

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205692Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 205692

SUPPL # N/A

HFD # N/A

Trade Name Basaglar

Nonproprietary Name insulin glargine

Applicant Name Eli Lilly and Company

Approval Date, If Known August 18, 2014

### 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)(2)

c) 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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES  NO

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

5

e) 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?

N/A

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# 21081

Lantus

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:

N/A

(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:

Study 14L-MC-ABEB *A Prospective, Randomized, Open-Label Comparison of a Long-Acting Basal Insulin Analog LY2963016 to LANTUS® in Combination with Mealtime Insulin Lispro in Adult Patients with Type 1 Diabetes Mellitus (ELEMENT 1 Study)*

Study 14L-MC-ABEC *A Prospective, Randomized, Double-Blind Comparison of a Long-Acting Basal Insulin Analog LY2963016 to Lantus in Adult Patients with Type 2 Diabetes Mellitus (ELEMENT 2 Study)*

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:

N/A

- 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:

N/A

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"):

*Study 14L-MC-ABEB A Prospective, Randomized, Open-Label Comparison of a Long-Acting Basal Insulin Analog LY2963016 to LANTUS® in Combination with Mealtime Insulin Lispro in Adult Patients with Type 1 Diabetes Mellitus (ELEMENT 1 Study)*

*Study 14L-MC-ABEC A Prospective, Randomized, Double-Blind Comparison of a Long-Acting Basal Insulin Analog LY2963016 to Lantus in Adult Patients with Type 2 Diabetes Mellitus (ELEMENT 2 Study)*

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 # 105423 YES  ! NO   
! Explain:

Investigation #2 !

IND # 105423      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:

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Name of person completing form: Callie Cappel-Lynch

Title: Regulatory Project Manager  
Date: July 28, 2014

Name of Office/Division Director signing form: Lisa Yanoff (on behalf of Jean-Marc Guettier)  
Title: Team Leader, Acting

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CALLIE C CAPPEL-LYNCH  
08/18/2014

LISA B YANOFF  
08/18/2014  
signing on behalf of Dr. Jean-Marc Guettier

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 205692	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: Basaglar Established/Proper Name: insulin glargine Dosage Form: injection		Applicant: Eli Lilly and Co. Agent for Applicant (if applicable): N/A
RPM: Callie Cappel-Lynch		Division: Metabolism and Endocrinology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" 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><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li>• Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (notify CDER OND IO)          Date of check: December 10, 2015</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>
<p>• Actions</p> <ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is December 16, 2015</li> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		
❖ 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR  <input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> 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.

<sup>2</sup> 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).

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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): Type 5 – New Formulation or New Manufacturer  
 (*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 |   |

NDAs: Subpart H

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

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- Approval based on animal studies

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

Comments: none

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	N/A
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	N/A
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• 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 checked="" type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other information advisory
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<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

<b>Action Letters</b>	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	AP – December 16, 2015 TA- August 18, 2014 (labeling was not attached to the TA letter per recommendation of ORP)
<b>Labeling</b>	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included – See labeling attached to approval letter.
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<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 type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included – See labeling attached to approval letter.
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels <b>(full color carton and immediate-container labels)</b> <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included – See labels attached to approval letter.
❖ Proprietary Name <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>• Review(s) <i>(indicate date(s))</i></li> </ul>	January 23, 2014 January 17, 2014
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: December 9, 2013 DMEPA: April 10, 2014 DMPP/PLT (DRISK): July 29, 2014 OPDP: August 7, 2014 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
<b>Administrative / Regulatory Documents</b>	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i> ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	December 11, 2013 June 23, 2014 December 7, 2015
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	

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

<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: It was determined that this application did not trigger PREA.</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ 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, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	December 11, 2015 December 7, 2015 November 24, 2015 (2) October 26, 2015 October 19, 2015 August 18, 2014 August 12, 2014 August 11, 2014 (2) July 22, 2014 June 27, 2014 June 24, 2014 June 10, 2014 May 23, 2014 April 21, 2014 April 14, 2014 April 8, 2014 March 18, 2014 February 4, 2014 December 31, 2013 December 5, 2013 November 21, 2013 October 28, 2013 October 22, 2013
<ul style="list-style-type: none"> <li>❖ 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)</li> </ul>	June 27, 2014
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	August 28, 2013
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	N/A

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	See CDTL Review dated December 16, 2015 August 18, 2014
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	December 16, 2015 August 18, 2014
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )	See CDTL Reviews dated December 16, 2015 and August 18, 2014
• 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 CDTL Review dated August 18, 2014 (page 9)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	July 10, 2014 (OBP) April 10, 2014 (OBP) February 28, 2014 (OBP) February 4, 2014 (OBP)
❖ 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 checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	July 17, 2014 June 23, 2014 April 29, 2014
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <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> )	May 29, 2014 December 19, 2013

<b>Clinical Pharmacology</b> <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>	July 21, 2014 December 20, 2013
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	July 22, 2014 March 18, 2014
<b>Nonclinical</b> <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>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	June 23, 2014 March 14, 2014 December 3, 2013
❖ 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
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	August 12, 2014 July 21, 2014 November 20, 2013
❖ Microbiology Reviews	
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	March 3, 2014 November 15, 2013
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	August 12, 2014 (CDRH) July 16, 2014 (CDRH) June 12, 2014 (CDRH) March 14, 2014 (CDRH) December 5, 2013 (CDRH)
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	July 21, 2014 (page 148-149 of CMC review)
<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>	

<p>❖ Facilities Review/Inspection</p>	
<p><input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup></i>)</p>	<p>Date completed: November 20, 2015 August 12, 2014</p> <p><input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable (EER Summary Report included in CMC review pages 150-153)</p>
<p><input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) (<i>original and supplemental BLAs</i>)</p>	<p>Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation</p>
<p>❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)</p>	<p><input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)(pg. 4)</p>

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

**From:** CappellLynch, Callie  
**To:** "Joerg Pfeifer"  
**Subject:** RE: NDA 205692 Labeling comments - Lilly response to 7Dec2015 FDA version  
**Date:** Friday, December 11, 2015 1:20:00 PM  
**Attachments:** [12.11.15 FDA edits basaglar-kwikpen-proposed-ifu.docx](#)  
[12.11.15 FDA Edits nda205692-basaglar-proposed-uspi\(3\).docx](#)  
[12.11.15 FDA edits proposed-ppi.docx](#)  
**Importance:** High

---

Hi Joerg,

Please see the attached labeling documents with FDA edits. Please return revised documents by noon Monday, December 14<sup>th</sup>.

Thanks,  
Callie

---

**From:** Joerg Pfeifer [mailto:pfeifer\_joerg@lilly.com]  
**Sent:** Wednesday, December 09, 2015 5:10 PM  
**To:** CappellLynch, Callie  
**Cc:** Joerg Pfeifer  
**Subject:** RE: NDA 205692 Labeling comments - Lilly response to 7Dec2015 FDA version

Hi Callie,

Attached please find our response to the FDA label comments we received on Monday. Lilly has accepted most requests and made a few editorial corrections as well. As usual, we accepted FDA's comments as applicable which are thus no longer shown as tracked changes, and listed a rationale for any new proposals.

You will see that we agreed to removing [REDACTED] (b) (4) as FDA requested. Thank you again for arranging the TC this morning to discuss that issue. Lilly proposes some additional text to provide information on Basaglar in that section and we are proposing to just remove [REDACTED] (b) (4) instead of replacing it with a Basaglar only one.

Best regards,  
Joerg

**Joerg Pfeifer, Ph.D.**  
Advisor, Regulatory Affairs - US - Diabetes  
**Eli Lilly and Company**  
Drop Code 2543, Lilly Corporate Center, Indianapolis IN 46285 U.S.A.  
317.276.2146 (office) | [REDACTED] (b) (6) (mobile)  
[j\\_pfeifer@lilly.com](mailto:j_pfeifer@lilly.com) | [www.lilly.com](http://www.lilly.com)



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---

**From:** CappelLynch, Callie [<mailto:Callie.CappelLynch@fda.hhs.gov>]  
**Sent:** Monday, December 07, 2015 10:07 AM  
**To:** Joerg Pfeifer  
**Subject:** NDA 205692 Labeling comments  
**Importance:** High

Hi Joerg,

Please see the attached insulin glargine PI with FDA comments. We request that you send revised labeling by COB Wednesday, December 9<sup>th</sup>.

Thanks,  
Callie

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

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CALLIE C CAPPEL-LYNCH  
12/11/2015

**From:** CappellLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Subject:** NDA 205692 Labeling comments  
**Date:** Monday, December 07, 2015 10:07:00 AM  
**Attachments:** [12.7.15 FDA Edits-basaglar-proposed-uspi.docx](#)  
**Importance:** High

---

Hi Joerg,

Please see the attached insulin glargine PI with FDA comments. We request that you send revised labeling by COB Wednesday, December 9<sup>th</sup>.

Thanks,  
Callie

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

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CALLIE C CAPPEL-LYNCH  
12/07/2015

**From:** CappelLynch, Callie  
**To:** ["Joerg Pfeifer"](#)  
**Subject:** RE: process question about NDA 205,692  
**Date:** Tuesday, November 24, 2015 11:35:00 AM  
**Importance:** High

---

Hi Joerg,

We request that you submit a copy of the consent judgement referenced in the cover letter of your 10/16/15 resubmission. Please submit this document ASAP.

In regard to your email below, we plan to send labeling comments prior to the holiday (hoping for today). I will follow up on your inquiry regarding the orange book.

Thanks,  
Callie

---

**From:** Joerg Pfeifer [mailto:pfeifer\_joerg@lilly.com]  
**Sent:** Tuesday, November 24, 2015 7:03 AM  
**To:** CappelLynch, Callie  
**Cc:** Joerg Pfeifer  
**Subject:** RE: process question about NDA 205,692

Hi Callie,

Thank you so much for this information. That really assists Lilly in our planning.

I have a couple of additional questions.

Can you provide me an update on the review status in general. I am assuming that the review is continuing and no questions or inquiries have been identified at this time. Specifically, is there a time when I could expect label comments requiring a response? Also, will the Agency make a decision on Orange Book listing code for Basaglar at the time of approval or later. This is my first time of getting a new product to this stage and I am not familiar with the process. I anticipate a (b)(4) code but want to be sure I am prepared to provide any additional information you might need at that time.

Thank you again for your continued assistance to me on this application.

Best regards,  
Joerg

---

**From:** CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]  
**Sent:** Monday, November 23, 2015 2:45 PM  
**To:** Joerg Pfeifer  
**Subject:** RE: process question about NDA 205,692

Hi Joerg,

It is our current thinking that if approved, FDA would issue a press release. I'll update you if thinking changes.

Thanks,  
Callie

---

**From:** Joerg Pfeifer [[mailto:pfeifer\\_joerg@lilly.com](mailto:pfeifer_joerg@lilly.com)]  
**Sent:** Friday, November 13, 2015 10:01 AM  
**To:** CappelLynch, Callie  
**Subject:** Re: process question about NDA 205,692

Thank you. Have a great weekend

**Joerg Pfeifer, Ph.D.**  
Advisor, Regulatory Affairs - US - Diabetes  
**Eli Lilly and Company**  
Drop Code [2543, Lilly Corporate Center, Indianapolis IN 46285 U.S.A.](#)  
[317.276.2146](#) (office) | (b) (6) (mobile)  
[j\\_pfeifer@lilly.com](mailto:j_pfeifer@lilly.com) | [www.lilly.com](http://www.lilly.com)



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Sent from my iPhone

On Nov 13, 2015, at 10:00, CappelLynch, Callie <[Callie.CappelLynch@fda.hhs.gov](mailto:Callie.CappelLynch@fda.hhs.gov)> wrote:

Hi Joerg,

I can confirm the second part and I'm inquiring about the first. I'll get back to you as soon as I can.

Thanks,  
Callie

---

**From:** Joerg Pfeifer [[mailto:pfeifer\\_joerg@lilly.com](mailto:pfeifer_joerg@lilly.com)]  
**Sent:** Thursday, November 12, 2015 12:09 PM  
**To:** CappelLynch, Callie  
**Cc:** Joerg Pfeifer  
**Subject:** process question about NDA 205,692

Hello Callie,

I have two process questions for you on the topic of the Basaglar KwikPen NDA 205,692. Lilly is planning for the scenario that FDA takes approval action and would like to learn what actions FDA would take in that scenario.

- If approved, would FDA issue a press release? I understand that is typically done for new molecular entities and usually not done for fixed dose combinations. I don't know if there is a typical approach on a 505(b)(2) application such as this one.

- Unlike the tentative approval step, I assume FDA would post the approval letter and label (as well as other review documentation in the future) on *Drugs@FDA* if taking a final approval action. Can you please confirm.

Thank you for your assistance with this inquiry. This would help inform internal planning activities.

Joerg

**Joerg Pfeifer, Ph.D.**

Advisor, Regulatory Affairs - US - Diabetes

**Eli Lilly and Company**

Drop Code 2543, Lilly Corporate Center, Indianapolis IN 46285 U.S.A.

317.276.2146 (office) | [REDACTED] (b)(6) (mobile)

[j\\_pfeifer@lilly.com](mailto:j_pfeifer@lilly.com) | [www.lilly.com](http://www.lilly.com)

<image001.jpg>

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/s/  
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CALLIE C CAPPEL-LYNCH  
11/24/2015

**From:** CappelLynch, Callie  
**To:** ["Joerg Pfeifer"](#)  
**Subject:** RE: process question about NDA 205,692  
**Date:** Tuesday, November 24, 2015 12:04:00 PM  
**Attachments:** [FDA edits 11.24.15 Basaglar PL.docx](#)

---

Hi Joerg,

Please see attached labeling with FDA edits. We ask that you return revised labeling by COB December 1, 2015. Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "COMPANY'S response to FDA change or COMPANY comment."

If you have any questions, please contact me.

Thanks,  
Callie

---

**From:** Joerg Pfeifer [mailto:pfeifer\_joerg@lilly.com]  
**Sent:** Tuesday, November 24, 2015 7:03 AM  
**To:** CappelLynch, Callie  
**Cc:** Joerg Pfeifer  
**Subject:** RE: process question about NDA 205,692

Hi Callie,

Thank you so much for this information. That really assists Lilly in our planning.

I have a couple of additional questions.

Can you provide me an update on the review status in general. I am assuming that the review is continuing and no questions or inquiries have been identified at this time. Specifically, is there a time when I could expect label comments requiring a response? Also, will the Agency make a decision on Orange Book listing code for Basaglar at the time of approval or later. This is my first time of getting a new product to this stage and I am not familiar with the process. I anticipate a (b)(4) code but want to be sure I am prepared to provide any additional information you might need at that time.

Thank you again for your continued assistance to me on this application.

Best regards,  
Joerg

---

**From:** CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]

**Sent:** Monday, November 23, 2015 2:45 PM  
**To:** Joerg Pfeifer  
**Subject:** RE: process question about NDA 205,692

Hi Joerg,

It is our current thinking that if approved, FDA would issue a press release. I'll update you if thinking changes.

Thanks,  
Callie

---

**From:** Joerg Pfeifer [[mailto:pfeifer\\_joerg@lilly.com](mailto:pfeifer_joerg@lilly.com)]  
**Sent:** Friday, November 13, 2015 10:01 AM  
**To:** CappellLynch, Callie  
**Subject:** Re: process question about NDA 205,692

Thank you. Have a great weekend

**Joerg Pfeifer, Ph.D.**  
Advisor, Regulatory Affairs - US - Diabetes  
**Eli Lilly and Company**  
Drop Code [2543, Lilly Corporate Center, Indianapolis IN 46285 U.S.A.](#)  
[317.276.2146](#) (office) | (b) (6) (mobile)  
[j\\_pfeifer@lilly.com](mailto:j_pfeifer@lilly.com) | [www.lilly.com](http://www.lilly.com)



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Sent from my iPhone

On Nov 13, 2015, at 10:00, CappellLynch, Callie <[Callie.CappellLynch@fda.hhs.gov](mailto:Callie.CappellLynch@fda.hhs.gov)> wrote:

Hi Joerg,

I can confirm the second part and I'm inquiring about the first. I'll get back to you as soon as I can.

Thanks,  
Callie

---

**From:** Joerg Pfeifer [[mailto:pfeifer\\_joerg@lilly.com](mailto:pfeifer_joerg@lilly.com)]

**Sent:** Thursday, November 12, 2015 12:09 PM  
**To:** CappelLynch, Callie  
**Cc:** Joerg Pfeifer  
**Subject:** process question about NDA 205,692

Hello Callie,

I have two process questions for you on the topic of the Basaglar KwikPen NDA 205,692. Lilly is planning for the scenario that FDA takes approval action and would like to learn what actions FDA would take in that scenario.

- If approved, would FDA issue a press release? I understand that is typically done for new molecular entities and usually not done for fixed dose combinations. I don't know if there is a typical approach on a 505(b)(2) application such as this one.
- Unlike the tentative approval step, I assume FDA would post the approval letter and label (as well as other review documentation in the future) on *Drugs@FDA* if taking a final approval action. Can you please confirm.

Thank you for your assistance with this inquiry. This would help inform internal planning activities.

Joerg

**Joerg Pfeifer, Ph.D.**

Advisor, Regulatory Affairs - US - Diabetes

**Eli Lilly and Company**

Drop Code 2543, Lilly Corporate Center, Indianapolis IN 46285 U.S.A.

317.276.2146 (office) | (b)(6) (mobile)

[j\\_pfeifer@lilly.com](mailto:j_pfeifer@lilly.com) | [www.lilly.com](http://www.lilly.com)

<image001.jpg>

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CALLIE C CAPPEL-LYNCH  
11/24/2015



NDA 205692

**ACKNOWLEDGE -  
CLASS 1 COMPLETE RESPONSE**

Eli Lilly and Company  
Attention: Joerg Pfeifer, Ph.D.  
Advisor, Global Regulatory Affairs- U.S.  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Dr. Pfeifer:

We acknowledge receipt of your resubmission to your new drug application, dated and received, October 16, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Basaglar (insulin glargine) injection.

We consider this resubmission a complete, class 1 response to our action letter. Therefore, the user fee goal date is December 16, 2015.

If you have any questions, call me, at (301) 796- 8436.

Sincerely,

*{See appended electronic signature page}*

Callie Cappel-Lynch, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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CALLIE C CAPPEL-LYNCH  
10/26/2015

**From:** CappellLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Subject:** NDA 205692 information request  
**Date:** Monday, October 19, 2015 1:37:00 PM  
**Importance:** High

---

Hi Joerg,

Please see the information request below for NDA 205692.

Please **confirm that all the commercial manufacturing/testing/packaging facilities listed in the NDA at the time of the Tentative Approval currently have acceptable GMP status.**

Thanks,  
Callie

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CALLIE C CAPPEL-LYNCH  
10/19/2015

**From:** CappelLynch, Callie  
**To:** "[Joerg Pfeifer](#)"  
**Subject:** RE: NDA 205692 action  
**Date:** Monday, August 18, 2014 10:24:00 AM

---

Hi Joerg,

We have one very minor edit on the PPI and IFU pen sharing language in order to maintain consistency with the language in the safety labeling change request letter. Please correct the third sentence of this section to the following and submit this to the NDA:

You may give another person an infection or get an infection from them.

Please contact me if you have any questions. With regard to timing of the action, we are finalizing a number of things and at this time, I do not have an update.

Thanks,  
Callie

---

**From:** Joerg Pfeifer [mailto:pfeifer\_joerg@lilly.com]  
**Sent:** Monday, August 18, 2014 10:15 AM  
**To:** CappelLynch, Callie  
**Subject:** NDA 205692 action

Good morning Callie,

I understand you have, as usual, a lot going on today. Can you give me any comments on when I might receive an action letter from FDA on NDA 205692 if one is issued today? As you can imagine, I am getting a lot of inquiries about timing (will it happen today, likely in afternoon or late afternoon).

Thank you if you can share anything with me.

Joerg

**Joerg Pfeifer, Ph.D.**

Advisor, Regulatory Affairs - US - Diabetes

**Eli Lilly and Company**

Drop Code 2543, Lilly Corporate Center, Indianapolis IN 46285 U.S.A.

317.276.2146 (office) | (b) (6) (mobile)

[j\\_pfeifer@lilly.com](mailto:j_pfeifer@lilly.com) | [www.lilly.com](http://www.lilly.com)



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CALLIE C CAPPEL-LYNCH  
08/18/2014

**From:** CappelLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Subject:** NDA 205692 PPI and IFU  
**Date:** Thursday, August 14, 2014 11:17:00 AM  
**Attachments:** [FDA comments 8.14.14 NDA 205692 PPI.docx](#)

---

Hi Joerg,

Please see the attached PPI with very minor revision. We do not have any additional comments on the IFU and agree to the changes you made in the label which you emailed on 8/11/14. I hope to have the PI out to you later this afternoon.

Regarding the c/c labeling, I apologize, but we do have one additional comment : Please revise the "Rx Only" statement to be less prominent than the "For Single Patient Use Only" statement on both the Carton and Container. If you wish to send me this by email, I'll have the requesting reviewer look at it before final submission.

If you have any questions, please let me know.

Thanks,

Callie Cappel-Lynch  
Regulatory Project Manager  
Food and Drug Administration  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
301-796-8436

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CALLIE C CAPPEL-LYNCH  
08/14/2014

**From:** CappelLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Subject:** RE: NDA 205692 PPI and IFU  
**Date:** Thursday, August 14, 2014 11:29:00 AM  
**Attachments:** [FDA Comments 8.14.14 NDA 205692 PI.docx](#)

---

Hi Joerg,

Earlier than expected, please also see the attached FDA comments on the PI for NDA 205692. I'll be out of my office until around 1:30, but feel free to call after that if you have any questions.

Thanks,  
Callie

---

**From:** CappelLynch, Callie  
**Sent:** Thursday, August 14, 2014 11:18 AM  
**To:** Joerg Pfeifer (pfeifer\_joerg@lilly.com)  
**Subject:** NDA 205692 PPI and IFU

Hi Joerg,

Please see the attached PPI with very minor revision. We do not have any additional comments on the IFU and agree to the changes you made in the label which you emailed on 8/11/14. I hope to have the PI out to you later this afternoon.

Regarding the c/c labeling, I apologize, but we do have one additional comment : Please revise the "Rx Only" statement to be less prominent than the "For Single Patient Use Only" statement on both the Carton and Container. If you wish to send me this by email, I'll have the requesting reviewer look at it before final submission.

If you have any questions, please let me know.

Thanks,

Callie Cappel-Lynch  
Regulatory Project Manager  
Food and Drug Administration  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
301-796-8436

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CALLIE C CAPPEL-LYNCH  
08/14/2014

**From:** CappelLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Subject:** NDA 205692 Information Request  
**Date:** Tuesday, August 12, 2014 8:42:00 AM

---

Hi Joerg,

I believe this information is in the NDA submission, but for ease of review, we request that you send HbA1c and insulin dose plots for the following two patients who appeared to have a relatively high titer antibody response:

In trial ABEB patient 2009

In trial ABEC patient 1005

Please also include relevant hypoglycemia data for these two patients. We are requesting this as soon as possible, but no later than the end of the day today. If there are any issues, please reach me at this number (b) (4).

Thanks,

Callie Cappel-Lynch  
Regulatory Project Manager  
Food and Drug Administration  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
301-796-8436

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/s/  
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CALLIE C CAPPEL-LYNCH  
08/12/2014

**From:** CappelLynch, Callie  
**To:** ["Joerg Pfeifer"](#)  
**Subject:** NDA 205692 PI  
**Date:** Thursday, August 07, 2014 4:45:00 PM  
**Attachments:** [PI 8.7.14 nda205692-basaglar-proposed-uspi.docx](#)  
[Clean PI 8.7.14 nda205692-basaglar-proposed-uspi.docx](#)  
[image001.png](#)

---

Hi Joerg,

Please see the attached PI for NDA 205692 with additional FDA comments. We request that you return all labeling pieces by COB Monday, August 11, 2014. If you have any questions, please contact me (with the exception of tomorrow when Julie will be covering).

Thanks,  
Callie

---

**From:** Joerg Pfeifer [mailto:pfeifer\_joerg@lilly.com]  
**Sent:** Thursday, August 07, 2014 2:08 PM  
**To:** CappelLynch, Callie  
**Cc:** Van der Waag, Julie  
**Subject:** RE: NDA 205692 PPI and IFU

Hi Callie,

Thank you for providing me these documents today. I will follow up with you on Monday about returning them or do you have a deadline for me on these?

Best regards,  
Joerg

Joerg Pfeifer PhD  
Regulatory Advisor, Diabetes Regulatory Affairs  
**Eli Lilly and Company**  
Office: 317-276-2146   
Mobile:  (b) (6)   
Email: [j\\_pfeifer@lilly.com](mailto:j_pfeifer@lilly.com) | Web: <http://www.lilly.com>



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**From:** CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]  
**Sent:** Thursday, August 07, 2014 2:06 PM  
**To:** Joerg Pfeifer  
**Cc:** Van der Waag, Julie  
**Subject:** NDA 205692 PPI and IFU

Hi Joerg,

Please see the attached PPI and IFU with FDA comments (both tracked changes and clean versions attached). If you have any questions, please contact me.

I will be on leave tomorrow, Friday, August 8<sup>th</sup>. However, should the comments on the PI be ready for send out, Julie Van der Waag (Chief, Project Management Staff) will be covering for me and will send these out to you. She is copied on this email and will be covering for me for emergencies only while I'm out. I'll return to the office on Monday, August 11<sup>th</sup>.

Thanks,

Callie Cappel-Lynch  
Regulatory Project Manager  
Food and Drug Administration  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
301-796-8436

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CALLIE C CAPPEL-LYNCH  
08/11/2014

**From:** CappelLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Cc:** [Van der Waag, Julie](#)  
**Subject:** NDA 205692 PPI and IFU  
**Date:** Thursday, August 07, 2014 2:06:00 PM  
**Attachments:** [Clean insulin glargine injection \(basaglar\) 205692 PPI Review 8.7.14.docx](#)  
[Clean insulin glargine injection \(basaglar\) KwikPen 205692 IFU Review 8.7.14.doc](#)  
[Tracked Changes insulin glargine injection \(basaglar\) 205692 PPI Review 8.7.14.docx](#)  
[Tracked Changes insulin glargine injection \(basaglar\) KwikPen 205692 IFU Review 8.7.14.doc](#)

---

Hi Joerg,

Please see the attached PPI and IFU with FDA comments (both tracked changes and clean versions attached). If you have any questions, please contact me.

I will be on leave tomorrow, Friday, August 8<sup>th</sup>. However, should the comments on the PI be ready for send out, Julie Van der Waag (Chief, Project Management Staff) will be covering for me and will send these out to you. She is copied on this email and will be covering for me for emergencies only while I'm out. I'll return to the office on Monday, August 11<sup>th</sup>.

Thanks,

Callie Cappel-Lynch  
Regulatory Project Manager  
Food and Drug Administration  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
301-796-8436

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CALLIE C CAPPEL-LYNCH  
08/11/2014

**From:** CappelLynch, Callie  
**To:** ["Joerg Pfeifer"](#)  
**Subject:** RE: labeling comments and review status for NDA 205692  
**Date:** Tuesday, July 22, 2014 4:17:00 PM  
**Attachments:** [image001.png](#)  
[PI sent to Lilly 7.22.14.docx](#)  
[PI sent to Lilly 7.22.14 clean.docx](#)

---

Hi Joerg,

Please see attached the PI with FDA comments as well as a clean version of the PI for NDA 205692. We are requesting that you return the labeling by COB July 29, 2014. If you have any questions, please do not hesitate to contact me.

Thanks,  
Callie

---

**From:** Joerg Pfeifer [mailto:pfeifer\_joerg@lilly.com]  
**Sent:** Tuesday, July 22, 2014 6:03 AM  
**To:** CappelLynch, Callie  
**Subject:** RE: labeling comments and review status for NDA 205692

Good morning Callie,

Thank you very much for the update yesterday late afternoon. That allowed me to have a calm evening without work. 😊

Best regards,  
Joerg

Joerg Pfeifer PhD  
Regulatory Advisor, Diabetes Regulatory Affairs  
**Eli Lilly and Company**  
Office: 317-276-2146   
Mobile: (b) (6)   
Email: [j\\_pfeifer@lilly.com](mailto:j_pfeifer@lilly.com) | Web: <http://www.lilly.com>

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**From:** CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]  
**Sent:** Monday, July 21, 2014 5:53 PM  
**To:** Joerg Pfeifer  
**Subject:** RE: labeling comments and review status for NDA 205692

Hi Joerg,

I just wanted to provide an update that I still have not received final clearance on the labeling comments. I will continue to wait for this, however, we may need to send the comments tomorrow.

Thanks,  
Callie

---

**From:** CappelLynch, Callie  
**Sent:** Monday, July 21, 2014 3:00 PM  
**To:** 'Joerg Pfeifer'  
**Subject:** RE: labeling comments and review status for NDA 205692

Hi Joerg,

I am waiting on final clearance of the labeling comments. I'm still hopeful that I will be able to send them by the end of the day today. The CMC information is being review and thus far there are no additional comments. I do not expect that there will be additional inquiry.

Thanks,  
Callie

---

**From:** Joerg Pfeifer [[mailto:pfeifer\\_joerg@lilly.com](mailto:pfeifer_joerg@lilly.com)]  
**Sent:** Monday, July 21, 2014 2:13 PM  
**To:** CappelLynch, Callie  
**Subject:** labeling comments and review status for NDA 205692

Hi Callie,

I am contacting you to learn if you can share anything with me about the status of the FDA label response and the status of the CMC review for this BASAGLAR KwikPen (insulin glargine) NDA. Is it still likely that you will send me label comments by the end of business today? Also, are you able to let me know if the review of CMC information we submitted, including the specifications proposal a couple of weeks ago, has been completed by the team or if there still is a possibility of getting further inquiries on that topic.

Thank you,  
Joerg

Joerg Pfeifer PhD  
Regulatory Advisor, Diabetes Regulatory Affairs  
**Eli Lilly and Company**  
Office: 317-276-2146   
Mobile: (b) (6)   
Email: [j\\_pfeifer@lilly.com](mailto:j_pfeifer@lilly.com) | Web: <http://www.lilly.com>

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CALLIE C CAPPEL-LYNCH  
07/22/2014

## MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** June 26, 2014

**Application Number:** NDA 205692

**Product Name:** insulin glargine injection

**Sponsor/Applicant Name:** Eli Lilly and Company

**Subject:** Clarification of Chemistry, Manufacturing, and Controls Information Request

### FDA Participants

Suong Tran, Ph.D.	CMC Lead, ONDQA
Danae Christodoulou, Ph.D.	Branch Chief, (Acting) ONDQA
Muth Ramaswamy, Ph.D.	CMC Reviewer, ONDQA
Xavier Ysem, Ph.D.	CMC Reviewer, ONDQA
Callie Cappel-Lynch, Pharm.D.	Regulatory Project Manager, DMEP

### Sponsor Participants

Joerg Pfeifer	US Regulatory Affairs
Elizabeth Bearby	US Regulatory Affairs
David MacLaren	CMC Regulatory Affairs
Allison Kennington	CMC Regulatory Affairs
Elizabeth Kramer	Analytical Chemistry
Patrick Blacha	Manufacturing Science
Rebecca Elliott	Statistics
Ben Dai	Drug Product Formulation
Karin Kirch	CMC Project Management

### 1.0 BACKGROUND:

On October 18, 2013, NDA 205692 was submitted by Eli Lilly and Company to FDA. On June 10, 2014, the following information request was sent:

“We are reviewing the limits you are proposing for your total product related impurities, (b) (4) (b) (4), and largest unspecified impurity (b) (4) (b) (4). The proposed limits differ across the NDA, and it’s not clear which product impurity limits you are proposing to be the regulatory limits. In addition, there is very limited information provided to support your proposed limits, i.e. a 4-week rat toxicity study #8259267 with lot number A889460. In this study (b) (4) % total impurities and (b) (4) % (b) (4) (b) (4) were tested. Your proposed limits for total product related impurities, (b) (4) (b) (4), and largest unspecified impurity (b) (4) (b) (4).

(b) (4) are not supported by the levels observed in toxicology study batch (A889460) and therefore we cannot conclude that these limits on impurities have been adequately justified.”

On June 23, 2014, Lilly responded to this information request.

On June 24, 2014, the following information request was sent:

“Based on all available data in your NDA, revise your product specification to NMT (b) (4)% Total impurities, NMT (b) (4)% for Specified Impurity (b) (4) NMT (b) (4)% for largest unspecified impurity , and (b) (4)% for (b) (4) . Update your drug product section with revised specification.”

On June 25, 2014, Lilly requested a teleconference to discuss and gain alignment on how to address this information request.

## 2.0 DISCUSSION:

Lilly asked if FDA’s revised specification is for both the shelf life expiration and in use expiration.

FDA replied that it is for both because it will be the regulatory specification for the NDA.

FDA stated the following: “The data currently in the NDA does not support the applicant’s proposed limits. We acknowledge the E.U.- Lantus certificate of analysis (C of A) that you provided to us on June 23, 2014. Since the NDA is a 505(b)(2) application relying on FDA’s finding of safety and efficacy for Lantus, proposed limits of impurities that are higher than the limits in the E.U.- Lantus certificate of analysis should be supported by impurity exposure levels in clinical and toxicology batches. You have provided primary stability data in support of your proposed limits, but we need stability data showing the same level of impurities as the exposure levels from clinical and toxicology studies.

Lilly stated that the specification on Lantus C of A is related to their analytical method. Their method does not have same capability for determining impurities as the Lilly method. In addition, the in use stability data provided in the NDA is representative of impurity exposure in clinical studies because patients were taking the product home for 4 weeks at room temperature and using it as they normally would as prescribed. The in use stability study simulated the actual patient use in the clinical studies. The applicant believes that the in use data represents the worst-case scenario.

Lilly would like to propose (b) (4)% total impurity, (b) (4)% (b) (4) and (b) (4)% (b) (4) and accept other recommendation such as (b) (4)% for the largest unspecified impurity. FDA requested this new proposal to be submitted as an amendment to the NDA for consideration.

FDA’s additional comments regarding the drug substance specification:

1. Modify the acceptance criteria for the identity to be more precise:

- a. For the Peptide Map test, instead of “(b) (4)”, provide criteria of comparison to the sample digestion (i.e. relative retention times of the sample digestion are within (b) (4)% of the reference digestion, and the relative peaks heights (b) (4)%).
  - b. Revise the acceptance criteria similarly for the HPLC test (i.e. retention time sample within (b) (4)% of the retention time of the standard)
2. Regarding impurities, provide acceptance criteria for:
    - a. Each known impurity
    - b. Largest unknown impurity, and
    - c. Total impurities (known + unknown)
  3. Tighten the acceptance criteria of (b) (4) (currently NMT (b) (4)%)  
Lilly agreed to take our request under consideration and follow-up.

### **3.0 ACTION ITEMS:**

Lilly will submit their counter proposal for our review.

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CALLIE C CAPPEL-LYNCH  
06/27/2014

**From:** CappellLynch, Callie  
**To:** "Joerg Pfeifer"  
**Subject:** RE: information and request regarding today's TC on NDA 205692  
**Date:** Friday, June 27, 2014 9:25:00 AM  
**Attachments:** [image001.png](#)

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Hi Joerg,

Please see the below FDA comments regarding the drug substance specifications.

1. Modify the acceptance criteria for the identity to be more precise:
  - a. For the Peptide Map test, instead of “ (b) (4) ”, provide criteria of comparison to the sample digestion (i.e. relative retention times of the sample digestion are within (b) (4) % of the reference digestion, and the relative peaks heights (b) (4) %).
  - b. Revise the acceptance criteria similarly for the HPLC test (i.e. retention time sample within (b) (4) % of the retention time of the standard)
2. Regarding impurities, provide acceptance criteria for:
  - a. Each known impurity
  - b. Largest unknown impurity, and
  - c. Total impurities (known + unknown)
3. Tighten the acceptance criteria of (b) (4) (currently NMT (b) (4) %)

If you have any questions, please contact me.

Thanks,  
Callie

---

**From:** Joerg Pfeifer [mailto:pfeifer\_joerg@lilly.com]  
**Sent:** Thursday, June 26, 2014 2:30 PM  
**To:** CappellLynch, Callie  
**Subject:** RE: information and request regarding today's TC on NDA 205692

Thank you.

Joerg Pfeifer PhD  
Regulatory Advisor, Diabetes Regulatory Affairs  
**Eli Lilly and Company**  
Office: 317-276-2146   
Mobile: (b) (6)   
Email: [j\\_pfeifer@lilly.com](mailto:j_pfeifer@lilly.com) | Web: <http://www.lilly.com>



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**From:** CappelLynch, Callie [<mailto:Callie.CappelLynch@fda.hhs.gov>]  
**Sent:** Thursday, June 26, 2014 2:26 PM  
**To:** Joerg Pfeifer  
**Subject:** RE: information and request regarding today's TC on NDA 205692

Hi Joerg,

Below are the FDA attendees for the teleconference. I will follow up on the drug substance specifications.

Suong Tran, Ph.D.	CMC Lead, ONDQA
Danae Christodoulou, Ph.D.	Branch Chief, ONDQA
Muth Ramaswamy, Ph.D.	Reviewer, ONDQA
Xavier Ysern, Ph.D.	Reviewer, ONDQA
Callie Cappel-Lynch, Pharm.D.	Regulatory Project Manager, DMEP

Thanks,  
Callie

---

**From:** Joerg Pfeifer [[mailto:pfeifer\\_joerg@lilly.com](mailto:pfeifer_joerg@lilly.com)]  
**Sent:** Thursday, June 26, 2014 12:42 PM  
**To:** CappelLynch, Callie  
**Cc:** Joerg Pfeifer  
**Subject:** information and request regarding today's TC on NDA 205692

Hi Callie,

Thank you again for scheduling the teleconference this morning on the drug product specifications requested by FDA for the insulin glargine drug product described in NDA 205692. Please find below the attendee list from Lilly which includes those who spoke during the meeting and were in the room observing.

Joerg Pfeifer – US Regulatory Affairs  
Elizabeth Bearby – US Regulatory Affairs  
David MacLaren – CMC Regulatory Affairs  
Allison Kennington – CMC Regulatory Affairs  
Elizabeth Kramer – Analytical Chemistry  
Patrick Blacha – Manufacturing Science  
Rebecca Elliott – Statistics  
Ben Dai – Drug Product Formulation  
Karin Kirch – CMC Project Management

Can you send me a list of FDA participants? Also, we took note of the request on changes to the drug substance specifications made at the end of the call. Would it be possible to send those to

me by email as well? We took notes but want to make sure we respond appropriately and quickly to those as well. We are already working on the counterproposal for the drug product specifications verbalized during the call and will submit that asap in an amendment to the NDA.

Best regards,  
Joerg

Joerg Pfeifer PhD  
Regulatory Advisor, Diabetes Regulatory Affairs  
**Eli Lilly and Company**  
Office: 317-276-2146   
Mobile:  (b) (6)   
Email: [j\\_pfeifer@lilly.com](mailto:j_pfeifer@lilly.com) | Web: <http://www.lilly.com>

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*Lilly*

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CALLIE C CAPPEL-LYNCH  
06/27/2014

**From:** CappelLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Subject:** NDA 205692 Information Request  
**Date:** Tuesday, June 24, 2014 11:28:00 AM

---

Hi Joerg,

Please see the below information request. If you have any questions, please contact me.

Based on all available data in your NDA, revise your product specification to NMT <sup>(b)</sup><sub>(4)</sub>% Total impurities, NMT <sup>(b)</sup><sub>(4)</sub>%, for Specified Impurity <sup>(b)</sup><sub>(4)</sub> NMT <sup>(b)</sup><sub>(4)</sub>% for largest unspecified impurity, and <sup>(b)</sup><sub>(4)</sub>% for <sup>(b)</sup><sub>(4)</sub>. Update your drug product section with revised specification.

Thanks,  
Callie Cappel-Lynch  
Regulatory Project Manager  
Food and Drug Administration  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
301-796-8436

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CALLIE C CAPPEL-LYNCH  
06/24/2014

**From:** CappelLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Subject:** NDA 205692 Information Request  
**Date:** Tuesday, June 10, 2014 3:35:00 PM

---

Hi Joerg,

Please see the information request below for NDA 205692. If you have any questions, please contact me.

We are reviewing the limits you are proposing for your total product related impurities, (b) (4) and largest unspecified impurity (b) (4). The proposed limits differ across the NDA, and it's not clear which product impurity limits you are proposing to be the regulatory limits. In addition, there is very limited information provided to support your proposed limits, i.e. a 4-week rat toxicity study #8259267 with lot number A889460. In this study (b) (4) % total impurities and (b) (4) % (b) (4) were tested. Your proposed limits for total product related impurities, (b) (4) and largest unspecified impurity (b) (4) are not supported by the levels observed in toxicology study batch (A889460) and therefore we cannot conclude that these limits on impurities have been adequately justified.

We request that you:

Provide clarification of the specifications you are seeking for your product impurities in Basiglar that differ from Lantus.

Provide the data to support your proposed limits on impurities or revise your drug product specification to have limits based on level of impurities observed in clinical and non-clinical batches.

Please provide the requested information by COB Friday, June 13, 2014.

Thanks,  
Callie Cappel-Lynch  
Regulatory Project Manager  
Food and Drug Administration  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
301-796-8436

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CALLIE C CAPPEL-LYNCH  
06/10/2014

## **Kumar, Priyanka**

---

**From:** Kumar, Priyanka  
**Sent:** Monday, May 12, 2014 9:17 AM  
**To:** 'j\_pfeifer@lilly.com'  
**Subject:** Regarding NDA 205692

We understand that you are seeking further clarification on question 3d of the CMC information request sent on 4/14/14. The intent of this communication is to clarify our information request. We infer that you may not have data for some of the questions raised in our information request and that additional studies will have to be conducted.

We requested additional characterization information on the self-associated states of your insulin glargine drug product (relative content of monomers, dimers, hexamers) and characterization data by methods such as digital scanning calorimetry or analytical ultracentrifugation in support of the proposed zinc content of (b) (4) mcg per 100 Units of product.

Similar type of characterization information, on Lantus as additional comparative information on the two products, would be helpful to our understanding of your product as a stand-alone product and also as compared to Lantus, with the understanding that any difference(s), if observed, may already be qualified by the existing nonclinical and/or clinical information in the NDA. (Such difference(s) will be considered as part of our totality-of-the-evidence review approach). Therefore, we request that you provide us this characterization data to the extent available and practicable during this NDA review cycle for our ongoing review.

If you have any questions please let me know,

Thank you,

*Priyanka Kumar, Pharm.D.  
Regulatory Project Manager  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
CDER, FDA  
Phone: (240)-402-3722  
Fax: (301)-796-9749*

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/s/  
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PRIYANKA KUMAR  
05/23/2014

**From:** CappellLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Subject:** NDA 205692 CMC Information Request  
**Date:** Monday, April 14, 2014 1:51:00 PM

---

Hi Joerg,

Please see the CMC information request below for NDA 205692. If you have any question feel free to contact myself or the CMC project manager, Priyanka Kumar.

1. We note that the accelerated stability data (i.e., higher rate of (b) (4) formation under thermal stress) show differences between your drug product and Lantus. While we agree that the formation of (b) (4) can be controlled via appropriate storage conditions, we also recommend that you revise your (b) (4) specification from NMT (b) (4) % to NMT (b) (4) % as additional control.
2. Revise your % total impurities (by RP HPLC) for drug product to NMT (b) (4) % or to the levels observed in toxicology study batches. Monitor and report all individual product related impurities exceeding the level of (b) (4) % during release and stability.
3. Provide the following:
  - a. Additional real-time stability data to support the 24 month shelf-life for your drug product manufactured at Lilly France (b) (4) or propose a shorter expiration dating period to reflect the actual real-time stability data in the application.
  - b. A comparison of intact mass data for non-reduced form, reduced (b) (4), and reduced (b) (4) for Lantus and Lilly Glargine.
  - c. Dose response curves for a representative batch of Lantus, LY2963016 drug product and the reference standard used in the potency comparability assessment. If applicable, provide a comparison of the dose response curve for a comparable concentration of human insulin.
  - d. What is the self-associated state of insulin Glargine in (b) (4) zinc containing (b) (4) drug product formulation?



Thanks,

Callie

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CALLIE C CAPPEL-LYNCH  
04/14/2014

**From:** CappellLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Subject:** NDA 205692 Labeling Comments  
**Date:** Monday, April 21, 2014 10:46:00 AM

---

Hi Joerg,

Please see the following labeling comments below for NDA 205692. If you have any questions, please contact me.

**Pen Label**

1. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name.

**Carton Labeling**

1. See number 1 above.
2. Add “For Single Patient Use Only” to the principal display panel.

Thanks,  
Callie

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CALLIE C CAPPEL-LYNCH  
04/21/2014



NDA 205692

## INFORMATION REQUEST

Eli Lilly and Company  
Attention: Joerg Pfeifer, Ph.D.  
Advisor, Global Regulatory Affairs- U.S.  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Dr. Pfeifer:

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

We are reviewing your application, as amended, and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

### **Clinical**

1. Our review findings indicate that the treatment difference between LY2963016 and US-approved Lantus in T1DM patients was +0.19% in HbA1c change from baseline to week 24. The 95% confidence interval showed that the criterion was met for LY2963016 being non-inferior to US-approved Lantus (the upper limit of the CI of +0.36% < 0.4%). The criterion was also met for LY2963016 being inferior to US-approved Lantus (the lower limit of the confidence interval of +0.02% is greater than 0). The sensitivity analysis, MMRM was similar to the primary ANCOVA analysis with LOCF. However, LY2963016 was not inferior to EU-approved Lantus (lower limit of the confidence interval -0.08 was less than 0).

Please submit any available data that can help explain these findings, including, but not limited to, subject demographics, subject disease characteristics, extent of titration of insulins, chemistry, manufacturing, and/or pharmacokinetic or pharmacodynamic differences between US-approved and EU-approved Lantus.

### **Statistics**

2. For Study ABEB, please provide subgroup analyses for the primary efficacy endpoint, HbA1c change from baseline to Week 24 using the same subgroups as the Week 52 endpoint.

## **Device**

3. You have indicated that LY2963016 will be made available in a 3 mL cartridge sealed in a prefilled pen injector (KwikPen). The submission indicates that changes were made with regard to the pen injector, i.e., the plunger component which can impact the patient safety. Please provide the side-by-side comparison of the previous KwikPen device and the new and modified KwikPen in terms of design, patient/drug contacting device components, materials used in manufacturing including [REDACTED] (b) (4) [REDACTED] etc., of the new prefilled pen injector (KwikPen). Information in regards to the device is limited.
4. Page 44/171 states “KwikPen is classified as a limited duration skin contact device. ... plastic materials used in the KwikPen platform have been evaluated according to the guidance in ISO 10993-1”. As FDA clears or approves medical devices and biocompatibility assessments in medical device applications are considered for evaluating post-manufacturing residuals in the final finished device, limitations apply when utilizing raw material biocompatibility for medical product clearance or approval. Based on the identified classification, please provide complete biocompatibility study reports for FDA evaluation. If you have leveraged the biocompatibility studies based on existing predicate device or have submitted the reports elsewhere in the submission, you may provide the information for evaluation.
5. We cannot locate performance testing information on your glass cylinder and the enclosed plunger. We recommend that you follow ISO 13926-1 and ISO 13926-2 when conducting your performance testing. Please provide us your reports including test protocol, test data, pass/fail criteria, and test results.

## **Immunogenicity**

6. Your data indicated that the number of patients with detectable insulin antibodies at week 52 in study ABEB was similar to LANTUS (LY2963016: 40.4% to LANTUS: 39.3%). However, in the 24 week ABEC study, at least 4% more subjects had [REDACTED] (b) (4) antibodies than those treated with LANTUS (Table ABEC 12.14). There is concern regarding the clinical impact of these antibodies. To help elucidate this concern please provide the following information:
  - a. Samples that are positive for the presence of anti-drug antibody at least one time point during the course of the study, should be considered to be an anti-drug antibody (ADA) positive sample, regardless of the patient’s ADA status at baseline. Confirm that overall number of ADA+ patient from both treatment group included patients who were ADA+ for at least one time-point of the study.
  - b. You are using antibodies raised against LY2963016 in your assays as reference standards. Provide data demonstrating that these antibodies bind with equal affinity to Lantus and LY2963016.

- c. Provide the titer of the antibodies induced in ADA positive samples.
7. Please provide data on the crossreactivity of the antibodies to LY2963016 with native insulin. Additionally, if you have data on the neutralizing capacity of these antibodies, please provide it for review.

**Clinical Pharmacology**

8. We appreciate your timely response with the submission of the bioanalytical reports for the PKPD studies ABEO, ABEN, and ABEM. However, we are looking for additional specific information on the c-peptide assay as the primary PK comparison was based on the baseline-corrected data. Please provide us the following information:
  - a. Assay method validation report(s) for the c-peptide assay and any associated c-peptide bioanalytical reports for individual PKPD studies.
  - b. Clarify the site(s) where this assay was conducted.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796 8436.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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JEAN-MARC P GUETTIER  
04/08/2014

**From:** CappelLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Subject:** NDA 205692 Information Request  
**Date:** Tuesday, March 18, 2014 2:30:00 PM

---

Hi Joerg,

Please see the information request below. If you have any questions, please contact me. We request that you respond by COB Friday, March 21, 2014.

We are unable to locate the full bioanalytical reports for Studies ABEO, ABEN, and ABEM in your submission. Although sections 11.2 of these study reports summarize the bioanalytical results, it appears that separate reports exist describing the details for the bioanalytical methods, e.g., for the study ABEO under section 11.2 it is mentioned that "Detailed records from study sample analysis are located in study files for project 8269-194". Similarly, section 11.2 for Study ABEN refers to study files for project 8265-736, and STUDY ABEM refers to project 8265-928. Please submit the full bioanalytical reports for studies ABEO, ABEN, ABEM, ABEA and ABEE for Agency's review or indicate where we can locate them.

Thank you,  
Callie

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/s/  
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CALLIE C CAPPEL-LYNCH  
03/18/2014



NDA 205692

**INFORMATION REQUEST**

Eli Lilly and Company  
Attention: Joerg Pfeifer, Ph.D.  
Advisor, Global Regulatory Affairs- U.S.  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Dr. Pfeifer:

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

We are reviewing the microbiology section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response by March 4, 2014.

1. We refer to the (b) (4) validation studies conducted to support manufacture at the (b) (4) site. The submitted validation studies did not include the establishment of (b) (4) product. We note the inclusion of results from (b) (4) . Please provide data to support the proposed in process (b) (4)
2. (b) (4)
3. We refer to the dye ingress test described in the January 22, 2014, submission that was part of the pharmaceutical development program to support the proposed container-closure system. We also refer to the container-closure test proposed (b) (4)

4. We refer to the January 22, 2014, response regarding the (b) (4) studies conducted in 2011, 2012, and 2013. Confirm that the proposed (b) (4) no new worst case products were required to support the proposed manufacturing process.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796-8436.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, MD  
Director, Acting  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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JEAN-MARC P GUETTIER  
02/04/2014



DEPARTMENT OF HEALTH AND HUMAN  
SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 205692

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Eli Lilly and Company  
Lilly Corporate Center  
Drop Code 2543  
Indianapolis, IN 46285

Attention: Joerg Pfeifer, Ph.D.  
Advisor – US Regulatory Affairs

Dear Dr. Pfeifer:

Please refer to your New Drug Application (NDA) dated October 17, 2013, received October 18, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Insulin Glargine [rDNA origin] Injection, 100 units/mL.

We also refer to your December 6, 2013, correspondence, received December 6, 2013, requesting review of your proposed proprietary name, Basaglar. We have completed our review of the proposed proprietary name, Basaglar, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your December 6, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Callie Cappel Lynch at (301) 796-8436.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
01/23/2014



NDA 205692

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Eli Lilly and Company  
Attention: Joerg Pfeifer, Ph.D.  
Advisor, Global Regulatory Affairs- U.S.  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Dr. Pfeifer:

Please refer to your New Drug Application (NDA) dated October 17, 2013, received October 18, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for insulin glargine [rDNA origin] for injection.

We also refer to your amendments dated December 6 (2), 9, 16, and 19, 2013.

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 August 18, 2014.

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 July 21, 2014.

During our filing review of your application, we identified the following potential review issues and request that you submit the following information:

### Clinical Pharmacology

1. We are unable to run the S-Plus scripts for PKPD studies provided with the submission using the datasets indicated within the scripts (Note that we used SAS to read \*.xpt files and export as \*.csv files). For example, the "abee\_pd\_analysis.ssc" script, using the dataset "ABEE\_WNL\_PD\_29JAN2013\_O\_MOD.csv" does not run beyond the initial data read steps. Please recheck the submitted S-plus scripts and data-sets and provide clear instructions on any necessary steps that the reviewer need to follow in order to re-run your analyses.

### Statistics

2. Please submit the Statistical Analysis Plans (SAPs) for studies ABEB and ABEC.

### Microbiology

3. DMF 16307 does not contain a letter of authorization for NDA 205-692. We note inclusion of the letter of authorization dated September 10, 2013 in the NDA but the DMF does not include similar authorization. Please have the DMF holder submit a copy of the authorization letter to the DMF.
4. The container-closure integrity studies described in Module 3.2.P.2.4.1.3 do not contain sufficient details to evaluate the test method and results. Provide the following information for the dye ingress test method:
  - a. The concentration of (b) (4) used;
  - b. The test conditions. Include the duration of (b) (4) used;
  - c. The inspection method (i.e., visual or spectrophotometric);
  - d. A description of the positive control and/or the limit of detection for the assay.
5. The proposed manufacturing process at (b) (4) includes collection of a bioburden sample after (b) (4) thus has minimal microbial value. Revise the bioburden step to (b) (4).
6. Minimal information was provided on (b) (4) site. Provide a summary of the validation results for (b) (4) process. Alternately, provide the incoming endotoxin specification if components are received (b) (4).
7. The sterilization validation summaries provided in the (b) (4) validation package did not provided sufficient detail on the proposed (b) (4). Provide the following information:  
(b) (4)

(b) (4)

8. We note that the (b) (4) and Lilly sites propose (b) (4) drug product stored at 2-8°C. Justify the proposal to allow for an (b) (4) storage of the drug product.
9. We note your December 6, 2013 submission in response to our November 21, 2013 information request regarding the (b) (4) Lilly manufacturing sites. Your submission did not contain sufficient detail to allow for evaluation of the proposed sterilization process at each facility. Submit the (b) (4) reports or a more detailed description of the studies conducted. The following information is required:

(b) (4)

Device

10. Please provide samples of the pen devices you plan to use with this product. If these are not available, please provide photos or detailed illustrations.

Regulatory

11. You have provided a patent certification pursuant to 21 USC 355(b)(2)(A)(iii) (“Paragraph III certification”) stating that U.S. Patent No. 5,656,722 (the ‘722 patent) will expire on August 12, 2014. However, the pediatric exclusivity attached to the ‘722 patent will expire on February 12, 2015 (see FDA’s Approved Drug Products with Therapeutic Equivalence Evaluations (the “Orange Book”). Submit a revised patent certification that correctly states the date (February 12, 2015) on which the ‘722 patent will expire for purposes of your 505(b)(2) application (see 21 CFR 314.50(i)(1)(i)(A)(3)).

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.

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.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).
2. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: **“These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).”**

***Comment:*** Please remove space before paragraph.

3. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
  - “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

***Comment:*** All pieces of labeling are not referenced.

4. Please submit the patient package insert (PPI) in a one page format.

We request that you resubmit labeling that addresses these issues by January 21, 2014. The resubmitted labeling will be used for further labeling discussions.

### **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), patient package insert (PPI), and

instructions for use (IFU). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), patient package insert (PPI), and instructions for use (IFU), and you believe the labeling is close to the final version.

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796-8436.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, MD  
Director, Acting  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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JEAN-MARC P GUETTIER  
12/31/2013

**From:** CappellLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Subject:** NDA 205692 Information Request  
**Date:** Thursday, December 05, 2013 11:58:00 AM

---

Hi Joerg,

We are reviewing your application and have the following requests for information:

1. Please provide all detailed test reports for tests conducted based on ISO 11608. Including test protocol, test data, pass/fail criteria and test results.
2. Please provide biocompatibility test reports on the final and finished product. You have submitted the MSDS for the device componen (b)(4). However, we require biocompatibility tests results based on the final and finished product.
3. Please provide the sterility report for device components.

Please provide this information as soon as possible, no later than December 17, 2013. If the information cannot be provided before this date please contact me as soon as possible.

Thank you,  
Callie

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/s/  
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CALLIE C CAPPEL-LYNCH  
12/05/2013

**From:** CappellLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Subject:** NDA 205692 Information Request  
**Date:** Thursday, November 21, 2013 9:51:00 AM

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Hi Joerg,

We are reviewing the microbiology section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. The NDA does not contain the (b) (4) validation studies for the (b) (4) proposed for use at the (b) (4) Lilly commercial manufacturing sites. Please submit a description of the proposed commercial (b) (4) and a summary of the bacterial retention studies that support adequate sterilization of the drug product. For more information on the data to be submitted please refer to the following Guidance: Sterile Drug Products (b) (4) Processing- Current Good Manufacturing Practice (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/> (b) (4) ).

If you have any questions, please contact me.

Thanks,  
Callie

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/s/  
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CALLIE C CAPPEL-LYNCH  
11/21/2013

**From:** CappelLynch, Callie  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](mailto:Joerg.Pfeifer@lilly.com)  
**Cc:** [Elizabeth Claire Bearby \(bearby\\_elizabeth@lilly.com\)](mailto:Elizabeth.Claire.Bearby@lilly.com)  
**Subject:** NDA 205692  
**Date:** Monday, October 28, 2013 3:29:00 PM

---

Hi Joerg,

Could you please submit DMF (b) (4) which is referenced in NDA 205692? This is for the plunger contained in the device. If this is included in the original NDA I apologize, but would greatly appreciate if you could direct me to the location.

Thank you,  
Callie

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/s/  
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CALLIE C CAPPEL-LYNCH  
10/28/2013



NDA 205692

**NDA ACKNOWLEDGMENT**

Eli Lilly and Company  
Attention: Joerg Pfeifer, Ph.D.  
Advisor, Global Regulatory Affairs- U.S.  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Dr. Pfeifer:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: insulin glargine [rDNA origin] for injection

Date of Application: October 17, 2013

Date of Receipt: October 18, 2013

Our Reference Number: NDA 205692

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 December 17, 2013, 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications. If you have any questions, call me, at (301) 796- 8436.

Sincerely,

*{See appended electronic signature page}*

Callie Cappel-Lynch, Pharm.D.  
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/  
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CALLIE C CAPPEL-LYNCH  
10/22/2013



IND 105423

**MEETING MINUTES**

Eli Lilly and Company  
Attention: Joerg Pfeifer, Ph.D.  
Advisor, Global Regulatory Affairs- U.S.  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Dr. Pfeifer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LY2963016 (insulin glargine [rDNA origin]) injection.

We also refer to the meeting between representatives of your firm and the FDA on August 28, 2013. The purpose of the meeting was to discuss the format and content of your planned 505(b)(2) New Drug Application.

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 Callie Cappel-Lynch at (301) 796-8436.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, MD  
Director, Acting  
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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** August 28, 2013 3:00pm- 4:00pm  
**Meeting Location:** White Oak Building 22 Room 1315

**Application Number:** IND 105423  
**Product Name:** LY2963016 (insulin glargine [rDNA origin]) injection  
**Indication:** (b) (4) of adult and pediatric patients with type 1 diabetes mellitus or adults patients with type 2 diabetes mellitus (b) (4)

**Sponsor/Applicant Name:** Eli Lilly and Company

**Meeting Chair:** Jean-Marc Guettier  
**Meeting Recorder:** Callie Cappel-Lynch

**FDA ATTENDEES**

**Center for Drug Evaluation and Research**

**Office of New Drugs**

Leah Christl, Ph.D.	Associate Director for Therapeutic Biologics
Mary Parks, M.D.	Deputy Director, Office of Drug Evaluation II
Amy Egan, M.D.	Deputy Director Safety, Division of Metabolism and Endocrinology Products (DMEP)
Mehreen Hai, Ph.D.	Safety Regulatory Project Manager, DMEP
Jean-Marc Guettier, M.D.	Director (Acting), DMEP
Lisa Yanoff, M.D.	Reviewer, DMEP
Callie Cappel-Lynch, Pharm.D.	Regulatory Project Manager, DMEP
Julie Van der Waag, M.P.H.	Chief, Project Management Staff, DMEP

**Office of Regulatory Policy**

Janice Weiner, J.D., M.P.H.	Senior Regulatory Counsel, Division of Regulatory Policy I (DRP I)
Nisha Shah, J.D., M.Sc.	Regulatory Counsel, DRP I

Meeting Minutes  
Pre-NDAOffice of New Drug Quality Assessment

Olen Stephens, Ph.D.	CMC Reviewer, Branch VII, Division III
Suong Tran, Ph.D.	CMC Lead, Division III
Eric Duffy, Ph.D.	Division Director, Division III

Office of Clinical Pharmacology

Manoj Khurana, Ph.D.	Reviewer
Suryanarayana Sista, Ph.D.	Reviewer

Office of Surveillance and Epidemiology

Yelena Maslov, Pharm.D.	Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)
Ali Niak, M.D.	Medical Officer, Division of Pharmacovigilance (DPV)
Christine Chamberlain, Pharm.D.	Safety Evaluator, DPV

Office of Biostatistics

Mark Rothmann, Ph.D.	Team Leader, Division II
Cynthia Liu, M.A.	Reviewer

**Center for Devices and Radiological Health**

QuynhNhu Nguyen	Human Factors Reviewer, General Hospital Devices Branch, Division of Anesthesiology, General Hospital, Infection
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**SPONSOR ATTENDEES**

Joerg Pfeifer, Ph.D.	Advisor, Global Regulatory Affairs- US
Melvin Prince, M.D.	Senior Medical Director, Diabetes
David Staehler, M.B.A.	Senior Advisor, Lilly Diabetes Project Management
John Kaiser, Pharm.D.	Regulatory Associate, Regulatory Affairs-US
Helle Linnebjerg, Pharm.D.	Research Advisor, Clinical (Clinical Pharmacology)
Elizabeth Bearby, Pharm.D.	Senior Director, Global Regulatory Affairs- US
David Ceryak, J.D.	Senior Director, Regulatory Legal
David Brill, Ph.D.	Director, Regulatory Affairs
Robert Metcalf, Ph.D.	Vice President, Global Regulatory Affairs- US

## 1.0 BACKGROUND

The purpose of this meeting is to discuss the format and content of the planned 505(b)(2) NDA for LY2963016 (insulin glargine [rDNA origin] injection). Lilly's development program for LY2963016 seeks to rely on FDA's finding of safety and effectiveness for Lantus (insulin glargine [rDNA origin] injection) for the treatment of T1DM and T2DM.

The IND for LY2963016 was submitted May 12, 2011. A Type C meeting was held between Lilly and FDA on July 20, 2012. The purpose of that meeting was to provide guidance on Lilly's proposed biopharmaceutics strategy, Human Factors protocol, and 505(b)(2) submission content for LY2963016 (insulin glargine [rDNA origin]), injection. Lilly has now completed all phase 1 clinical pharmacology and phase 3 clinical studies and has plans for submission of an NDA in October. This meeting will help to ensure that the sponsor is prepared for US submission and submits a complete application.

## 2. DISCUSSION

### 2.1. Content and Format of the 505(b)(2) NDA

**Background:** Lilly intends to file a NDA as a 505(b)(2) submission for this product. This briefing document includes a comprehensive overview of the submission including:

- proposed table of contents in eCTD format
- summary of key CMC information
- listing of completed nonclinical studies and a summary of nonclinical data
- listing of completed clinical studies and a summary of Phase 1 and Phase 3 clinical data
- summary of clinical exposure in completed Phase 3 studies
- summary of how data from the Phase 3 clinical studies were integrated for analyses of safety
- categories of notable patients and format of patient narratives for Phase 1 and Phase 3 clinical studies
- description of the data set format for the Phase 3 clinical studies
- details of the human factors studies supporting development of the prefilled pen
- listing of previous interactions with FDA on LY2963016

Refer to Section 4 for additional supportive information.

Meeting Minutes  
Pre-NDA

**Question 1:** In principle, does FDA agree that the LY2963016 submission package meets the requirements for filing of the application under Section 505(b)(2) based upon proposed table of contents, regulatory guidance, interaction to date, as well as other supportive information noted in the background to this question.

**FDA Response to Question 1:** In principle, we agree but a final determination will be made after we receive and review the 505(b)(2) application for LY2963016.

**Discussion:** No discussion occurred.

**Question 2:** Does FDA agree on the structure of the table of contents provided in Appendix 2, including the location of the regional documents (part III of the OSI request in Module 5.3.5.4, and listing of clinical and manufacturing sites in Module 1 sections 1.11.3 and 1.1.2 with form 356h, respectively)?

**FDA Response to Question 2:** Yes, we agree.

**Discussion:** No discussion occurred.

**Background:** All clinical studies in support of the US NDA (including the 28-week extension period of 52-week Study ABEB) will be complete at the time of initial NDA submission projected for October 2013). All clinical study reports will be included in Module 5. Currently, there are no ongoing clinical studies. Based upon the projected October submission date, it is anticipated that no clinical studies will be ongoing at the time of the 4-month safety update.

**Question 3:** Because no additional clinical data, safety data, or study reports are planned to be submitted during the review of this NDA, does FDA agree that a 4-month safety update is not warranted?

**FDA Response to Question 3:** No, we do not agree, a 4-month safety update that includes new relevant information from published literature for Lantus and LY2963016 and/or new world-wide adverse event reports [i.e., pre or post-marketing (if applicable)] for LY2963016 should be provided.

**Discussion:** No discussion occurred.

**Background:** On 09 July 2013, Lilly and FDA discussed another Phase 3 program planned to be submitted to the Division of Metabolism and Endocrinology Products. In this discussion, FDA noted that, although not a filing issue, their review preference is to have all laboratory data presented in conventional (US) units. Although Lilly has not received the same request for LY2963016, Lilly will be presenting data in this application in the following manner:

- Summary of Clinical Efficacy: Self-monitored blood glucose (SMBG) data will be presented in conventional units.
- Summary of Clinical Safety: Laboratory data for Phase 3 studies will be presented in conventional units.
- Phase 3 study reports: Laboratory data will be presented in international units. Self-monitored blood glucose data will be presented in both conventional and international units; however, textual summaries and hand-generated summary tables use international units.
- Datasets for Phase 3 studies: Laboratory and SMBG data will be presented in both conventional and international units.
- Datasets for integrated analysis of safety in Phase 3 studies: Laboratory and SMBG data will be presented in both conventional and international units.
- Phase 1 study reports, CTD summaries, and datasets: Laboratory data will be presented in international units.

**Question 4:** Does FDA agree with this approach for presenting units in the LY2963016 NDA?

**FDA Response to Question 4:** In Phase 3 study reports, laboratory data should be presented in conventional units. Otherwise, your proposal for Phase 1 and Phase 3 data presentation is acceptable.

**Please submit analysis ready electronic data sets for Insulin, Glucose Infusion Rate (GIR) and Glucose for each PK/PD study along with SAS/R codes that may have been used for baseline correction and other analyses.**

**In addition to analyzing laboratory data and vital signs as continuous variables, your submission should also include outlier analyses for these endpoints.**

***Discussion:*** FDA verified that the units selected for presentation of laboratory data is not a filing issue. FDA stated, however, that it strongly prefers that phase 3 study reports contain analyses of laboratory data in conventional units. Data presentation in SI units can slow down the review process. This issue is particularly problematic with blood glucose and common safety laboratory (e.g., creatinine, bilirubin). FDA acknowledged that phase 3 study reports may have already been generated using SI units. FDA suggested that Lilly provide hyperlinks within the phase 3 study reports to important laboratory data tables and figures presented in conventional units to facilitate the review process. Lilly agreed to consider this suggestion and try to accommodate FDA's request.

**Background:** As requested by FDA during the Type C meeting in July 2012, Lilly will provide an Integrated Summary of Safety (ISS) from two Phase 3 studies: Study ABEB (52-week study of 536 randomized patients with T1DM) and Study ABEC (24-week study of 759 randomized patients with T2DM). During the Type C meeting, FDA agreed that Lilly did not need to provide an Integrated Summary of Efficacy (ISE) for the Phase 3 studies.

Per FDA recommendation: Most analyses (e.g., deaths, serious adverse events, adverse events leading to discontinuation, treatment-emergent adverse events, immune-related adverse events, immunogenicity) will be presented separately by trial in the respective clinical study reports and pooled in the Summary of Clinical Safety (SCS; Module 2.7.4). Certain analyses that were not appropriate for pooling, such as hypoglycemia, will be presented separately by trial in the respective clinical study reports (CSRs) and in the SCS (Module 2.7.4). Although Lilly plans to present the pooled analyses in the SCS (Module 2.7.4), Lilly will submit an ISS (Module 5.3.5.3) that will include a reviewer's guide containing cross-references/hyperlinks to the locations of the required data in the CTD, as well as details of the statistical methodology for the integrated analyses. More details regarding the parameters integrated for the ISS, as well as the statistical methodology, are provided in Section 4.4.3 of this briefing document.

**Question 5:** Does FDA agree with Lilly's plan for integration of the Phase 3 data for the ISS?

**FDA Response to Question 5:** Yes, we agree.

#### **Requests for Clarifications and Additional Comments:**

- **We note that earlier advice about providing an adequate scientific bridge to justify the relevance of comparative data with a non-US-approved product in a Phase 3 trial was not intended to support the “pooling” of data regarding US-approved Lantus and EU-approved insulin glargine in a single study arm, and we have not specifically considered whether your proposed pooling approach would be acceptable. Accordingly, we are requesting further information about your subgroup analyses, and continuing our internal discussion about your approach.**
  - **Describe the nature and types of analyses comparing LY2963016 to the individual active comparator subgroups (i.e., EU-approved insulin glargine and US-approved Lantus) you have performed and will provide in the reports. Clarify if all efficacy and safety analyses were repeated for these subgroups or only some.**
  - **Provide topline efficacy data across these subgroups (i.e., LY2963016 vs. US-approved Lantus in ABEB and ABEC).**

- **Confirm that the active comparators (i.e., EU-approved insulin glargine and US-approved Lantus) will be readily identifiable in the datasets submitted to support the efficacy and safety analyses.**
- **We note your plan to perform adverse event analysis treatment comparisons using Cochran-Mantel-Haenszel (CMH) test stratified by study. Since the studies were not powered to detect those safety signals, the statistical significance will only be treated as exploratory.**
- **Explain the scientific rationale for your definition of treatment-emergent antibody response (TEAR).**

***Discussion:*** *Lilly provided clarification that they used both US-approved Lantus and EU-approved insulin glargine as the active comparator in their clinical trials. Lilly informed FDA that the analysis of the 2 comparative clinical efficacy trials pooled clinical data from patients treated with either US-approved Lantus or EU-approved insulin glargine into one data set against which to compare Lilly's proposed product. Lilly did indicate that they were adequately powered for a non-inferiority margin of 0.4% in both trials for the comparison to US-approved Lantus; however, Lilly intends to provide this information as a subgroup analysis and has conducted their primary analysis against the "full data set" from patients treated with either the US or EU product. Lilly clarified that only US-approved Lantus and EU-approved insulin glargine were used in the clinical studies. Specifically, only the US-approved Lantus was used in sites based in the US and Puerto Rico; at all other international sites, EU-approved insulin glargine was used in the clinical studies.*

*FDA reiterated that the advice about providing an adequate scientific bridge to justify the relevance of comparative data with a non-US-approved product in a Phase 3 trial was not intended to support the "pooling" of data regarding US-approved Lantus and EU-approved insulin glargine in a single study arm. FDA stated that based on the clarification provided by Lilly during the meeting that further internal discussion would need to occur before they could provide advice to Lilly on the acceptability of their analysis,*

***Post Meeting Comment: While the primary analysis may combine the US-approved Lantus and EU-approved insulin glargine data, differences between these two strata (e.g., test vs. reference by US vs. EU interaction) should be evaluated and submitted. The acceptability of Lilly's proposed primary analysis will be a review issue. FDA notes that Lilly's proposed approach involves some risk; for example, in the event that the subgroup analyses trend in different directions. In addition, FDA notes that any discussion of the combined analysis in product labeling, if necessary, would reflect the use of "insulin glargine" and "a non-US-approved insulin glargine" in the comparator group.***

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## 2.2. CMC Comparability Protocol

**Background:** Lilly plans to submit a comparability protocol in the initial NDA, which provides for a duplicate equipment set for the manufacture of the drug substance. Lilly will share the key elements of the comparability protocol in Section 5 of the briefing document.

**Question 6:** Does FDA agree with the scope and comparability criteria of the planned comparability protocol as outlined in Section 5?

**FDA Response to Question 6:** The comparability protocol appears reasonable, but your proposal to change the [REDACTED] (b) (4) will be determined during the review process in the context of all submitted CMC data. At the time of your NDA filing, reiterate this request.

**Discussion:** No discussion occurred.

## 2.3. PDUFA V Program

**Background:** Lilly would like to confirm if this NDA will be reviewed under the PDUFA V NME review program. The PDUFA technical letter does not specifically define a New Molecular Entity nor limit the ability for this application to qualify.

**Question 7:** Will the LY2963016 NDA be considered under the PDUFA V NME review program? If classified as a non-NME PDUFA V program NDA submission, would components of the NME NDA program, such as mid-cycle communication and late-cycle meeting, still apply?

**FDA Response to Question 7:** The 505(b)(2) application for LY2963016 would not be considered an NME for purposes of the PDUFA V NME review program. Therefore components such as the mid-cycle communication and late-cycle meeting would not apply.

**Discussion:** No discussion occurred.

## 2.4. Tentative Approval and Procedural Matters

**Background:** The 505(b)(2) registration path allows for a tentative approval to be granted. Final approval could then be granted after expiry of the patent and/or exclusivity period.

**Question 8:** In case of a tentative approval, what action if any does the applicant need to take to allow FDA to issue a final approval and what is the process and time frame for FDA to issue that final approval?

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**FDA Response to Question 8:** If you submit a 505(b)(2) application that otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act (FD&C Act), but cannot be approved until the expiration of a period of patent and/or exclusivity protection for the listed drug relied upon, the expiration of a 30-month stay of approval, or because a court order pursuant to 35 U.S.C. 271(e)(4)(A) orders that the application may be approved no earlier than the date specified, then a tentative approval would be issued. Acceptable draft product labeling is required for a tentative approval. However, we note that an applicant with a tentatively approved application may need to update draft product labeling to incorporate any relevant revisions to the labeling of the listed drug relied upon that were made after the tentative approval.

Tentative approval is based upon information available at the time of action. This determination is subject to change on the basis of any new information that may come to our attention.

To obtain final approval of a 505(b)(2) application after a tentative approval, you should submit an amendment two or six months prior to the (1) expiration of the patent(s) and/or exclusivity protection or (2) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as “REQUEST FOR FINAL APPROVAL.” This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment, settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and Risk Evaluation and Mitigation Strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

A drug product that is granted tentative approval is not an approved drug and will not be approved until FDA issues an approval letter after any necessary additional review of the NDA.

Please consult the FD&C Act and FDA’s regulations at 21 CFR Part 314 for further information.

**Discussion:** FDA clarified that the 2- or 6-month time frame corresponds to whether we determine the submission to be class 1 or 2, which will depend on the changes made from the time of the tentative approval to the time of the request for final approval. FDA explained that a sponsor’s request for final approval should not be submitted prematurely (e.g., six months and 1 day prior to patent expiry) because the sponsor could, at best, receive another tentative approval.

**Background:** Lilly plans to file [REDACTED] (b) (4)  
[REDACTED] NDA will be for a prefilled pen leveraging the previously

approved device technology of the KwikPen platform. (b) (4)

[Redacted]

**Question 9:** Can FDA confirm that (b) (4) ?

**FDA Response to Question 9:** (b) (4)

[Redacted]

[Redacted] (b) (4)

**Discussion:** *No discussion occurred.*

**Question 10:** (b) (4)

[Redacted]

***FDA Response to Question 10:***

(b) (4)

(b) (4)

**2.5. Package Insert**

**Background:** Lilly and FDA discussed labeling in July 2012 at the Type C meeting. FDA commented, at that time, that labeling will be based on and similar to the LANTUS® label, as appropriate, and to the extent that the 505(b)(2) application for LY2963016 relies on the listed drug LANTUS®. Also, FDA indicated that labeling will likely be adjusted to reflect data generated for LY2963016.

Lilly appreciates that information. In order to have a starting point for the proposed USPI in the upcoming NDA, Lilly is seeking more specific advice at this time on the labeling questions

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listed at the end of this section. Lilly understands and recognizes that the formal label review by FDA will not occur at this time. A draft USPI is being provided in Appendix 4, which is only to serve as a reference point for the labeling questions. The labeling questions are focused on the format and location of information within the label, as well as an overall strategy for its development.

Please note that this is not the final draft USPI that will be provided within the NDA submission as final data tables and final text still need to be established. As stated above, this draft USPI document is being included solely as a reference point from which to discuss relative positioning of information and formatting for the final “to be submitted” draft USPI.

The draft USPI (Appendix 4) is based on a combination of clinically relevant information from the currently approved LANTUS® label and original data generated from the clinical development program for LY2963016. LY2963016 product-related information is provided in the draft USPI within sections 3, 11, and 16. Key biopharmaceutics (pharmacokinetics [PK]/pharmacodynamics [PD]) data demonstrating the similarity between LY2963016 and LANTUS® are included within draft USPI sections 12.2 and 12.3 and include Figure 2. The Phase 3 clinical safety and efficacy data in patients with T1DM and T2DM, which is in agreement with a finding of similarity to the reference product LANTUS®, is included within draft USPI section 6.1 (tables 4, 5, and 9, as well as draft USPI section 14 (tables 12 and 15), respectively.

For this 505(b)(2) application, Lilly strongly believes that the LY2963016 biopharmaceutical (PK/PD) data and the LY2963016 Phase 3 clinical safety and efficacy information in patients with T1DM and T2DM are essential in support of the approval of LY2963016 and warrant inclusion within the LY2963016 USPI. The inclusion of this LY2963016 information in conjunction with the existing LANTUS® information, will help ensure that a complete and balanced presentation of the most clinically relevant information on LY2963016 will be presented. This is important for the overall safe and effective use of LY2963016 by prescribers and patients.

**Question 11:** While specific wording and data to be shown in a final label is a review issue, does FDA conceptually agree with the plans to [REDACTED] (b) (4)

**FDA Response to Question 11:** Discussion of the data to be included in final product labeling is premature. In general, drug product labeling does not describe [REDACTED] (b) (4)

**Thus, our preliminary view is that your draft labeling should only include information describing PK/PD characteristics of LY2963016. However, the contents of the final labeling will be a review issue.**

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**Discussion:**

**Lilly proposed** (b) (4) **in the draft product labeling.** (b) (4)

**FDA reiterated that** (b) (4) **drug product labeling.**

**Question 12:** While specific wording and data to be shown in a final label is a review issue, does FDA conceptually agree (b) (4) to the LY2963016 USPI?

**FDA Response to Question 12:** Data (b) (4) **in product labeling if it is determined that they provide important information regarding the safe and effective use of the product. We cannot agree at this time with your plans to include the LY2963016** (b) (4) **in labeling as this decision will be made after review of the data. Please also refer to our response to Question 11.**

**Discussion:** See discussion for Question 11.

**Question 13:** Throughout the label, (b) (4) Since there is (b) (4) application, can FDA comment on this proposal?

**FDA Response to Question 13:** At this time, we recommend that you refer to data on US-approved Lantus as data o (b) (4) ”

Please clarify the reference on page 41 of your briefing package to a subgroup analysis (b) (4) ”

**Discussion:** No discussion occurred.

**Background:** Lilly understands that prior to submission of this NDA, the draft LY2960316 USPI may need to be revised in specific sections (b) (4) (b) (4)

FDA already commented in July 2012 regarding the need to update draft product labeling to incorporate any relevant revisions to the labeling of the listed drug relied upon that were made after the tentative approval.

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**Question 14:** Can FDA comment on the specific process for changes to the LY2963016 label (b) (4)? Does Lilly need to contact FDA in such cases or does FDA notify Lilly if a change is needed? Is there a difference in process or expected time frame for submitting any such required LY2963016 label updates, (b) (4) label change occurs during the NDA review, after tentative approval, or post-approval?

**FDA Response to Question 14:** The process for labeling changes depends on the timing (pre- vs. post-approval) and nature (related to safety and/or efficacy) of the proposed labeling change. For example, in general, FDA expects Lilly to monitor information (including product labeling) (b) (4) as part of its pharmacovigilance activities, and submit proposed safety-related changes to its labeling, as appropriate (see, e.g., 21 CFR 314.60, 314.70, and 314.80).

**Discussion:** No discussion occurred.

**Background:** In order to prepare for the submission, Lilly needs to develop a labeling strategy (b) (4)

**Question 15:** Does FDA agree with this plan?

**FDA Response to Question 15:** Your proposed strategy appears reasonable. However, you should monitor (b) (4) during the review process and update your proposed labeling prior to product approval if appropriate.

**Discussion:** No discussion occurred.

**Question 16:** Is it acceptable to use the approved PI for LANTUS as the reference for LANTUS/insulin glargine information when annotating the label for LY2963016 within this 505(b)(2) application?

**FDA Response to Question 16:** Your proposal appears acceptable.

**Discussion:** No discussion occurred.

## 2.6. Non-Proprietary Name

**Background:** FDA has stated that the decision on the non-proprietary name for LY2963016 will be a review decision. Lilly will be proposing the name insulin glargine in the submission, given the weight of evidence to be presented in Modules 3 and 5 of the submission. However, Lilly would like to learn more about the process or information needed to reach a final decision on the non-proprietary name.

**Question 17:** Can FDA comment on timing for such a decision or information influencing it?

**FDA Response to Question 17:** It is reasonable to submit your 505(b)(2) application with the non-proprietary name “insulin glargine.” FDA will make a decision regarding the non-proprietary name of your proposed product by the date of approval.

**Discussion:** *No discussion occurred.*

**Question 18:** Should FDA require a unique non-proprietary name, can FDA comment if agreement between Lilly and FDA would be acceptable on a prefix or suffix (to insulin glargine) to arrive at a unique name (prior to final approval), or if a USAN would be required?

**FDA Response to Question 18:** Refer to our response to question 17.

**Discussion:** *Lilly expressed concern regarding the timeliness of FDA feedback on the proposed nonproprietary name during the review of the planned NDA. If Lilly needed to apply for and receive a USAN for a unique nonproprietary name prior to NDA approval, adequate time for review by USAN would be needed.*

*FDA stated that we are not able to comment further at this time, but could provide additional information during review of the planned NDA. FDA noted that they are aware of USAN review timelines.*

## 2.7. Risk Management Plan

**Background:** Lilly proposes to include only pharmacovigilance activities consistent with other long-acting insulins in the risk management plan section of the NDA. No additional risk minimization or risk mitigation activities will be proposed beyond that contained in the product labeling. This seems appropriate given the knowledge about LANTUS® and results for LY2963016 to be shown in the submission.

LANTUS® was granted marketing approval in 2000. Since then, LANTUS® has been approved in over 120 countries and has accumulated global post-approval exposure data of approximately 47 million patient-years. Lilly considers LANTUS® a well-characterized insulin, based on the investigational data submitted to the FDA (amounting to approximately 80,000 patients in clinical studies) and on the US post-approval spontaneous safety data accumulated since.

Lilly’s understanding is that the risk profile of LANTUS® includes the following:

### **Important Identified Risks:**

- Hypoglycemia (including severe hypoglycemia)

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- Medication error (incorrect insulin)
- Hypersensitivity reactions
  - Fluid retention and heart failure from concomitant use of insulin and thiazolidinedione (TZD)

**Important Potential Risks:**

- Neoplasia
- Antigenicity

**Important Missing Information:**

- Use in pregnancy
- Use in children with T2DM and use in children with T1DM under the age of 6 years

Lilly believes the same list of Important Identified Risks, Important Potential Risks, and Important Missing Information also applies to LY2963016. Other than the potential risk for neoplasia, all risks and missing information are addressed within the LANTUS® US label and would be addressed similarly in the LY2963016 US label. The neoplasia risk has been explored in both epidemiologic surveys and in completed and ongoing prospective studies, with no findings, to date, to indicate any added statement or activities in labeling. Any findings from these LANTUS®-based studies would apply to LY2963016.

On this basis, Lilly believes that if the FDA, following its review of the NDA for LY2963016, concludes that LY2963016 meets the FDA's criteria for a therapeutic protein [REDACTED]<sup>(b) (4)</sup>, then the FDA would also conclude that:

- Standard pharmacovigilance activities, as defined in the labeling, would be adequate to address the risks and missing information described above;
- and
- no additional risk minimization or risk mitigation plan would be required.

**Question 19:** Does FDA agree with this approach to risk management, minimization and mitigation?

**FDA Response to Question 19:** As a preliminary matter, it should be noted that your reference to “FDA’s criteria for a therapeutic protein [REDACTED]<sup>(b) (4)</sup>” is unclear and does not have an established regulatory meaning.

**At this time, we agree with your approach. We have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be**

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**necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.**

**Discussion: No discussion occurred.**

In addition to the responses above we also have the following comments:

**Clinical and Statistics:**

1. We note that your study nomenclature scheme does not follow a strict alphabetical ordering. Please clarify whether you have carried out any other clinical studies with LY2963016 which were not described in the background package.
2. We note that the Last Observation Carried Forward (LOCF) technique is your primary imputation method as stated in the protocols submitted in May 12, 2011. This was accepted by the Agency at that time. However, the Division is reconsidering this LOCF approach following the publication in 2010 of a report on missing data by the National Academy of Sciences (NAS), *The Prevention and Treatment of Missing Data in Clinical Trials*. The FDA commissioned this report. The report states “The panel believes that in nearly all cases, there are better alternatives to [LOCF]...which are based on more reasonable assumptions and hence result in more reliable inferences about treatment effects”. A version of the report can be found online at [http://www.nap.edu/catalog.php?record\\_id=12955](http://www.nap.edu/catalog.php?record_id=12955). Therefore, please amend your primary imputation method and specify a primary statistical analysis which does not rely on LOCF and which is in line with NAS recommendations.

***Discussion: The sponsor stated that since they are planning to submit their NDA in 4-6 weeks, they would still like to submit the results based on the LOCF method for missing data and retain this method as their primary analysis, but will provide additional analyses such as mixed model repeated measures as sensitivity analyses. The sponsor will also provide justification and the details regarding the sensitivity analyses. The Division reiterated the current position regarding missing data handling, but agreed with the sponsor’s proposal at this time since the data were already unblinded and analyzed, and the dropout rate was not high. The Division also informed the sponsor that the analysis method whose results are to be included in the label will be a review issue.***

**Medication Error Prevention and Analysis:**

3. You have submitted Human Factors Validation Study Results for Insulin Glargine Kwikpen in your background package. Submit this report to the NDA as this information will be a review issue and will be evaluated during NDA review.

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4. As a background to Questions 9 and 10 in the Briefing Package you state that you are planning (b) (4)

**Discussion:** *No discussion occurred.*

**Microbiology**

5. The NDA should contain the results from antimicrobial effectiveness tests consistent with USP<51> using at least three different drug product batches. At least one test should be conducted at, or below, the minimum metacresol specification.
6. Please refer to the following documents when preparing your NDA.

Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf>

Sterile Drug Products (b) (4) Processing- Current Good Manufacturing Practice

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf> (b) (4)

**Discussion:** *No discussion occurred.*

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7. We acknowledge your request for a copy of the official minutes of the July 2012 meeting between Lilly and FDA regarding this application. FDA intends to provide these minutes as soon as feasible. In the meantime, we address your inquiry regarding pediatric study requirements for this NDA below.

**Discussion:** *No discussion occurred.*

**Post Meeting Comment:** *Meeting minutes were provided to the sponsor on August 27, 2013.*

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### **3.0 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. Further, section 506 of the Food and Drug Administration Safety and Innovation ACT (FDASIA) amended PREA, to set forth a process for reaching agreement between applicants and FDA on initial pediatric study plans (PSPs)

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>.

Because none of the criteria apply at this time to your application, your application does not trigger PREA. If there are any changes to your development plans that would cause your application to trigger PREA, your status would change.

### **4.0 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. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.
- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[*see Warnings and Precautions (5.2)*]".

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.

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Pre-NDA**5.0 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.				

**6.0 505(b)(2) REGULATORY PATHWAY**

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's

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interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. You should establish a "bridge" between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug or published literature describing a listed drug (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also

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include that information in the cover letter for your marketing application in a table similar to the one below.

<b>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature</b>	
<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

## **7.0 ISSUES REQUIRING FURTHER DISCUSSION**

No issues requiring further discussion.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JEAN-MARC P GUETTIER  
09/27/2013