFA V, we consider this information of a type that would not be expected to materially impact the initiation of the NDA review. We request that any supplementary analysis that we submit be provided to the Agency within 30 days of the NDA submission.

Does the Agency agree?

Discussion: FDA agreed that Sanofi can submit supplementary analysis within 30 days of the NDA submission. See Discussion of the Contents of a Complete Application below.

2. Based on the results from non-clinical studies and clinical trials with lixisenatide and other GLP-1 receptor agonists, the sponsor proposes to implement voluntary risk management activities that will include routine pharmacovigilance, an epidemiology program, and voluntary risk mitigation activities to monitor and communicate the safety profile of lixisenatide after product launch. The Sponsor considers the risks management program described in the background below to be sufficient to assess and mitigate the risks of lixisenatide in the indicated patient population without a formal Risk Evaluation and Mitigation Strategy (REMS).

Does the Agency agree?

FDA Response: Since other glucagon-like peptide-1 (GLP-1) receptor agonists have been approved with REMS communication plans because they share the same key risks of medullary carcinoma of the thyroid and pancreatitis, we cannot rule out the possibility that your product will require a REMS, if approved.

Therefore, we encourage you to submit a proposed REMS with your application. A complete review of the REMS, in conjunction with the full clinical review of the NDA, will be necessary to determine that the REMS adequately addresses the safety risks and meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act.

We agree that, should lixisenatide be approved, you would be required to conduct a Medullary Thyroid Cancer Case Series Registry as a postmarketing required study under FDAAA. You are encouraged to participate in the the GLP-1 receptor agonist MTC registry consortium.

Sanofi response dated 11/28/12: A REMS will be submitted with our application and we are exploring participation in the GLP-1 receptor agonist MTC registry consortium.

3. Does the Agency agree that the totality of the nonclinical data to be presented in the NDA is sufficient to support the NDA application for the proposed indication?

FDA Response: Yes, the nonclinical study reports intended to be included in the NDA appear to be sufficient to support the NDA submission.

Discussion: No discussion occurred.

4. a. Does the Agency agree with the sponsor's proposal (b) (4) (b) (4)?

FDA Response: No, per the regulations stipulated in PDUFA V, all major components of an NDA must be submitted at the time of the initial NDA submission.

Sanofi response dated 11/28/12: (b) (4)

Discussion: No discussion occurred.

- b. Does the Agency agree with the sponsor's proposal (b) (4) (b) (4)

FDA Response: See the response for 4a.

Discussion: No discussion occurred.

Sanofi response dated 11/28/12: (b) (4)

therefore the results of these studies will not be included in the initial application or in the 120 day safety update.

- c. Would the Agency be willing to include the results of the (b) (4) study in their review of the lixisenatide application and consider it together with the other mechanistic studies when evaluating the prescribing information?

FDA Response: Yes, provided that the data are submitted at the time of the NDA submission.

Discussion: No discussion occurred.

5. Does the Agency agree with the sponsor's proposal for submitting the human factor and usability information for the delivery device (lixisenatide pen injector) per format described below in the background for question 5?

FDA Response: The format appears acceptable. We note that the results of the human factors validation study must be submitted at the time of NDA submission.

Please note that we expect that your study report to begin with a conclusion that the device is reasonably safe and effective for the intended users, uses, and use conditions. A summary of relevant portions of preliminary analyses, evaluations, the validation testing should be used as support of this conclusion. The test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to identified risks and whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. Your data analysis should be prioritized based on identified risk and task priority (from highest to lowest) to determine the magnitude and significance of the use errors, failures and difficulties that occurred during the testing. Residual risk associated with use that cannot be further reduced through modifications of training, labeling, or modifications to the design of the user interface should be discussed and rationale provided for why it cannot be further reduced. Note that stated plans to modify design flaws that could result in clinical impact on patients in future versions of the device are generally unacceptable.

Discussion: No discussion occurred.

6. The Sponsor has established a fire-walled group (FWG) as proposed by the Agency and will follow the process outlined below for submission of the ELIXA (ongoing CV trial, EFC11319) interim results. Does the Agency agree?

FDA Response: The process for establishment of the fire-walled group and planned submission of the interim ELIXA results are acceptable.

Discussion: No discussion occurred.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

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.

The interim analysis of the ongoing ELIXA trial will be submitted separately to the NDA but will occur on the same day. The firewalled team was informed that FDA intends to speak with the non-firewalled team prior to the planned submission. Please note that the acceptability of your proposed NDA submission date of December 19 through 22, 2012, is contingent on the discussions held between FDA and this non-firewalled team.

- A preliminary discussion on the need for a REMS was held. See Question 2.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
 1. Exposure/dose-response analysis of plasma lixisenatide and plasma calcitonin data from Phase 3 trials.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA 204961: LATE COMPONENT - CLINICAL PHARMACOLOGY

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

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
12/11/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 62,724

Sanofi-aventis U.S. Inc.
Attention: Pierre Mugnier, Ph.D.
Sr. Project Leader, Corporate Regulatory Affairs
200 Crossing Blvd., Mail Stop: BX4-206A
Bridgewater, NJ 08807

Dear Dr. Mugnier:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AVE0010 solution for injection.

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on December 19, 2007. The purpose of the meeting was to discuss issues pertaining to the AVE0010 development program.

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.

The Agency is internally discussing the advice given during the July 2008 Diabetes Advisory Committee Meeting. We plan to inform sponsors developing drugs for the treatment of type 2 diabetes mellitus that are in Phase 3 what additional data will be necessary for a marketing application.

If you have any questions, please call John Bishai, Ph.D., Regulatory Project Manager, at (301) 796-1311.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - End-of-Phase 2 minutes from meeting held on December 19, 2007

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Wednesday, December 19, 2007
TIME: 10:00 to 11:30 am
LOCATION: White Oak Campus – Silver Spring, MD
APPLICATION: IND 62,724
DRUG NAME: AVE0010 solution for injection
TYPE OF MEETING: Type B, End-of-Phase 2

MEETING CHAIR: Mary Parks, M.D.

MEETING RECORDER: Lina AlJuburi, Pharm.D., M.S.

FDA ATTENDEES: (Title and Office/Division)

Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, M.D.	Director
Hylton Joffe, M.D.	Acting Clinical Diabetes Team Leader
Robert Misbin, M.D.	Clinical Reviewer
Karen Davis-Bruno, Ph.D.	Pharmacology/Toxicology Team Leader
Dylan Yao, Ph.D.	Pharmacology/Toxicology Reviewer
Lina AlJuburi, Pharm.D.	Chief, Project Management Staff

Division of Biometrics 2/Office of Biostatistics (OB)

Lee-Ping Pian, Ph.D.	Reviewer
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Quantitative Safety and Pharmacoepidemiology Group (QASP)/Division of Biometrics 6/Office of Biostatistics

George Rochester, Ph.D.	Team Leader
Owen McMaster, Ph.D.	Reviewer

Office of Clinical Pharmacology (OCP)

Sally Choe, Ph.D.	Team Leader
Manoj Khurana, Ph.D.	Reviewer

Office of New Drug Quality Assessment (ONDQA)

Stephen Moore, Ph.D.	Pharmaceutical Assessment Lead
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Division of Medication Error Prevention and Analysis (DMEPA)/Office of Surveillance and Epidemiology (OSE)

Carol Holquist, R.Ph.	Director
Felicia Duffy, RN, BSN, MSED	Safety Evaluator

EXTERNAL CONSTITUENT ATTENDEES:

Drug Safety Evaluation

Agnes Seeberger, D.V.M., Ph.D. Senior Toxicologist

Drug Metabolism and Pharmacokinetics

Yan Hong Liu, M.D., Ph.D. Pharmacokineticist
Martin Gerl, Ph.D. Section Head Biomarkers/Biologicals

Clinical Pharmacology

Peter Ruus, M.D. Clinical Research Director

Clinical Development- Metabolism and Diabetes

Gabor Boka, M.D. Clinical Research Director
Louise Silvestre, M.D. Deputy Therapeutic Area Head

Clinical Biostatistics

Peng-Liang Zhao, Director Biostatistics TA Head - Metabolism & Diabetes
Richard Wu, Ph.D. Senior Manager

Regulatory Development

Alan Kerr Global Metabolism and Diabetes Domain Head
Rima Nassar, Ph.D. Director – Diabetes
Pierre Mugnier, Pharm.D., Ph.D. Senior Project Leader - Diabetes

Analytical Chemistry

Werner Mueller, Ph.D. Analytical Science Department

Device Development

Gerard Linnane Design Authority – Medical Devices

Regulatory CMC

Julie Doerr Senior Manager

Project Direction

Heinz Haenel, Prof. Dr.phil.nat. Project Director

BACKGROUND:

IND 62,724 for AVE0010 solution for injection was submitted on June 8, 2001. AVE0010 is a glucagon-like peptide (GLP)-1 analog under study for the treatment of type 2 diabetes mellitus. This drug formulation is an immediate release solution for subcutaneous injection. The proposed maintenance dose is 20 mcg once daily. (b) (4)

Study EFC10743 has been added to the drug development program.

Proposed Phase 3 Clinical Program

At the time the briefing document was submitted, the Sponsor listed seven pivotal safety and efficacy studies in Phase 3. Five are placebo-controlled “add-on” studies, one is an active-controlled study, and one is a monotherapy placebo-controlled study in patients with type 2 diabetes mellitus.

Study EFC6014: *A randomized, double-blind, placebo-controlled, parallel-group, multicenter study with a 24-week main treatment period and an extension period assessing the efficacy and safety of AVE0010 on top of metformin in type 2 diabetes not adequately controlled with metformin. (Metformin)*

Study EFC6015: *A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter 24-week study with an extension assessing the efficacy and safety of AVE0010 on top of a sulfonylurea in patients with type 2 diabetes not adequately controlled with sulfonylurea. (Sulfonylurea with or without metformin)*

Study EFC6016: *A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week main treatment period and an extension assessing the efficacy and safety of AVE0010 in patients with Type 2 diabetes insufficiently controlled with basal insulin (Basal insulin with or without metformin)*

Study EFC10743: (draft title) *A randomized, double-blind, placebo-controlled, parallel-group, multicenter, 24-week study followed by an extension assessing the efficacy and safety of AVE0010 in two titration regimens on top of metformin in patients with type 2 diabetes not adequately controlled with metformin*

Study EFC6018: *A randomized, double-blind, placebo-controlled, parallel-group, multicenter 12-week study assessing the efficacy and safety of VE0010 in drug naïve patients with type 2 diabetes (NA)*

Study EFC6019: *A randomized, open-label, active-controlled, 2-arm parallel-group, multicenter 24-week study assessing the efficacy and safety of A VE0010 versus exenatide on top of metformin in patients with type 2 diabetes not adequately controlled with metformin (Metformin)*

The Sponsor requested this Type B End-of-Phase 2 meeting on September 28, 2007, and the background package was submitted on November 15, 2007.

MEETING OBJECTIVES:

To discuss issues pertaining to the AVE0010 development program; specifically Phase 3 clinical plans regarding study designs, endpoints and the clinical safety program.

DISCUSSION POINTS:

The Sponsor's questions are repeated below followed by the Agency's comments, sent to Sponsor via email on December 17, 2007, in bold font and then discussion from industry meeting in bold italics.

Nonclinical questions

1. Based upon a review of the Reproduction Toxicity studies, the sponsor concluded that the effects seen in rat and rabbit studies were secondary to the considerably decreased maternal food consumption, body weight and body weight gain, resulting from the exaggerated pharmacological effect of the test compound in non-diabetic non-obese animals. Such scenario is not expected when AVE0010 is used in patients with type 2 diabetes.

Does the Division agree with the conclusions of the sponsor with regard to reproductive toxicity study results?

These studies are currently under review. The Division notes that rat fertility and embryo-fetal development as well as two rabbit embryo-fetal developmental studies have been submitted. However, a rat peri-/postnatal study has not been submitted and will be needed if you plan to enroll into your phase 3 trials women of childbearing potential not using adequate birth control. The second rabbit embryo-fetal developmental study uses lower doses and establishes a no-observed-adverse-effect-level (NOAEL) for maternal toxicity at the lowest dose 0.3 mcg/kg/day. There are some fetal variations (incomplete ossification, artery positioning and size and lung anomalies) noted at this dose. A comparison of these findings and their incidence against historical control data is needed.

Sponsor presented historical control data. Please see attached slides 2, 3, and 4.

2. The sponsor has integrated a neutralization assay and a cross reactivity assay (endogenous GLP-1) – as requested by the FDA Carcinogenicity Assessment Committee (15 May 2006) – in the rat carcinogenicity study. Due to technical limitations, there is no plan to perform these assays in a mouse model.

Does the Division agree with the sponsor's plan?

The Executive Carcinogenicity Assessment Committee (ECAC) requested this assessment in both rat and mouse as part of their contingent acceptance of the carcinogenicity study dose selection. The basis of the technical difficulty has not been provided and is needed if the Sponsor is requesting ECAC concurrence.

The Sponsor provided explanation regarding the limitations for cross reactivity and neutralization assays in the mouse 2-year carcinogenicity study. Please refer to attached Sponsor slide numbers 5 and 6. The Sponsor was asked to submit a rationale as an amendment to this IND for deliberation by ECAC. The Sponsor did so with a submission dated January 29, 2008. The ECAC's were comments conveyed to the Sponsor in a letter dated March 5, 2008, as follows:

The ECAC concurs with your proposal that the mouse antibody assays in the 2-year carcinogenicity study can be exempted based on technical difficulties of obtaining sufficient serum volumes. However, the committee does not concur with the scientific rationale you proposed that the immunogenicity data obtained from the rat and human would predict antibody response in mice.

Additional comment: Submission of chronic toxicity study reports is needed to support initiation of Phase 3.

The Sponsor was also told that if they plan to study co-administration of AVE0010 and rimonabant in Phase 3, they would need to conduct and submit a combination toxicity study with AVE0010 and rimonabant.

Clinical questions

1. Following the completion of the 13-week dose-finding study DRI6012, the clinical development plan for AVE0010 will consist of seven efficacy and safety studies (Phase III), including five placebo-controlled studies in combination with other antidiabetic medications, a placebo-controlled monotherapy study, as well as an active comparator study. This program is designed to support a label claim for the treatment of patients with type 2 diabetes (b) (4)

Does the Division agree that the clinical development plan of AVE0010 is appropriate to support the target product profile [appendix 9] and the proposed indication?

The clinical development plan appears appropriate to support the proposed indication. The dose of background metformin therapy should be at least 1500 mg per day. Patients should be taking at least half-maximal doses of a sulfonylurea in your add-on to sulfonylurea study.

Please note that the Division is no longer issuing separate indications for specific combinations of drugs and biologics for the treatment of type 2 diabetes. The indication section in labeling is instead being replaced by a single, simplified indication (Drug X is indicated as an adjunct to diet and exercise to improve glycemic control in

adults with type 2 diabetes mellitus). If the risk/benefit profile is favorable when AVE0010 is used in combination with other drugs, the study findings and conclusions will be described in the Clinical Studies section of the label, effectively providing support for the combination use in clinical practice. If AVE0010 is not studied in combination with anti-hyperglycemic medications that are likely to be commonly co-administered with AVE0010 in clinical practice, we will require that the label contain a statement reflecting this limitation under “Important Limitations of Use”.

The Sponsor was asked to choose rosiglitazone maleate or pioglitazone hydrochloride for the study with thiazolidinediones (not both) to better interpret the study results. Patients should be on stable, near-maximal or maximal effective doses of the chosen thiazolidinedione prior to randomization.

2. In the pivotal safety and efficacy studies the dosage regimen will be based on the results of the 13-week dose finding study DRI6012. The fasted plasma glucose limits used in the algorithm proposed for rescue medication are based on regulatory precedents.

Does the Division agree with the proposed dosage regimen and rescue algorithm?

Although the Sponsor proposes that 20 mcg once daily is the likely maintenance dose, results of the 13 week trial (trial DR16012) suggest that 10 mcg twice daily may be a better dosing regimen. The Division believes that it is premature to conclude that twice daily dosing should not be studied in Phase 3.

During the meeting, the Sponsor was strongly urged to also study twice daily dosing in the Phase 3 program.

The glycemic rescue criteria through Week 12 are acceptable. Because HbA1c accurately reflects overall glycemic control after 3 months of therapy, you should incorporate this parameter into your glycemic rescue criteria as follows: “Fasting plasma glucose >200 mg/dL (11.1 mmol/L) or HbA1c >8.0% after Week 12”.

The Sponsor raised concerns that this HbA1c cutpoint may be too conservative and will submit a modified glycemic rescue algorithm with justification for the modifications.

The informed consent form should explain that randomization to placebo in the trials may result in worsening of glycemic control and that monitoring throughout the study will be necessary to ensure patient subject safety regarding glycemic control.

3. Based on the results of the 13-week dose-response DRI6012 study, the sponsor is aiming at using titration steps with AVE0010 in order to reach the maintenance dose in phase III studies. However, a titration scheme including less intermediate titration levels, as long as well tolerated, might decrease the risk of dose error and simplify the treatment regimen. The sponsor plans to evaluate this simplified one-step treatment titration scheme in the 12-week placebo-controlled monotherapy trial.

Does the Division agree that the design of the 12-week monotherapy study for the one-step titration scheme could generate the type of data necessary to support the intended “Dosage and Administration” of AVE0010?

The study to compare a one-step versus two-step titration scheme appears appropriate. As noted earlier, the Division believes that it is premature to conclude that 20 mcg once daily is the best regimen.

No further discussion at meeting.

4. An effect of AVE0010 in slowing gastric emptying may reduce the extent and rate of absorption of orally administered drugs. This may be relevant for the medications that are dependent on threshold concentrations for efficacy. The sponsor’s plan includes four interaction studies and is aimed to address the impact of the delayed gastric emptying induced by AVE0010 on the pharmacokinetics and pharmacodynamics of concomitant treatments.

Does the Division agree that these proposed interaction studies would be appropriate to support product approval?

The proposed plan for evaluating drug interactions with AVE0010 appears to be appropriate, including interaction studies with acetaminophen, an oral contraceptive combination product (ethinylestradiol and levonorgestrel), warfarin and a statin.

No further discussion at meeting.

5. Although preclinical studies did not reveal findings suggesting a pro-arrhythmic activity of AVE0010, the 4-week thorough ECG study (TES6865) will investigate the possible effect of AVE0010 on QT interval, in compliance with the ICH E14 guidelines. The highest dose to be tested in this study (maximum of 30 mcg BID) will allow covering supratherapeutic conditions.

Does the Division concur that the TES6865 study is adequate to assess possible effects of AVE0010 on QT interval?

Please submit your thorough ECG study protocol to the Agency for review by the QT Internal Review Team (IRT).

The Sponsor notified the Division that the study was ongoing in Europe. According to the Sponsor, the study was designed in accordance with ICH E14 Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. The Sponsor submitted the protocol to the IND on January 24, 2008. Since the study is ongoing, the QT-IRT will not comment on the protocol at this time.

6. The therapeutic use of protein and peptide pharmaceuticals can be associated with antibody formation. In the previous 4-week dose titration study (ACT6011) and 13-week dose titration study (DRI6012), the presence of anti-AVE0010-antibodies was shown in about 50% of the

subjects at the end of the 4th week and 13th week of treatment, respectively. In phase III trials, therefore, sanofi aventis is proposing a plan to measure anti-AVE0010 antibody titers and investigate the potential for neutralization of effect, as well as cross-reactivity with endogenous GLP-1 and glucagon.

Does the Division agree with the anti-AVE0010 antibody monitoring plan proposed for phase III?

The Sponsor's plan for measurement of antibodies is appropriate. Analysis of the antibody data will be a review issue. The Sponsor will need to determine to what extent (if any) the development of antibodies interferes with pharmacological activity or poses safety issues.

The Agency notes the difficulty the Sponsor has had in developing a selective quantification method for free AVE0010 in samples from subjects who are antibody-positive. The Agency encourages the Sponsor to try to develop an assay method that can capture the free AVE0010 concentration in all pharmacokinetic samples without being affected by the antibody titer status since the utility of total concentration measurement is not well understood in terms of its relationship with efficacy.

No further discussion at meeting.

7. Sanofi aventis is proposing to defer pediatric development of this product until adequate safety and efficacy are demonstrated in adult patients.

Does the agency agree with the proposed pediatric development plan for AVE0010 and defer clinical studies in children until the product is approved in the adult population?

We agree that you should not conduct pediatric studies with AVE0010 prior to NDA approval. If you wish to obtain a deferral for postmarketing pediatric studies, you should submit a formal request with justification at the time of the NDA submission.

Additional Clinical Comments:

- A. **You mention in your briefing package that your phase 3 trials might include patients from the United States. To support a new drug application, the racial/ethnic makeup of patients in your trials must be representative of the racial/ethnic demographics in the United States.**

The Sponsor confirmed 15 to 20% enrollment in the United States.

- B. **Prior to the face-to-face meeting (or, if that is not possible, at the face-to-face meeting), please show the duration of exposure to AVE0010 (number of patients with exposure to AVE0010 ≥ 6 months, ≥ 12 months, ≥ 18 months, ≥ 24 months) separately for the monotherapy and each of the combination therapy settings that will be included in the NDA.**

Exposure numbers were submitted as an amendment to the IND on January 24, 2008. FDA response with additional comments issued in a letter dated February 5, 2008. In that letter, the Sponsor was notified that a total of approximately 2500 patients would need to be exposed to AVE0010 in the Phase 3 program.

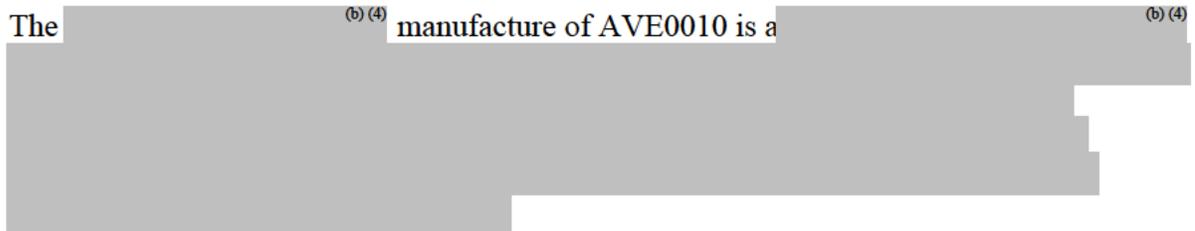
- C. For your phase 3 trials, you should exclude patients with a history of unexplained pancreatitis (Byetta, another GLP-1 analogue, has been associated with pancreatitis). If you permit enrollment of patients who have previously been treated with Byetta, you should obtain blood for measurement of anti-AVE0010 antibodies in these patients prior to treatment with AVE0010.**

Further discussion on pancreatitis and GLP-1 analogs. Currently unknown if this is a class-effect. Sponsor is measuring amylase and lipase in the phase 3 program.

- D. For all phase 3 trials, you should prospectively define in the protocols the criteria and assessment of hypoglycemia.**

No further discussion at meeting.

CMC questions

- 1. The ^{(b) (4)} manufacture of AVE0010 is a ^{(b) (4)}


Does the agency have comments on the proposed starting materials?



Additional discussion during the meeting included the following:

The sponsor indicated that there are only ^{(b) (4)} of the AVE0010 drug substance. The FDA explained that the foregoing is still the case nevertheless, ^{(b) (4)}. The FDA further explained that the analytical procedures used to qualify the starting materials should be capable of discriminating the starting materials from closely related compounds ^{(b) (4)}. The sponsor proposed to use ^{(b) (4)}. The FDA indicated that ^{(b) (4)} would be acceptable.

The response to this question is revised as follows:

(b) (4)

2. Sanofi aventis intends to apply a bracketing approach to drug product stability. Three commercial-scale batches of the most concentrated formulation used for the maintenance dose, and three batches (one commercial scale and two pilot-scale) of the least concentrated formulation used for the initial titration dose will be included in the primary stability protocol.

Does the agency have comments on the drug product primary stability study plans to support approval, including the bracketing design, tests and acceptance criteria?

The bracketing design of the stability protocol is acceptable.

Additional discussion during the meeting included the following:

The FDA indicated that potential aggregate formation should be addressed in the drug substance and drug product stability testing. The sponsor proposed to add aggregation testing (b) (4) to the drug substance and drug product specifications, and stability protocols. The FDA indicated that this would be acceptable.

The FDA indicated that cartridge rotation testing at 30-37°C may needed for in-use stability testing to simulate patient use. This is considered a characterization test. The sponsor proposed to use 30°C maximum as the preferred temperature for the in-use stability studies, and since there is no air bubble in the cartridge, that cartridge rotation is not necessary. The FDA indicated that this would be acceptable.

3. The marketed solution for injection is planned to be administered using a pen device. It is intended to be used for self-injection by the patients. The same basic device (internal components and external shape) will be used for the different drug product formulations. Different color, tactile features and label design will be used to distinguish the different formulations in the pen.

Are the differentiation concepts proposed for the pen acceptable?

In general, the concepts described for differentiation of the proposed pen appear to be acceptable. However, the Agency believes there are additional areas of risk the Sponsor may wish to consider when developing the pen.

The Agency cannot comment on the colors used to distinguish the pen (black and white copy provided in the meeting briefing document), but it seems the Sponsor has thoughtfully chosen the colors to accommodate patients with color-impaired vision.

Additionally, the concept of using different colors for each of the strengths may help to distinguish the pens within the product line and reduce the risk of confusion.

The design of the pen labels appears to provide additional differentiation within the product line. However, the Agency recommends that the text area be made larger to improve readability of the drug information.

The Sponsor also proposes using tactile cues on the body of the pen device. The Agency does not object to the use of tactile cues but is concerned about potential use of the pen device in visually-impaired populations. Visual acuity is required to set up pens and use them properly. In addition, patients with neuropathy may not benefit from the tactile cues.

Post-marketing experience with other pen devices used in the diabetic patient population has demonstrated that the feedback mechanism used to indicate that a dose is delivered is crucial to the safe use of pens. In many cases, patients overdose when using pen devices because they are unsure if the dose has been delivered. The proposed pen device will deliver a very small volume of drug, which means patients may not feel the medication that is injected. Effective feedback mechanisms would help inform patients that a dose is delivered, and generally could include a combination of auditory (e.g. clicking noise) and sensory components.

Patients will have to attach a pen needle. Safety issues often arise with re-capping and needle sticks. Additionally, if pen needles are not provided, patients may potentially withdraw the medication into a syringe. Please comment in regard to whether or not needles for the commercial product will be co-packaged with the pen device.

The diagram of the pen includes marking on the cartridge to indicate the number of doses remaining. Although this may be helpful if patients understand the meaning of the calibrations, these markings may inadvertently be a source of error if patients believe they can be used to measure the dose (i.e. by withdrawing the contents of the cartridge into a syringe) or if patients rely on the movement of the plunger and decreased volume of liquid medication to indicate a dose has been delivered. The Agency recommends that the Sponsor consider these risks and develop clear labeling in both the insert and user manual to prevent misunderstanding and errors.

Note: A model of the device was not available for evaluation prior to the meeting. The sponsor will provide working models of the device from each strength, when available, to possibly identify additional areas of vulnerability for consideration.

Additional comments regarding the Safety Analysis Plan for AVE0010

The Quantitative Safety Analysis Plan (QSAP) provides the framework to ensure that the necessary data to understand the pre-marketing safety profile are obtained, analyzed and presented appropriately. The Statistical Analysis Plan, which generally addresses statistical issues for efficacy, must include a QSAP. The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The Clinical Data Interchange

Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).

The following safety issues have been identified for your consideration as you prepare your safety plan.

1. **Loss of efficacy.** Anti-AVE0010 antibodies have been detected in patients exposed to AVE0010. A similar product (BYETTA) also produced antibodies and the glycemic response was attenuated in about half the patients with antibodies. The agency notes that the sponsor has an antibody monitoring plan to assess the potential neutralizing effect of anti-AVE0010 antibodies. Please ensure that data is collected according to our QSAP guidelines.
2. **Pancreatitis and GI side effects.** Post marketing cases of acute pancreatitis have been recorded with BYETTA. A prominent symptom of pancreatitis is abdominal pain, which is also increased in patients treated with 30 µg doses of AVE0010 (QD or BID). Please ensure that any patients with abdominal pain are carefully evaluated and followed until the pain has resolved.
3. **Hypoglycemia.** Hypoglycemia was experienced by 2-6% of patients in study DR16012. The incidence of hypoglycemia and severe hypoglycemia should be evaluated in the phase III study.
4. **Anaphylaxis.** One patient in study DR16012 experienced an anaphylactic reaction after 3 weeks of treatment with 10 µg doses of AVE0010. The risk, time course and if possible, prediction of this side effect need to be assessed in phase III.
5. **Testicular toxicity.** Dogs treated with AVE0010 showed increased incidence of hypo spermatogenesis with focal and multifocal vacuolation and atrophy of the seminiferous tubules and focal sperm stasis in the testes. The sponsor discussed the fact that these findings are occasionally spontaneously seen in dogs, and postulated that these findings may be related to malnutrition/weight loss in these animals, but agreed that the incidence and severity were greater in drug-treated animals. The sponsor should include an evaluation of the effect of AVE0010 on the male reproductive system during Phase III. Repeated evaluations of sperm counts, over a period of months, would begin to address this question.

At a minimum the Safety Analysis Plan should address the following components:

- Study design considerations
See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*,
<http://www.fda.gov/CDER/guidance/6357fml.pdf>
- Safety endpoints for Adverse Events of Special Interest (AESI)
- Definition of Treatment Emergent Adverse Event (TEAE)
- Expert adjudication process (Expert Clinical Committee Charter)
- Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
- Analytical methods (e.g., data pooling or evidence synthesis): statistical principles

and sensitivity analyses considered.

- When unanticipated safety issues are identified the QSAP may be amended.

Study Data Tabulation Model (SDTM) Issues

1. Format

The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed. Refer to the SDTMIG section on Conformance (3.2.3)

2. Domains

a. There are additional domains listed below that are not included in the current SDTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.

- (DV) Protocol deviations
- (DA) Drug Accountability
- (PC, PP) Pharmacokinetics
- (MB, MS) Microbiology
- (CF) Clinical Findings

b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.

- Tumor information
- Imaging Data
- Complex Inclusion/Exclusion Criteria

2. Variables

- All required variables are to be included.
- All expected variables should be included in all SDTM datasets.
- Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.
- A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.
- A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.
- Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.

4. Specific issues of note

- SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.
- Only MedDRA preferred term and system organ class variables are allowed

in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.

- c. These issues can be addressed through the request for ADaM datasets

Analysis Data Model (ADaM) Issues:

1. Please specify which ADaM datasets you intend to submit.
2. Please include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
3. Please discuss the structure of the datasets with the reviewing division and specify in the QSAP.
4. Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.
5. Please indicate which core variables will be replicated across the different datasets, if any.
6. SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.

General Items: Controlled terminology issues

- a. Please use a single version of MedDRA for a submission. This does not have to be most recent version.
- b. We recommend that the WHO drug dictionary be used for concomitant medications.
- c. Please refer to the CDISC terminology for lab test names.
- d. Issues regarding ranges for laboratory measurements should be addressed.

ATTACHMENTS/HANDOUTS:

Slides presented by Sponsor during meeting for discussion.

Linked Applications

Sponsor Name

Drug Name

IND 62724

AVENTIS
PHARMACEUTICAL
PRODUCTS INC

AVE0010 INJECTION

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

/s/

LINA ALJUBURI
09/09/2008

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

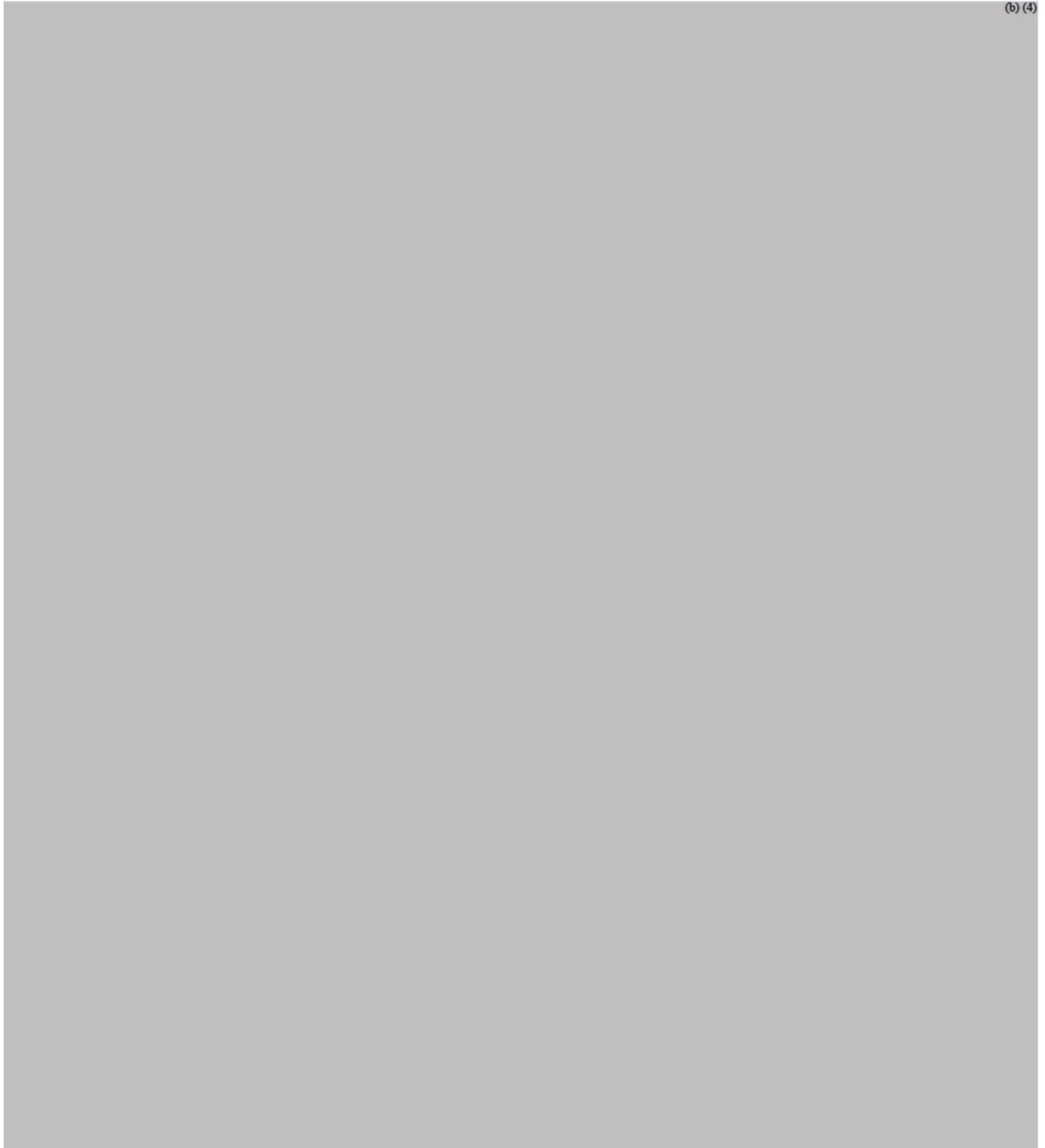
Welcome, Introductions, Ground rules, Objectives of the meeting

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.



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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.

(b) (4)



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

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Sanofi expressed their concerns

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(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

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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



NDA 208471
NDA 208673

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

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

Dear Ms. Goyal and Mr. Faunce:

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

We also refer to the Late-Cycle Meeting (LCM) scheduled for May 11, 2016. Attached is our background package, including our agenda, for this meeting.

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Background Package

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

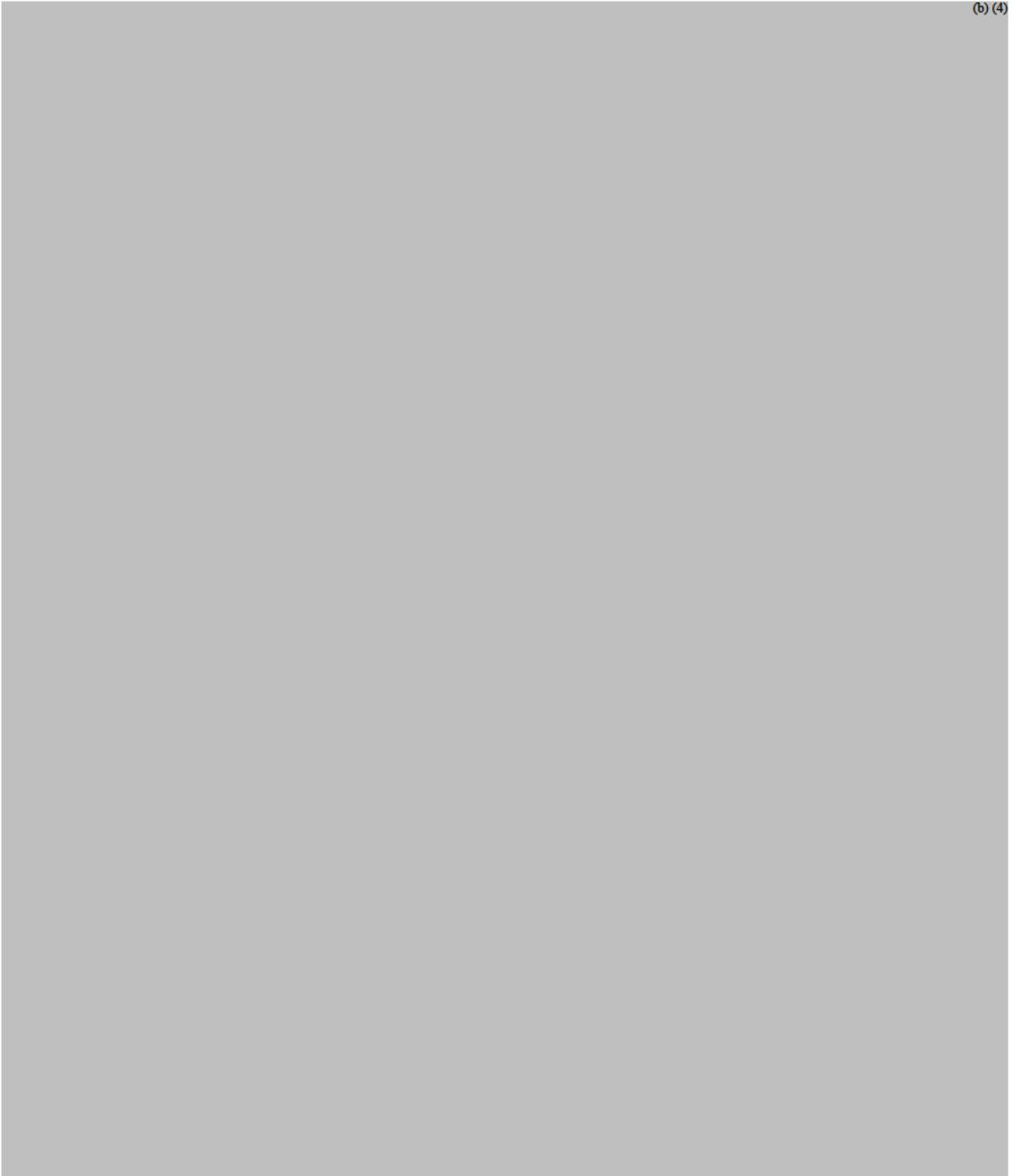
The following substantive review issues have been identified to date:

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.

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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:

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- 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.

NDA 208673



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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.

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
05/05/2016