

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125469Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
BLA # 125469	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Trulicity Established/Proper Name: dapagliflozin Dosage Form: injection		Applicant: Eli Lilly and Company Agent for Applicant (if applicable):
RPM: Abolade (Bola) Adeolu		Division: Metabolism & Endocrinology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>September 18, 2014</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

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

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

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. 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
 Chemical classification (new NDAs only):
 (*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:

❖ 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>)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ 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 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	No
❖ 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 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 type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action and date: 9/18/2014
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included. See labeling attached to approval letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included. See labeling attached to approval letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included. See labels attached to approval letter for final labels
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	Trulicity: Acceptable Letter: 1/11/2014; Review: 1/9/2014 ----- (b) (4) Acceptable Letter: 10/21/2013; Review 10/17/2013 Withdrawal Letter: 1/10/2014
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 11/13/2013 DMEPA: 3/19/2014 DMPP/PLT: 8/22/2014 DRISK: None OPDP: 8/20/2014 OBP CMC: : 8/29/2014 SEALD: <input type="checkbox"/> None CSS: None Other: None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	11/13/2013
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included

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

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	No
• This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	No
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ 	7/16/2014
❖ 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>)	Included
❖ 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)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	N/A
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	7/9/2013
• EOP2 meeting (<i>indicate date of mtg</i>)	11/10/2009
• Mid-cycle Communication (<i>indicate date of mtg</i>)	3/3/2014
• Late-cycle Meeting (<i>indicate date of mtg</i>)	6/2/2014
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	Type C CMC Meeting 5/15/2014
❖ Advisory Committee Meeting(s)	No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	9/18/2014
Division Director Summary Review (<i>indicate date for each review</i>)	9/18/2014
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	9/18/2014
PMR/PMC Development Templates (<i>indicate total number</i>)	12
Clinical	
❖ 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>)	8/13/2014; 11/5/2013
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 24 and page 242 of 8/13/2014 clinical review

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None added the OSE Human Factors review to this section
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) 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>) 	9/18/2013 9/12/2014; 8/25/2014 (2); 5/30/2014
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	9/15/2014; 6/6/2014
Clinical Microbiology <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>)	
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None DBVII: 5/16/2014; 11/12/2013 DBII: 5/16/2014; 11/5/2013
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	6/6/2014
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	6/18/2014; 11/1/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	SPA-3 : 2/4/2011 SPA-1: 8/13/2009
❖ ECAC/CAC report/memo of meeting	SPA-3: 1/28/2011 SPA-1 8/5/2009
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	9/10/2014; 8/27/2014; 8/1/2014; 5/30/2014; 5/22/2014; 11/13/2013; 11/5/2013
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 8/14/2014; 6/20/2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	CDRH Human Factors review 6/23/2014; CDRH /OC review 6/17/2014; CDRH Reliability & Mechanical Engineering review 5/15, and 3/12/2014
❖ 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>	See part IV of Summary of Quality Assessment in review dated 5/30/2014
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: 9/18/2014 Acceptable
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ 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.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/

ABOLADE ADEOLU
09/18/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Thursday, September 18, 2014 12:54 PM
To: Kenneth F Mace
Cc: Elizabeth Claire Bearby; John J Kaiser; Adeolu, Abolade
Subject: BLA 125469: Package Insert for Trulicity(dapagliflozin)

Dear Ken,

We accept your revisions dated September 18, 2014.

Bola Adeolu
301 796-4264

From: Kenneth F Mace [mailto:mace_kenneth_f@lilly.com]
Sent: Thursday, September 18, 2014 12:10 PM
To: Adeolu, Abolade
Cc: Elizabeth Claire Bearby; John J Kaiser
Subject: RE: Trulicity: PI

Revised without the date at the end.

Kenneth F. Mace, PhD
Advisor, Global Regulatory Affairs - Diabetes
Eli Lilly and Company
Office: 317-433-3463 (please leave voice messages at this number only)
Mobile: (b) (6)
Fax: 317-276-1652
Email: mace_kenneth_f@lilly.com | Web: <http://www.lilly.com>



CONFIDENTIALITY NOTICE: This email message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying, or distribution is strictly prohibited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message.

From: Adeolu, Abolade [<mailto:Abolade.Adeolu@fda.hhs.gov>]
Sent: Thursday, September 18, 2014 12:00 PM
To: Kenneth F Mace
Cc: Elizabeth Claire Bearby; John J Kaiser
Subject: RE: Trulicity: PI
Importance: High

Please try and get this back to me before 1pm

thanks

Bola Adeolu
301 796-4264

From: Adeolu, Abolade
Sent: Thursday, September 18, 2014 11:28 AM
To: 'Kenneth F Mace'
Cc: Elizabeth Claire Bearby; John J Kaiser
Subject: RE: Trulicity: PI
Importance: High

PI is acceptable. Please update with date and send back . The date should not appear at the end of the PI, only at the end of the highlights of prescribing information section.

thanks

Bola Adeolu
301 796-4264

From: Kenneth F Mace [mailto:mace_kenneth_f@lilly.com]
Sent: Thursday, September 18, 2014 9:59 AM
To: Adeolu, Abolade
Cc: Elizabeth Claire Bearby; John J Kaiser
Subject: RE: Trulicity: PI

Bola,

Here is the revised PI. We have accepted the FDA changes and have corrected text as needed. Let me know if you have any questions.

Ken

Kenneth F. Mace, PhD
Advisor, Global Regulatory Affairs - Diabetes
Eli Lilly and Company
Office: 317-433-3463 (please leave voice messages at this number only)
Mobile: (b) (6)
Fax: 317-276-1652
Email: mace_kenneth_f@lilly.com | Web: <http://www.lilly.com>



CONFIDENTIALITY NOTICE: This email message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying, or distribution is strictly prohibited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message.

From: Adeolu, Abolade [<mailto:Abolade.Adeolu@fda.hhs.gov>]
Sent: Wednesday, September 17, 2014 7:33 PM
To: Elizabeth Claire Bearby; Kenneth F Mace; John J Kaiser
Cc: Adeolu, Abolade
Subject: Trulicity: PI
Importance: High

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND

Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993
Tel: 301 796-4264

19 Pages of Draft Labeling have been Withheld in Full as
B4(CCI/TS) Immediately Following this Page

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

/s/

ABOLADE ADEOLU
09/18/2014

Adeolu, Abolade

From: Hai, Mehreen
Sent: Wednesday, September 17, 2014 5:03 PM
To: Kenneth F Mace; John J Kaiser
Cc: Adeolu, Abolade; Elizabeth Claire Bearby
Subject: RE: dulaglutide

Ken, John and Elizabeth,
June 2015 for the Final Protocol Submission date is acceptable.

Thanks!

Mehreen Hai, Ph.D.
Safety Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Kenneth F Mace [mailto:mace_kenneth_f@lilly.com]
Sent: Wednesday, September 17, 2014 4:07 PM
To: Hai, Mehreen; John J Kaiser
Cc: Adeolu, Abolade; Elizabeth Claire Bearby
Subject: RE: dulaglutide

Mehreen,

As we discussed, Adverse Events of Interest as listed in the CVOT PMR are already being captured with the current approved protocol submitted to FDA in 2011, though not individually listed in that version.

Lilly will update the protocol to specifically list these AEs within an already planned protocol amendment. The timing of a meeting request to the agency on this protocol amendment is currently scheduled for the December 2014/January 2015 timeframe. As this protocol amendment will seek FDA comments, we propose a timeframe that allows for an interaction with the Agency and final agreement on the amendment. Our new proposal for Final Protocol Submission is therefore June 2015.

We appreciate the opportunity explain to you how we are capturing this important study data and the rationale for the proposed date.

Ken and John

Kenneth F. Mace, PhD
Advisor, Global Regulatory Affairs - Diabetes
Eli Lilly and Company
Office: 317-433-3463 (please leave voice messages at this number only)
Mobile: (b) (6)
Fax: 317-276-1652
Email: mace_kenneth_f@lilly.com | Web: <http://www.lilly.com>



CONFIDENTIALITY NOTICE: This email message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying, or distribution is strictly prohibited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message.

From: Hai, Mehreen [<mailto:Mehreen.Hai@fda.hhs.gov>]
Sent: Wednesday, September 17, 2014 3:31 PM
To: John J Kaiser
Cc: Adeolu, Abolade; Elizabeth Claire Bearby; Kenneth F Mace
Subject: RE: dulaglutide

Hello John,

Thank you for sending the milestone dates for the CVOT PMR, particularly the dates for final protocol submission. The protocol modifications that we anticipate (for capturing AESIs) are minor, and should not take until August 2015. We recommend a date three months from approval, i.e. December 2014.

Please let me know if you concur.
Thank you,

Mehreen Hai, Ph.D.
Safety Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: John J Kaiser [mailto:kaiser_john_joseph@lilly.com]
Sent: Wednesday, September 17, 2014 3:05 PM
To: Adeolu, Abolade; Elizabeth Claire Bearby; Kenneth F Mace
Subject: RE: dulaglutide

Hi Bola,

I believe this is what you are requesting:

3. A randomized, double-blind, placebo-controlled trial evaluating the effect of TRULICITY (dulaglutide) on the incidence of major cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the study should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) observed with dulaglutide to that observed in the placebo group is less than 1.3. The trial must also assess the following adverse events: thyroid cancer, pancreatic cancer, pancreatitis, immune-mediated reactions (including serious hypersensitivity reactions), serious hypoglycemic events, hepatic events, serious gastrointestinal events, clinically significant supraventricular arrhythmias, clinically significant conduction disorders and worsening renal function.

Final Protocol Submission: August 2015
Trial Completion: June 2019

John

John Kaiser, PharmD, RPh
Consultant, Global Regulatory Affairs - US
Eli Lilly and Company
317.277.5906 (Office) | (b) (6) (Mobile)
jkaiser@lilly.com | www.lilly.com

CONFIDENTIALITY NOTICE: This email message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying, or distribution is strictly prohibited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message.

From: Adeolu, Abolade [<mailto:Abolade.Adeolu@fda.hhs.gov>]
Sent: Wednesday, September 17, 2014 3:00 PM
To: Elizabeth Claire Bearby; Kenneth F Mace
Cc: John J Kaiser
Subject: RE: dulaglutide

Yes...thanks

Bola Adeolu
301 796-4264

From: Elizabeth Claire Bearby [mailto:bearby_elizabeth@lilly.com]
Sent: Wednesday, September 17, 2014 2:45 PM
To: Adeolu, Abolade; Kenneth F Mace
Cc: John J Kaiser
Subject: RE: dulaglutide

Bola – Ken and John are working on the email question.

Which PMR? The CV trial is August, 2015 for the final protocol. Do you need the other dates for that PMR or for a different one?

Thanks, Elizabeth

From: Adeolu, Abolade [<mailto:Abolade.Adeolu@fda.hhs.gov>]
Sent: Wednesday, September 17, 2014 2:42 PM
To: Kenneth F Mace
Cc: John J Kaiser; Elizabeth Claire Bearby
Subject: RE: dulaglutide
Importance: High

Please send me the last PMR date

Bola Adeolu
301 796-4264

From: Kenneth F Mace [mailto:mace_kenneth_f@lilly.com]
Sent: Wednesday, September 17, 2014 11:55 AM
To: Adeolu, Abolade

Cc: John J Kaiser; Elizabeth Claire Bearby
Subject: RE: dulaglutide

Bola,

In response to your email below, the REWIND protocol was finalized and submitted to the IND in 2011. The trial recently completed enrollment and is targeted for completion in 2019 .

We interpret the request below that Lilly needs to modify this protocol, even though the specific safety information as agreed in the PMR, is already being collected. While already being captured, we understand based on this request that FDA wants the protocol to be specific on these adverse events. We will coordinate this protocol amendment with another planned revision as this significantly conserves the efforts of the clinical investigators. Therefore, the final protocol submission date is August, 2015.

Importantly, our intent is to work toward a decision on this PMR as soon as possible. We are committed to having an on time FDA PDUFA decision on the Trulicity BLA.

Ken

Kenneth F. Mace, PhD
Advisor, Global Regulatory Affairs - Diabetes
Eli Lilly and Company
Office: 317-433-3463 (please leave voice messages at this number only)
Mobile: (b) (6)
Fax: 317-276-1652
Email: mace_kenneth_f@lilly.com | Web: <http://www.lilly.com>



CONFIDENTIALITY NOTICE: This email message from Eli Lilly and Company (including all attachments) is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure, copying, or distribution is strictly prohibited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message.

From: Adeolu, Abolade [<mailto:Abolade.Adeolu@fda.hhs.gov>]
Sent: Tuesday, September 16, 2014 2:23 PM
To: Kenneth F Mace
Cc: Adeolu, Abolade
Subject: dulaglutide
Importance: High

Dear Ken,

In a previous communication we omitted the final protocol submission milestone date for the CVOT postmarketing requirement. Upon further review, we note that your protocol will have to be amended to provide for adverse events of special interest (AESI) as already specified in the agreed-upon PMR language. Please provide a new milestone date for the submission of a final protocol providing for the collection of all of the AESIs specified in the PMR.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND

Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993
Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
09/18/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, September 05, 2014 1:07 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: dulaglutide

Dear Ken,

The Agency agrees that the USP <85> Bacterial Endotoxins Test (kinetic chromogenic method) can be used for dulaglutide drug substance and drug product release testing in parallel with completing the PMC.

Best,
Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
09/05/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Wednesday, September 03, 2014 1:11 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: dulaglutide

Importance: High

Dear Ken,

Please respond to the following by COB tomorrow

With regard to low endotoxin recovery in the formulated (b) (4) drug substance and drug product, we acknowledge the (b) (4) test results provided in amendment dated 8/25/2014 (Sequence 35). (b) (4)
(b) (4). There is insufficient evidence to conclude that your (b) (4) test is more sensitive (b) (4) (u) (4)
(b) (4)

(b) (4)
The data provided thus far indicate that the kinetic chromogenic method may not be an appropriate test for drug substance and drug product release. Other endotoxin test methods may be more suitable for testing your product. To meet regulatory requirements for release testing, the endotoxin test should be able to recover bacterial endotoxin present in the product without interference from the formulated product. Please commit to explore alternative test methods and to develop a more suitable endotoxin release test for dulaglutide drug substance and drug product. Please provide submission dates for the PMC study protocol and the PMC final study report.

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
09/03/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Wednesday, August 27, 2014 12:52 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: FW: Dulaglutide comments to the sponsor from DRISK
Attachments: REMS FDA 8 25 14.docx; rems-factsheet.FDA 8.25.14.docx; rems-hcp-letter-email. FDA 8.25.14.docx; rems-hcp-letter-print.FDA 8.25.14.docx; rems-prof-society-letter-email.FDA 8.25.14.docx; rems-prof-society-letter-print.FDA 8.25.14.docx; rems-supporting-document FDA 8 25 14.docx; us-rems-rems-landing-webpage.FDA 8.6.14.docx

Dear Ken,

Please see the attachments and comments for the REMS. The PI will follow shortly.

thanks

Bola Adeolu
301 796-4264

We acknowledge your submission of the proposed REMS for dulaglutide received on June 30, 2014 and have the following necessary revisions and comments:

1. REMS Document:
 - a) Update the placeholder for the month and year that the REMS document will be approved.
 - b) Remove (b) (4) when discussing the risk of pancreatitis.
2. REMS Supporting Document:
 - a) Update all of the language and attachments for the REMS materials with final approved labeling.
3. REMS Letters:
 - a) Remove (b) (4) when discussing the risk on pancreatitis.
 - b) Add this language for pancreatitis so that it may align with labeling: "Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other anti-diabetic therapies in patients with a history of pancreatitis."
 - c) Add this language for medullary thyroid carcinoma so that it may align with labeling: "Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors."
 - d) Add the 0.75mg/0.5ml strength to all the logos.
4. REMS Factsheet:
 - a) Remove (b) (4) when discussing the risk on pancreatitis.
 - b) Add this language for pancreatitis: "TRULICITY has not been studied in patients with a history of pancreatitis to determine whether these patients are at increased risk for (b) (4) pancreatitis."

c) Add the 0.75mg/0.5ml strength to the logos.

5. REMS Website

- a) Make the language discussing the risk of pancreatitis consistent with labeling and all other REMS materials.
- b) Add the 0.75mg/0.5ml strength to the logo.

Provide versions of all documents in Word, and include both clean and track changes versions within 3 business days.

We remind you that language in all REMS materials must reflect the approved final labeling, and that the REMS materials are not appropriate for use in a promotional manner. The REMS has not completed clearance within the Agency, and additional changes may be necessary.

ATTACHMENTS

1. Revised REMS Document
2. REMS Letters
 - REMS Letter for HCP (print version)
 - REMS Letter for HCP (email version)
 - REMS Letter for Professional Societies (print version)
 - REMS Letter for Professional Societies (email version)
3. REMS Factsheet
4. REMS Website
5. REMS Supporting Document

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

/s/

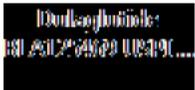
ABOLADE ADEOLU
08/28/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Wednesday, August 27, 2014 2:17 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: PMR/PMC

Dear Ken,

The attachment below contains our response to the PMR and PMC timelines. Please respond by September 3, 2014.



Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
08/27/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Monday, August 18, 2014 1:26 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com); John J Kaiser (kaiser_john_joseph@lilly.com)
Cc: Adeolu, Abolade
Subject: Information Request (IR) for 125469
Importance: High

Dear Ken,

We appreciate your prompt response to the August 5, 2014 IR. We evaluated your updated container label and carton labeling response that you emailed to FDA on August 14, 2014. We identified the following deficiencies that require your attention. Please respond by **COB August 25, 2014**.

A. General Comments for Container Label and Carton Labeling

1. Revise the dosage form "injection" to appear below the proper name. See recommended format below:

trulicity
(dulaglutide)
injection

1.5 mg/0.5 mL

Lilly's Response

(b) (4)

FDA's Response

Placement of the finished dosage form alongside the proper name of a CDER-regulated biological product is unacceptable. To further clarify, the position of the dosage form on the container labels and carton labeling for CDER-regulated biological products differs from prescription drug (NDA and ANDA) products. The aforementioned Guidance states that for CDER-regulated biological products, the proper name should not include the finished dosage form. The finished dosage form, injection, can appear on the line below the proper name.

We acknowledge your real estate constraints, though there appears to be sufficient space to relocate the dosage form below the proper name. Additionally, we propose the following options to create space to allow correct placement of the dosage form:

a. Carton Labeling Side Panels

- Delete (b) (4) from the side panels. (b) (4) appears on the Principal Display Panel, back panel instructions/chart of the Syringe Carton, inside panel instructions/chart of the Pen Carton, and the Instructions For Use.

b. Pen Container Labels

- Decrease the height of the purple bar at the top of the label,
- Delete (b) (4) or
- Delete (b) (4).

c. Prefilled Syringe Container Labels

We consider the Prefilled Syringe Container Label a partial label due to its small size per 21 CFR 610.60(c). Therefore, our goal is to provide the required and recommended information in the label and remove less important information. To create space estate, consider the following options:

- Revise "US License No. 1891" to "US Lic. No. 1891" and then relocating "Rx Only" next to it,
- Delete (b) (4)
- Delete (b) (4),
- Delete the bar code as it appears on the Syringe Carton Labeling. The bar code is not required on partial labels, or
- Delete NDC as it appears on the Syringe Carton Labeling. The NDC is not required on partial labels.

B. Prefilled Syringe Container Labels and Carton Labeling and

1. Revise the term (b) (4) to read "Single-Dose Pen". Single-Dose is the appropriate term for this pen per United States Pharmacopeia (USP) 8/1/2014 – 11/30/2014 <659> Packaging and Storage Requirements.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
08/18/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, August 15, 2014 8:19 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com); John J Kaiser (kaiser_john_joseph@lilly.com)
Cc: Adeolu, Abolade
Subject: dulaglutide

Dear Ken,

Please respond by Aug.25, 2015 to the following :

1. Due to the low endotoxin recovery results of DS in the endotoxin hold time study, please include the endotoxin limit and results from the [REDACTED] (b) (4) drug substance Certificate of Analysis until an alternative method for endotoxin testing is developed for [REDACTED] (b) (4) drug substance. In addition, clarify whether polysorbate 80 is tested for endotoxin and specify the established endotoxin limit.
2. Conduct post-marketing studies to understand the mechanism of low endotoxin recovery in the formulated [REDACTED] (b) (4) drug substance and drug product. Based on the results of these studies, modify the endotoxin release test and/or determine the suitability of alternative endotoxin test methods. Please provide submission dates for the PMC study protocol and the PMC final study report.
3. If the [REDACTED] (b) (4) test is able to detect endotoxin in the drug product, then [REDACTED] (b) (4) testing of the drug product will be required for drug product release in accordance CFR requirements until an alternative test method is developed.

Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
08/15/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Tuesday, August 05, 2014 9:50 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com); John J Kaiser (kaiser_john_joseph@lilly.com)
Cc: Adeolu, Abolade
Subject: BLA 125469

Dear Ken,

You submitted updated container label and carton labeling on May 6, 2014 and July 17, 2014 for BLA 125469. We identified a few deficiencies that require attention. Please respond by COB August 15, 2014.

A. General Comments for Container Label and Carton Labeling

1. The 356h forms accompanying your labeling submissions lack a US License Number. Ensure the US License Number is provided on the 356h form and also appears directly below the manufacturer information on the container labels and carton labeling per 21 CFR 610.60(2) and 21 CFR 610.61(b).
2. Confirm there is sufficient area on the container that remains uncovered for its full length or circumference to permit inspection of the contents when the label is affixed to the container per 21 CFR 610.60(e).
3. Revise the proper name [REDACTED] (b) (4) to read "dulaglutide" as [REDACTED] (b) (4) is not part of the official proper name or USAN.
4. Confirm the proper name, dulaglutide, is at least half as large as the proprietary name, Trulicity, per 21 CFR 201.10 (g)(2).
5. Revise the dosage form "injection" to appear below the proper name. See recommended format below:
trulicity
(dulaglutide)
injection

1.5 mg/0.5 mL
6. Clarify the significance of the codes (PS1431, PS1432, PS1433, and PS1431) that appear on the [REDACTED] (b) (4) of the principal display panels. Consider relocating this information toward the bottom of the labeling, away from the required and recommended information on the carton labeling. Additionally, consider deleting the codes from the small, partial Prefilled Syringe Container label (see comment C1).
7. Revise the statement [REDACTED] (b) (4) to "Store in original carton to protect from light".

B. Pen Container Label

1. Revise the term [REDACTED] (b) (4) to read "Single-Dose Pen". Single-Dose is the appropriate term for this pen per United States Pharmacopeia (USP) 8/1/2014 – 11/30/2014 <659> Packaging and Storage Requirements.
2. Add the route of administration statement, "For Subcutaneous Use Only" below the statement "Single-Dose Pen".
3. Add the Medication Guide statement, "Dispense accompanying Medication Guide to each patient Pen container labels per 21 CFR 610.60(a)(7) and 21 CFR 208.24(d). The Pen label is not considered a small or partial label.
4. Delete the [REDACTED] (b) (4) that appears below the NDC. It is duplicative [REDACTED] (b) (4)

C. Prefilled Syringe Container Label

1. Delete "PS1432, PS1431, 0.5 mL, Prefilled Syringe" to allow space to increase the font size of the required and recommended information to improve readability of this small, partial label.

D. Pen Carton Labeling

1. Add the statement "Single-Dose Only" to the principal display panel to appear below the statement "For subcutaneous use only".
2. Add the statement "No U.S. standard of potency" to the carton labels to comply with regulation 21 CFR 610.61(r).
3. Per USP 8/1/2014 – 11/30/2014, USP 37/NF 32, <1091> Labeling of Inactive Ingredients, please list the names of the inactive ingredients in alphabetical order in the following format: inactive ingredient (amount).

E. Prefilled Syringe Carton Labeling

1. Ensure that the image of the prefilled syringe accurately represents the actual size, shape, color, and imprint of the commercial product and is not a schematic or computer-generated image. In addition, this image should be less prominent than the proprietary name, established name and strength.¹
2. See D1, D2 and D3.

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

Kindly acknowledge receipt of this email

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121

10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

ⁱ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

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

/s/

ABOLADE ADEOLU
08/05/2014

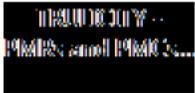
Adeolu, Abolade

From: Adeolu, Abolade
Sent: Monday, August 04, 2014 2:45 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: BLA 125469(dulaglutide): PMR/PMC

Dear Ken,

Please find attached PMR/PMC's for BLA 125469.
Kindly acknowledge receipt of this email and send your response by COB Aug. 11, 2014

Thanks, Bola



Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
08/04/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Tuesday, July 29, 2014 3:22 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: BLA 125469 (Eli Lilly, dulaglutide)

Dear Ken,

1. With regard to the Change Management Protocol provided in Section 3.2.R, you state that any changes to the [REDACTED] (b) (4) strategy will be reported in an Annual Report. Please clarify. Will changes to the [REDACTED] (b) (4) acceptance criteria of dulaglutide be reported in Annual Reports? Please justify the reporting category.
2. Please respond to the following comments regarding endotoxin testing.
 - a. Provide the protocols and reports for the endotoxin hold time study performed with [REDACTED] (b) (4) using three lots of drug substance and three lots of drug product.
 - b. In addition to the information already provided or requested, briefly describe any other completed, planned, or ongoing studies related to [REDACTED] (b) (4) the drug substance and drug product. If applicable, provide the study protocols and summary data.
3. In the CMC information provided in sequence 0032, you indicated that the CCI method specificity study would be completed by 30 July 2014. Please provide the study data, describe the visual positive control that will be used for CCI testing, and update the CCI test method to include the visual positive control.

Please acknowledge receipt and let me know when to expect your responses.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
07/29/2014

**PeRC PREA Subcommittee Meeting Minutes
July 16, 2014**

PeRC Members Attending:

Lynne Yao
George Greeley
Daiva Shetty
Wiley Chambers
Susan McCune
Rachel Witten
Shrikant Pagay
Tom Smith
Karen Davis Bruno
Susan McCune
Rosemary Addy
Dianne Murphy
Lily Mulugeta
Rachel Witten
Michelle Roth Cline
Rosemary Addy

PREA



(b) (4)

10:50	BLA	125469	Dulaglutide (Partial Waiver/Deferral/Plan)	Adjunct to diet and exercise to improve glycemic control in adults with T2DM
-------	-----	--------	--------------------------------------------	------------------------------------------------------------------------------



(b) (4)

TRULICITY Partial Waiver/Deferral/Plan

BLA 125469 seeks review of TRULICITY (dulaglutide) as adjunct to diet and exercise to improve glycemic control in adults with T2DM

- The application has a PDUFA goal date of September 18, 2014.
- The application triggers PREA as a new: dosage form and indication.
- *PeRC Recommendations:*
 - The PeRC agreed with the Division to grant a partial waiver in pediatric patients less than 10 years of age because studies are impossible or highly impractical and to a deferral in pediatric patients 10 years and older because the product is ready for approval in adults.
 - The PeRC recommends that the Division advance the timeline for studies and to ensure that the juvenile toxicity studies are underway. Additionally the PeRC recommended that if the sponsor is unable to meet the established timeline that the sponsor can request a deferral extension with appropriate justification.
 - The PeRC agreed with the Division's plan to collect PK data as part of the efficacy/safety trial rather than conduct a separate PK/PD study.

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

/s/

GEORGE E GREELEY
07/29/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, July 25, 2014 10:30 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: dulaglutide label

Importance: High

Dear Ken

Please find attached our initial comments/edits for the dulaglutide package insert. Kindly respond by COB Thursday, July 31, 2014.

Thanks, Bola



10/25/2014
[unreadable text]

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
07/25/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Thursday, July 24, 2014 11:12 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Subject: dulaglutide

Dear Ken,

Please submit the (b) (4) test results as soon as they are available. Indicate in your response to this email when the data will be submitted.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
07/24/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Monday, June 23, 2014 1:48 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com); John J Kaiser (kaiser_john_joseph@lilly.com)
Cc: Adeolu, Abolade; Chen, Elizabeth
Subject: dulaglutide

Dear Ken,

With regard to the (b) (4) test you committed to conduct in amendment dated 6/18/2014 (Sequence 30), please use three batches of DP in the (b) (4) test.

With regard to the Change Management Protocol provided in Section 3.2.R, please provide the (b) (4)

Kindly acknowledge receipt and let me know how soon to expect your response.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
06/23/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, June 20, 2014 11:19 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade; Chen, Elizabeth
Subject: dulaglutide

Dear Ken,

Please respond to the following comments by June 30, 2014

1. Endotoxin monitoring of the (b) (4) and endotoxin monitoring (b) (4) should be routinely performed as part of an overall endotoxin control strategy. Please implement endotoxin monitoring at these steps. Note that any strategies implemented to overcome (b) (4) for drug product testing would also need to be implemented for testing of (b) (4). The proposed limit (b) (4) endotoxin would be acceptable. In addition, the (b) (4) should be monitored for bioburden. The proposed limit (b) (4) would be acceptable.
2. Please provide data from the method specificity study for the dye ingress test and the updated dye ingress test method which includes the visual positive control. If the study has not yet been completed, provide the target date for study completion.
3. Please commit to provide summary data from the performance qualification shipments of the SFS and the PFS from (b) (4) to Eli Lilly in the first annual report.

Kindly acknowledge receipt of this email. I will be out of the office and I have copied my colleague who will cover me for emergencies only.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
06/20/2014



BLA 125469

MEETING MINUTES

Eli Lilly and Company
Attention: Kenneth Mace, Ph.D.
Advisor, Global Regulatory Affairs - Diabetes
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Mace:

Please refer to your Biologics License Application (BLA) 125469 submitted under the Public Health Service Act for dulaglutide.

We also refer to the meeting between representatives of your firm and the FDA on May 15, 2014. The purpose of the meeting was to discuss specifications for dulaglutide.

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

If you have any questions, contact me.

Sincerely,

{See appended electronic signature page}

Laurie Graham, M.S.
CMC Product Quality Team Leader
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: CMC Only

Meeting Date and Time: May 15, 2014 at 2:00PM
Meeting Format: Teleconference

Application Number: 125469
Product Name: dulaglutide
Sponsor/Applicant Name: Eli Lilly and Company

Meeting Chair: Laurie Graham
Meeting Recorders: Andrew Shiber

FDA ATTENDEES:

Center for Drug Evaluation and Research

Office of Biotechnology Products (OBP)

Sarah Kennett	Review Chief, Division of Monoclonal Antibodies (DMA)
Laurie Graham	CMC Product Quality Team Leader, DMA
Joel Welch	CMC Product Quality Reviewer, DMA
Andrew Shiber	Regulatory Project Manager, OBP

Office of New Drugs (OND)/Division of Metabolism and Endocrinology Products (DMEP)

William Chong	Team Lead, Medical Officer
Suchitra Balakrishnan	Medical Officer
Abolade Adeolu	Regulatory Project Manager

Office of Compliance/Biotech Manufacturing Assessment Branch

Patricia Hughes	Team Leader
Bo Chi	Microbiologist
Colleen Thomas	Microbiologist

SPONSOR ATTENDEES

Eli Lilly and Company

Ken Mace	Regulatory-Diabetes
Allison Kennington	Regulatory-CMC
Bruce Meiklejohn	Regulatory-CMC
Mike DeFelippis	Bioprocess Research and Development
Kristi Griffiths	Statistics
Sarah Demmon	Analytical Development
Ciaran Brady	Drug Substance Manufacturing (Kinsale, Ireland)
Patrick Blacha	Parenteral Manufacturing

1.0 BACKGROUND

Objectives: The Agency requested a meeting with the sponsor to discuss responses from an information request that was sent on May 13, 2014 and to discuss drug substance specifications for dulaglutide. A separate meeting was held on May 22, 2014 which discussed the drug product specifications and outstanding items from this meeting. The fifteen discussion items submitted by IR on May 13, 2014 are presented below in bold as “**Question**” and the sponsor’s response provided by email on May 14, 2014 are copied directly as “**Sponsor Response**”.

2.0 DISCUSSION

Question 1: The DS and DP specifications provided appear to be for end of shelf-life only. As certain quality attributes are expected to change during the shelf-life, it is unclear how quality at release will be controlled to assure that the end of shelf-life specifications will be met. For example, drug product and drug substance lots may meet the proposed acceptance criteria at release for certain attributes but would not be expected to meet acceptance criteria at the end of shelf-life. For product quality attributes that are expected to change during shelf-life, separate release and stability specifications are needed. This applies to both drug substance and drug product.

Sponsor Response to Question 1:

The drug substance is a (b) (4) solution stored at (b) (4). And, as discussed in Section 3.2.S.7.1, Stability Summary and Conclusions, dulaglutide drug substance is stable when packaged and stored as specified in Section 3.2.S.6, Container Closure System. Since degradation is not observed during storage of dulaglutide drug substance (b) (4), separate release and end of shelf-life specifications are not proposed for the drug substance.

The drug product exhibits change for certain quality attributes over the proposed shelf-life of 24 months, (b) (4). Table Q1-1 provides proposed release criteria for the drug product that take into consideration the proposed drug substance acceptance criterion, allowance for change during drug product manufacturing, predicted change over shelf-life, uncertainty of the change, and method variability. Table Q1-1 also provides the proposed end of shelf-life specification acceptance criteria. The drug product specification table in 3.2.P.5.1 and associated justifications in 3.2.P.5.6 will be updated to include the proposed release criteria.

Table Q1-1 Proposed Drug Product Release and End of Shelf-Life Acceptance Criteria

Analytical Property	Proposed Release Criteria	Proposed End of Shelf-Life Specification Acceptance Criteria
Purity		

Dulaglutide (b) (4) Purity (%)	NLT	(b) (4)	NLT	(b) (4)
Related Substances/Impurities: Total (%)	NMT		NMT	
(b) (4)	NM		NMT	
	NM		NMT	
	NLT		NLT	
	NM		NMT	
	NLT		NLT	

**Purity
 Other Tests**

(b) (4)	NLT	(b) (4)	NLT	(b) (4)
	NMT		NMT	
	NMT		NMT	

Meeting Discussion: The Agency stated that it was not prepared to discuss drug product (DP) specifications at this time. The proposal to have identical drug substance release and stability specifications was accepted by the Agency.

2. Additional information is needed to support the approach to setting specifications for DP. There are concerns that the projected changes on stability and during DP manufacturing are too large and do not accurately reflect clinical experience. We recommend that the following information be provided in order to have a meaningful discussion regarding the proposed DP specifications:

- a. Provide confirmation that the clinical lots used for the total predicted change information in table 3.2.P.5.6.1.5.6-1 are Phase 3 clinical lots. For each lot, provide the end of shelf life CQA levels based on the individual lot release results and the individual lot degradation results. A summary table of ranges at end of shelf-life should be provided based on this data.

Sponsor Response to Question 2a: The batches used for the total predicted change listed in Table 3.2.P.5.6.1.5.6-1 are Phase 3 clinical batches with the exception of the process validation batches which were not used in the Phase 3 clinical studies. The end of shelf life values are shown in Table Q2a-1 and the summary is shown in Table Q2a-2.

Table Q2a-1 Dulaglutide Drug Product Batches Used for Statistical Analysis of Total Change

Property	CT565054 (LYKE10)	CT565053 (LYKD09)	CT565052 (LYKE12)	CT565051 (LYKD08)	CT565050 (LYKE11)	CT565049 (LYKC05)	CT553650 (LYIL07)	CT553648 (LYIL06)	CT551777 (LYII04)	CT551776 (LYII03)
Dulaglutide	(b) (4)									
Purity	(b) (4)									
Related Substances/ Impurities: Total by	(b) (4)									

Table Q2a-1 (continued) Dulaglutide Drug Product Batches Used for Statistical Analysis of Total Change

Property	CT565054 (LYKE10)	CT565053 (LYKD09)	CT565052 (LYKE12)	CT565051 (LYKD08)	CT565050 (LYKE11)	CT565049 (LYKC05)	CT553650 (LYIL07)	CT553648 (LYIL06)	CT551777 (LYII04)	CT551776 (LYII03)
	(b) (4)									

Table Q2a-1 (continued) Dulaglutide Drug Product Batches Used for Statistical Analysis of Total Change

Property	CT565054 (LYKE10)	CT565053 (LYKD09)	CT565052 (LYKE12)	CT565051 (LYKD08)	CT565050 (LYKE11)	CT565049 (LYKC05)	CT553650 (LYIL07)	CT553648 (LYIL06)	CT551777 (LYH04)	CT551776 (LYH03)
(b) (4)										

Table Q2a-1 (continued) Dulaglutide Drug Product Batches Used for Statistical Analysis of Total Change

Property	CT565054 (LYKE10)	CT565053 (LYKD09)	CT565052 (LYKE12)	CT565051 (LYKD08)	CT565050 (LYKE11)	CT565049 (LYKC05)	CT553650 (LYIL07)	CT553648 (LYIL06)	CT551777 (LYH04)	CT551776 (LYH03)
(b) (4)										

Table Q2a-2 Summary of End of Shelf Life Ranges

Property	(b) (4)
(b) (4)	(b) (4)

Meeting Discussion: There was no discussion.

- b. For the projected changes during manufacturing, provide supportive summary data from actual DS and DP batches, manufactured with the proposed commercial process, demonstrating the rates of change for CQAs during DP manufacturing.

Sponsor Response to Question 2b: Manufacturing data showing the average change in the product quality attributes from drug substance release to drug product release are shown in Table Q2b-1.

Table Q2b-1 Average Difference between Drug Substance Incoming Quality and Drug Product Release Value

Property	Average Difference (%) (Drug Substance – Drug Product)
(b) (4)	(b) (4)

Meeting Discussion: The Agency requested an explanation for why differences exist between certain quality attributes for drug substance and drug product, given that no change is expected upon drug product manufacture. The Sponsor agreed to provide an explanation, including the origin for table Q2b-1.

- c. Provide any other information on the clinical levels for dulaglutide CQAs. This could include, for example, an estimate of the levels based on the ages of the lots used clinically.

Sponsor Response to Question 2c: The analysis of 10 batches of dulaglutide drug product administered near the end of shelf life is shown in Tables Q2c-1 and Q2c-2. The amount of each attribute was estimated based on the rates of change at 2-8°C shown in Table Q2c-1, with the exception of batches CT565052 and CT565054 which have real-time stability data associated with them.

Table Q2c-1 Rates of Change at 2-8°C

Property	Rate of Change per Month at 2-8°C
Dulaglutide (b) (4) Purity (b) (4)	(b) (4)

Related Substances/Impurities: Total by (b) (4)	(b) (4)
(b) (4)	

Table Q2c-2 Estimated/Actual Levels of Quality Attributes at the Time of Administration for 10 Drug Product Batches

Property	CT558494	CT561268	CT560277	CT562340	CT562898	CT563850	CT564624	CT565052 ¹	CT565054 ¹	CT568863
Age at Administration	22 Months	22 Months	24 Months ²	21 Months	23 Months	22 Months	24 Months ²	24 Months ²	24 Months ²	23 Months
Dulaglutide (b) (4) Purity by (b) (4)	(b) (4)									
Related Substances/ Impurities: Total by (b) (4)										

Property	CT558494	CT561268	CT560277	CT562340	CT562898	CT563850	CT564624	CT565052 ¹	CT565054 ¹	CT568863
(b) (4)	(b) (4)									

¹ Data from stability study.
² No material was administered past the expiry date.

- d. Provide the mean \pm 3 SD release results for the DP lots used clinically.

Meeting Discussion:

There was no discussion during the meeting.

Sponsor Response to Question 2d : The mean \pm 3 SD release results for the 40 drug product lots used clinically are presented in Table Q2d-1.

Table Q2d-1 Drug Product Batch Release Calculations of Mean \pm 3 SD

Analytical Property	Batch Release Process Average (n=40)	Batch Release Process Standard Deviation (n=40)	Avg - 3 SD	Avg + 3 SD
Assay				
Protein Content (%)	(b) (4)			
Potency (%)				
Purity				
Dulaglutide (b) (4) Purity by (b) (4)				
Total Related Substances/Impurities by (b) (4)				
(b) (4)				
Other Tests				
(b) (4)				

Meeting Discussion:

There was no discussion during the meeting.

3. Acceptance criteria for sub-visible particles should be based upon clinical experience. Provide updated acceptance criteria along with a justification.

Sponsor Response to Question 3: The (b) (4) release data from Phase 3 clinical batches and stability batches were analyzed. An acceptance criterion of Not More Than (b) (4) particles per container is proposed for the (b) (4) particle size particulate matter and Not More Than (b) (4) particles per container for the (b) (4) particle size particulate matter, based on clinical experience.

Meeting Discussion: The Agency requested that the sponsor provide a statistical analysis to support their proposed specification acceptance criteria for subvisible particles. The Sponsor agreed to provide this information.

- For DS specifications, we recommend that mean +/- 3SD data be provided for comparison to the tolerance intervals provided in table 3.2.S.4.5.6-1.

Sponsor Response to Question 4: For comparison to the tolerance intervals presented in Table 3.2.S.4.5.6-1, the batch release summary statistics and calculations of the mean +/- 3 SD are presented in Table Q4-1.

Table Q4-1 Drug Substance Batch Release Calculations of Mean +/- 3 SD for Comparison to 95/99.5 Tolerance Limits

Analytical Property	Batch Release Process Average (n=25)	Batch Release Process Standard Deviation (n=25)	Avg - 3 SD	Avg + 3 SD	95/99.5 Tolerance Limit
Purity					
Dulaglutide Purity	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Other Tests	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Meeting Discussion: The Agency recommended the following specification criteria for drug substance release and on stability specifications. These proposals were agreed upon by the sponsor.

Dulaglutide (b) (4) Purity
Total Related Substances/Impurities (b) (4)

(b) (4)

The Agency proposed the following criteria for Charge Variants:

(b) (4)

The sponsor stated they had performed additional statistical analysis and believe the following limits to be appropriate drug substance release and stability, and for drug product release.

(b) (4)

The Agency told the sponsor to provide their analysis and justification for these specification limits for the (b) (4) method in a response by Tuesday, May 20, 2014. The Agency also requested a standard deviation statistical analysis for drug substance and drug product potency results as well.

5. For both DS and DP specifications, provide additional information on how the presence of (b) (4) is controlled for in the (b) (4) assays.

Sponsor Response to Question 5: In the (b) (4) method, part of the method system suitability acceptance criteria contains a qualitative comparison of the profile of the system suitability standard to the figure example provided in the method. The (b) (4) method will be revised to include a qualitative assessment of the test sample profile to the reference standard for peaks above the limit of quantitation (b) (4)

The (b) (4) assay was designed to exclusively assess (b) (4) the GLP peptide. Due to the design of this assay, (b) (4)

(b) (4)

[REDACTED] (b) (4)
[REDACTED] The method does include method acceptance criteria for a qualitative comparison of the overall profile to that of the reference standard as well as a comparison of [REDACTED] (b) (4) ratios [REDACTED] (b) (4)
[REDACTED]

[REDACTED] (b) (4)

(b) (4)



Meeting Discussion: The Agency explained that it had concerns that (b) (4) are not controlled by the (b) (4) assays. The Agency mentioned specifically (b) (4) observed in stress stability samples, particularly, photostability samples. The proposal of the sponsor to revise the (b) (4) acceptance criteria to include a

qualitative assessment of the test sample profile compared to the reference standard for (b) (4) above the limit of quantitation ((b) (4)) was accepted by the Agency. Additionally, the justification provided for why the (b) (4) assay cannot include this same assessment was considered acceptable.

6. As DP shelf-life appears to be based on 24 months of data at 2-8⁰C and includes 1 month storage at 30⁰C, these conditions should be part of the drug product annual stability protocol. The DP stability commitment as well as on- going and future protocols involving real time stability data (e.g. validation and comparability protocols) should be updated accordingly.

Sponsor Response to Question 6: The drug product shelf life is based on 24 months of data at 2-8⁰C including a 14-day in-use period at 30⁰C. (b) (4)

The drug product stability commitment provided in Section 3.2.P.8.2.1 will be updated to include an end of shelf life study (14 days at 30⁰C). The process validation stability study protocol includes an end of shelf life study as described in Table 3.2.P.8.3.2.2.3-1 in the Supporting Stability Section. These batches were also part of the comparability study. Future stability study protocols to support activities such as validation and comparability studies will also include an end of shelf life study.

Meeting Discussion: The Agency accepted this proposal.

7. With regard to (b) (4) for DS, it is noted that there appear to be significant changes observed after (b) (4) days for the (b) (4) (b) (4) with storage at (b) (4) as detected by the (b) (4) assays. However, tno data were provided for these assays at the 24 hour time point. Provide clarification.

Sponsor Response to Question 7: The (b) (4) applied to the (b) (4) is restricted to (b) (4) during routine operations, which is supported by the process validation. As outlined in the response to Q8 (refer to [Table Q8-1](#)), the (b) (4) were satisfactorily held at room temperature for up to (b) (4) during dulaglutide process validation.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Meeting Discussion: There was no discussion.

- Update your drug substance primary stability data tables to include the 36-month potency value.

Sponsor Response to Question 9: The updated primary stability tables that include the 36 month bioassay results are shown in [Tables Q9-1](#) through [Q9-3](#). All results met the study acceptance criteria through 36 months of storage at (b) (4)

Table Q9-1 Stability Results for Primary Stability Lot PP0092-10, Stored in (b) (4)

Analytical Property	Acceptance Criteria	Method	Condition	Time Point (Months)							
				Initial	3	6	9	12	18	24	36
Identification Tests											
Identity	(b) (4)										
Identity	(b) (4)										
Quantity Test											
Quantity	(b) (4)										
Potency Test											
Potency	(b) (4)										

Table Q9-2 Stability Results for Primary Stability Lot PP0126-10, Stored in (b) (4)

Analytical Property	Acceptance Criteria	Method	Condition	Time Point (Months)							
				Initial	3	6	9	12	18	24	36
Identification Tests											
Identity	(b) (4)										
Identity											
Quantity Test											
Quantity											
Potency Test											
Potency											
Purity Tests											
LY2189265 Purity											

Table Q9-3 Stability Results for Primary Stability Lot PP0160-10, Stored in PETG

Analytical Property	Acceptance Criteria	Method	Condition	Time Point (Months)							
				Initial	3	6	9	12	18	24	36
Identification Tests											
Identity	(b) (4)										
Identity											
Quantity Test											
Quantity											
Potency Test											
Potency											
Purity Tests											
LY2189265 Purity											

Meeting Discussion: There was no discussion.

10. Provide a summary of method verification performed for the compendial methods used for assessment of dulaglutide drug substance and drug product.

Sponsor Response to Question 10: A summary of method verification studies performed for the compendial methods used for assessment of dulaglutide drug substance and drug product are provided in [Table Q10-1](#) (drug substance) and [Tables Q10-2 through Q10-4](#) (drug product).

Table Q10-1 Drug Substance Compendial Method Verification Summary

Compendial Method	Verification Study	Results
Color	(b) (4)	
Clarity and Degree of Opalescence		
pH		
Endotoxin		
Total Aerobic Microbial Count		

Table Q10-2 Drug Product Compendial Method Verification Summary

Compendial Method	Site	Verification Study	Results
Color	(b) (4)	[Redacted]	(b) (4)
	Lilly Indianapolis		
Clarity	(b) (4)		
	Lilly Indianapolis		
pH	(b) (4)		
	Lilly Indianapolis		

Table Q10-2 (continued) Drug Product Compendial Method Verification Summary

Compendial Method	Site	Verification Study	Results
Osmolality	(b) (4)		(b) (4)
	Lilly Indianapolis		

Table Q10-2 (continued) Drug Product Compendial Method Verification Summary

Compendial Method	Site	Verification Study	Results
Particulate Matter	(b) (4)		
	Lilly Indianapolis		
Endotoxin	(b) (4)		
	Lilly Indianapolis		

Table Q10-2 (continued) Drug Product Compendial Method Verification Summary

Compendial Method	Site	Verification Study	Results
Sterility	(b) (4)		
	Lilly Indianapolis		
Container Content USP <1>	(b) (4)		
	Indianapolis		

5 Pages have been Withheld in Full as B4 (CCI/TS)
Immediately Following this Page



Meeting Discussion:

The Agency stated that it would require additional time to evaluate the submitted information and would request clarification if needed. The Agency noted it had one preliminary observation, namely, that the (b) (4) testing for (b) (4) demonstrated a low value for particles, relative to historical trends, and far lower than the Lilly Indianapolis site. The sponsor clarified that the batch tested for verification was a “laboratory” batch, which had not previously been in a syringe. (b) (4)

(b) (4). The sponsor also clarified that the (b) (4) value in the test sample field is a typographical error.

11. It is noted that (b) (4) appears to be based only on viral clearance data. While there appears to be other data available (b) (4) it is noted that the (b) (4) used at reduced scale was different than the full scale process. Based on the available information, it appears that there are (b) (4) at commercial scale. Please confirm. If confirmed, (b) (4) should be limited to (b) (4).

Sponsor Response to Question 11: Lilly confirms that the (b) (4) presented in Section 3.2.S.2.5.3.2, (b) (4) is at commercial scale. We can also confirm that we are currently in dulaglutide production, as witnessed during PAI, to support product launch; (b) (4)

To date we have completed (b) (4) with an expected production completion date of 30 June 2014 to achieve a commercial scale validated (b) (4). The completed concurrent validation (b) (4) data will be available for submission to agency by the end of June. Interim data available to date (b) (4) are presented in [Figure Q11-1](#) below.

Data from laboratory scale studies supplied to date are considered to be supportive of the ongoing concurrent validation exercise outlined above; however the concurrent validation dataset is considered the primary data used (b) (4). Data generated at the reduced laboratory scale employed a (b) (4) which represents a worst-case scenario (b) (4) as compared to the commercial (b) (4). Lilly is currently executing an additional laboratory scale (b) (4) study in parallel with the commercial scale validation (b) (4) out to the viral clearance claim of (b) (4). This study, which employs the commercial scale (b) (4) and supports the previously provided laboratory scale and commercial scale data, will be available for submission by the end of June.



Meeting Discussion: The Agency noted approaching internal review deadlines, and the need to make final recommendations (b) (4). The Agency noted that the late June submission timeframe is too late, and that any extension (b) (4) could be made in an annual report as it would derive from a protocol approved with the BLA. The sponsor proposed submitting additional data prior to the May 22, 2014 telecon. This was accepted by the Agency.

12. We recommend that (b) (4) include limits for the (b) (4) validation studies.

Sponsor Response to Question 12: As recommended, the (b) (4) will be updated to include the limit (b) (4) achieved in the concurrent (b) (4) validation studies. In addition, Lilly Kinsale accepts your earlier recommendation (b) (4) and will update procedure (b) (4) accordingly.

Meeting Discussion:

There was no discussion.

13. DS and DP stability commitments should be updated with a list of stability studies that you are committed to completing.

Sponsor Response to Question 13: All studies provided in the submission will be completed as outlined in the stability protocols provided in both the primary and supporting stability sections for both drug substance and drug product. Sections 3.2.S.7.1 and 3.2.P.8.1 will be updated to reflect the commitment to complete these studies.

Meeting Discussion:

There was no discussion.

14. 3.2.S.2.2 of the BLA should be updated to (b) (4)

Sponsor Response to Question 14: We agree to update Section 3.2.S.2.2 of the BLA (b) (4)

Meeting Discussion:

There was no discussion.

15. It is not clear whether the microbial retention study (b) (4) was performed with the worst-case product strength. The product formulation used for the study was not indicated, and justification for performing the study with only one of the product strengths was not provided. In addition, viability data supporting the two-stage study design was not provided.

Sponsor Response to Question 15: The microbial retention study (b) (4) was performed with the high strength, 1.5 mg/0.5 mL, drug product. The high strength was selected as worst case to assess if the dulaglutide molecule had an impact on the (b) (4) properties studied during (b) (4) validation. The citrate (b) (4) components, mannitol and polysorbate 80, are the same in both strengths and therefore would not impact the study results. In addition, the two drug product strengths (1.5 mg/0.5 mL and 0.75 mg/0.5 mL) have similar (b) (4) properties, which further justifies using only the high strength in the study.

As requested, the viability data tables supporting the two-stage study design are provided below (extracted from the (b) (4)). Data obtained in the viability studies show that the drug product is (b) (4) and therefore the challenge portion of the retention study was conducted in two stages.

Additional Meeting Discussion: The sponsor was asked to confirm that the additional process parameters added to sections 3.2.S.2.2, 3.2.S.2.4, 3.2.P.3.3 and 3.2.P.3.4 at the request of the Agency are considered to be regulatory commitments.

The sponsor confirmed they would be considered regulatory commitments.

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

/s/

ANDREW J SHIBER
05/30/2014



BLA 125469

INFORMATION REQUEST

Eli Lilly and Company
Attention: Dr. Kenneth F. Mace
Advisor, Global Regulatory Affairs
DC 2543
Indianapolis, IN 46285

Dear Dr. Mace:

Please refer to your Biologics License Application received September 17, 2013, submitted under section 351(a) of the Public Health Service Act for dulaglutide.

We are reviewing your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to the teleconference scheduled for the week of May 11-17, 2014.

1. The DS and DP specifications provided appear to be for end of shelf-life only. As certain quality attributes are expected to change during the shelf-life, it is unclear how quality at release will be controlled to assure that the end of shelf-life specifications will be met. For example, drug product and drug substance lots may meet the proposed acceptance criteria at release for certain attributes but would not be expected to meet acceptance criteria at the end of shelf-life. For product quality attributes that are expected to change during shelf-life, separate release and stability specifications are needed. This applies to both drug substance and drug product.
2. Additional information is needed to support the approach to setting specifications for DP. There are concerns that the projected changes on stability and during DP manufacturing are too large and do not accurately reflect clinical experience. We recommend that the following information be provided in order to have a meaningful discussion regarding the proposed DP specifications:
 - Provide confirmation that the clinical lots used for the total predicted change information in table 3.2.P.5.6.1.5.6-1 are Phase 3 clinical lots. For each lot, provide the end of shelf life CQA levels based on the individual lot release results and the individual lot degradation results. A summary table of ranges at end of shelf-life should be provided based on this data.

- For the projected changes during manufacturing, provide supportive summary data from actual DS and DP batches, manufactured with the proposed commercial process, demonstrating the rates of change for CQAs during DP manufacturing.
 - Provide any other information on the clinical levels for dulaglutide CQAs. This could include, for example, an estimate of the levels based on the ages of the lots used clinically.
 - Provide the mean +/- 3 SD release results for the DP lots used clinically.
3. Acceptance criteria for sub-visible particles should be based upon clinical experience. Provide updated acceptance criteria along with a justification.
 4. For DS specifications, we recommend that mean +/- 3SD data be provided for comparison to the tolerance intervals provided in table 3.2.S.4.5.6-1.
 5. For both DS and DP specifications, provide additional information on how the presence of (b) (4) is controlled for in the (b) (4) assays.
 6. As DP shelf-life appears to be based on 24 months of data at 2-8⁰C and includes 1 month storage at 30⁰C, these conditions should be part of the drug product annual stability protocol. The DP stability commitment as well as on-going and future protocols involving real time stability data (e.g. validation and comparability protocols) should be updated accordingly.
 7. With regard to (b) (4) for DS, it is noted that there appear to be significant changes observed (b) (4).
(b) (4) However, no data were provided for these assays at the (b) (4) time point. Provide clarification.
 8. Provide any available information to support DS (b) (4)
 9. Update your drug substance primary stability data tables to include the 36-month potency value.
 10. Provide a summary of method verification performed for the compendial methods used for assessment of dulaglutide drug substance and drug product.
 11. It is noted that the (b) (4) appears to be based only on viral clearance data. While there appears to be other data available (b) (4) it is noted that the (b) (4) used (b) (4) was different than the full scale process. Based on the available information, it appears that there are (b) (4)

- (b) (4) at commercial scale. Please confirm. If confirmed, the (b) (4) should be limited (b) (4).
12. We recommend that (b) (4) include limits for the (b) (4) validation studies.
13. DS and DP stability commitments should be updated with a list of stability studies that you are committed to completing.
14. 3.2.S.2.2 of the BLA should be updated (b) (4).
15. It is not clear whether the microbial retention study (b) (4) was performed with the worst-case product strength. The product formulation used for the study was not indicated, and justification for performing the study with only one of the product strengths was not provided. In addition, viability data supporting the two-stage study design was not provided.

If you have any questions, please contact me.

Sincerely,

{See appended electronic signature page}

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Andrew.Shiber@fda.hhs.gov

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

/s/

ANDREW J SHIBER
05/13/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Monday, May 12, 2014 10:33 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: dulaglutide: CMC microbiology Information Request

Dear Ken,

Please provide the following information by May 26, 2014:

1. Provide the additional bioburden and endotoxin qualification data (b) (4) and (b) (4) intermediate samples when available at the end of June 2014.
2. With regard to your response to Question 8 provided in amendment dated 5/5/2014, the provided (b) (4) data do not support the use of (b) (4) in place of CSE/RSE in the endotoxin hold-time study. (b) (4) Please provide data from an endotoxin hold time study performed with (b) (4). The study should be done with three lots of DS and DP manufactured from three different lots of (b) (4) DP. Provide the study protocol and report. Provide an estimated study completion time.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
05/12/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Monday, May 12, 2014 10:06 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: dulaglutide

Dear Ken,

We previously requested that the you identify how you have controlled the time between injection activation and injection delivery to assure that the drug delivery does not begin until the needle reaches the target injection site.

Your response states that they have not established a requirement for this characteristic. Please provide one of the following:

Specification of time between injection initiation and activation to assure that drug delivery does not initiate prior to the needle reaching target injection site, and verification data supporting the specification.

Or

Provide documentation demonstrating that delivery accuracy studies were conducted in accordance with methods specified in ISO 11608-5, Section 5.1.9.

Thanks,
Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3121
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
05/12/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Thursday, May 01, 2014 12:47 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: Dulaglutide

Dear Ken,
The following are recommended prior to approval of this BLA

4.1.1 Prefilled Syringe Instructions for Use

A. Revise the numbered instructions as indicated below. We recommend this because several patients missed the bulleted lists under these steps as they may not read the bullet points.

1. Pull off and throw away the needle cover
2. Gently pinch a skin fold at the injection site
3. Insert the needle at 45 degree angle into your skin
4. Slowly push the plunger all the way in until all the medicine is injected
5. Remove the needle from your skin
6. Gently let go of the fold of your skin
7. Throw away the syringe in a puncture resistant container

B. Revise the pictures associated with the steps to ensure they match the descriptions of each step.

4.1.2 Single Use Pen Instructions for Use

A. Revise the numbered instructions as indicated below. We recommend this because of several patients missed the bulleted lists under these steps as they may not read the bullet points.

1. Pull off and throw away the (b) (4) base cap
2. Place the clear base flat and firmly against your skin at the injection site
3. Unlock by turning the Lock Ring
4. Press and hold the green injection button until you hear a loud click
5. Hold in place (b) (4) you hear a second click and the (b) (4)
6. Remove the pen from your skin
7. Throw away the pen in a puncture resistant container

B. Revise the pictures associated with the steps to ensure they match the descriptions of each step.

4.1.3 Prefilled Syringe Container Label and Carton Labeling

- A. Add the statement "Single Use Only"
- B. 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.

C. Ensure that the image of the prefilled syringe accurately represents the actual size, shape, color, and imprint of the commercial product and is not a schematic or computer-generated image. In addition, this image should be less prominent than the proprietary name, established name and strength.³

4.1.4 Single Use Pen Container Label and Carton Labeling

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

A. See 4.1.3 B and 4.1.3 C

Please acknowledge receipt of email.

Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
05/01/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Wednesday, April 16, 2014 10:53 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: BLA 125469(dulaglutide): CMC drug product and drug substance

Dear Ken,
Please respond to the following by April 29, 2014

Drug Product:

1. Provide a leachable/extractable risk assessment for [REDACTED] (b) (4) the dulaglutide drug product manufacturing process.
2. For the DP process characterization studies and hold time studies, provide a justification for the CQAs and assays that were excluded from each study.
3. Provide information to support that the [REDACTED] (b) (4) for drug product manufacturing, inclusive of assembly, packaging, and labeling operations, will not negatively impact dulaglutide CQAs.
4. 21 CFR 610.14 states that an identity test must be performed on products after all labeling operations have been completed. Provide information to confirm that identity testing of dulaglutide meets this CFR requirement.
5. Regarding drug product container closure system suitability, you state [REDACTED] (b) (4)
[REDACTED] " Based on these results, it was determined that [REDACTED] (b) (4). Provide this data.
6. The description of process validation data for drug product notes in the evaluation of their acceptability that "In addition, the statistical assessments to evaluate within-batch and between-batch variability met acceptance criteria". Provide this data.
7. In table 3.2.P.5.6.1.5.6-1 you include an estimate for the potential change during manufacture for various critical quality attributes. Provide an explanation and additional data for how these estimates were determined.
8. Regarding the DP Description of Manufacturing Process and Process Controls, Eli Lilly and Company and [REDACTED] (b) (4) additional process parameters should be included to ensure sufficient control of the DP manufacturing process. Inclusion of information in the pharmaceutical development section (3.2.P.2) only is not sufficient. Revise the description of the DP manufacturing process and/or control of critical steps and intermediates sections (3.2.P.3.3 and 3.2.P.3.4) to include the following process parameters operating ranges or control limits.

[REDACTED] (b) (4)

(b) (4)

9. Update P.2.P.3.4 to include (b) (4) for all applicable stage of the drug product manufacturing process.

Drug Substance:

10. It is noted that there were (b) (4)
(b) (4)
provide the relevant data to the BLA.
11. We note that (b) (4)
(b) (4)
12. From the information provided, it appears that the (b) (4)
(b) (4)
13. Provide an updated raw material risk assessment for all materials used in the dulaglutide manufacturing process. This should include a justification and any data demonstrating clearance of these materials in the manufacturing process.
14. Provide a leachable/extractable risk assessment for the consumables used in the dulaglutide drug substance manufacturing process.
15. With regard to the (b) (4) studies, the data provided in 3.2.S.2.3.2 appear to be from concurrent validation activities. Provide the product quality (b) (4) data, including yield data, from the small scale studies sufficient to support (b) (4).
16. Provide explanation for the absence of (b) (4) (b) (4)
(b) (4).
17. Provide additional information to support equivalent performance (b) (4)
(b) (4).
18. With regard to the process validation (b) (4) results provided in table 3.2.S.5.1.12-2, provide clarification on which (b) (4) assay was used for this analysis.
19. (b) (4) provide the product quality and (b) (4) data, including yield data from the small scale studies sufficient to support (b) (4)
20. Provide clarification on which (b) (4) can exceed the expiration dating from the vendor. Provide a risk assessment with regard to this practice. This should include information on how the (b) (4) will

be controlled such that they will not exceed the (b) (4) studied in small scale and concurrent validation studies. For those (b) (4) steps claimed as (b) (4) steps, provide clarification on how (b) (4) will be assessed.

21. With regard to the validation of the drug substance manufacturing process and the clearance of process related impurities, provide any available data to support the (b) (4) routine manufacturing. (b) (4)
22. Provide the (b) (4) protocols and interim report for the (b) (4) final (b) (4) unit operations.
23. Provide a justification for the testing performed in the small scale (b) (4) studies described in tables 3.2.S.2.5.4.1-1, 3.2.S.2.5.4.1-2, and 3.2.S.2.5.4.1-3.
24. Provide data to support the claim in Section 3.2.S.2.3 (b) (4).
25. Regarding the overall approach to qualification of replacement WCBs, Agency experience indicates that an assessment of at least three lots of DS manufactured with a new WCB is necessary to confirm product quality of DS manufactured with a new WCB. Clarify the number of DS lots that are required for qualification of dulaglutide replacement WCB. In addition, provide information on how the CQA acceptance criteria will be determined for each new working cell bank qualification assessment.
26. Sufficient information regarding how the stability of the dulaglutide MCB and WCB are monitored was not provided. Specifically, the number of vials that will be assessed at each monitoring period is not clearly specified and limits for viability and growth are not defined.
27. Provide an updated assessment for the identity, activity, and levels (b) (4) observed in both dulaglutide drug substance and drug product at release and on stability.
28. Provide any additional information available with regard to the impact of attributes on PK, such as (b) (4) information.
29. The analytical release tests for related substances and impurities result in an inability to distinguish between related compounds, and consequently a co-elution and collective reporting of multiple species. Provide additional data justifying the appropriateness of this approach both in general, and for the following specific examples:
(b) (4)
30. (b) (4) to support licensure of the dulaglutide manufacturing process, revise 3.2.S.2.2 and 3.2.S.2.4 to include the following process parameters and the operating ranges or control limits for each parameter. Ranges or limits for the parameters should be supported by historical data from material manufactured considered representative of the commercial process. Submit data that will support the filed ranges to provide the information needed to reach agreement on the proposed ranges or limits.

(b) (4)

(b) (4)

31. (b) (4) revise 3.2.S.2.2 and 3.2.S.2.4 to include the (b) (4) (b) (4) following process parameters and operating ranges or control limits:

(b) (4)

Thanks,Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
04/16/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Wednesday, April 16, 2014 10:53 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: BLA 125469(dulaglutide) CMC Microbiology

Dear Ken,

Please respond to the CMC microbiology information request by May 5, 2014.

1. Please update Section 3.2.S.2.4, "Controls of critical steps and intermediates" with (b) (4) .
2. The (b) (4) bioburden sample volume (b) (4) is low. (b) (4)
Please update Section 3.2.S.2.4, "Controls of critical steps and intermediates" with information of the additional bioburden sampling and the corresponding limits.
3. Please implement an (b) (4)
Provide the (b) (4) bioburden limit.
4. Please provide (b) (4) endotoxin action limits for (b) (4)
5. Please update Section 3.2.S.2.4, "Controls of critical steps and intermediates" with (b) (4) bioburden and endotoxin action limits for (b) (4) Express the bioburden action limits (b) (4) and endotoxin action limits (b) (4) .
In addition, please include the sample testing volume in the bioburden limits.
6. In your response to FDA question 13 in your amendment dated 2/21/2014, an (b) (4) endotoxin alert limit (b) (4) has been implemented for dulaglutide (b) (4)
Please provide the endotoxin action limit.
7. As communicated during the pre-license inspection, (b) (4)
(b) (4) . Please qualify (b) (4) (b) (4) and (b) (4) samples for the bioburden and endotoxin tests.
8. With regard to your response to Question 20 provided in amendment dated 2/21/2014,
 - a) We do not agree that (b) (4)

- Please tighten the acceptance criterion for recovery to (b) (4)
- b) (b) (4) is commercially available and may be used for the hold time studies. (b) (4)
- (b) (4) conduct an endotoxin hold time study using (b) (4).
- The cited sentence (answer to Question 3) from “U.S. Department of Health and Human Services, Food and Drug Administration, Guidance for Industry Pyrogen and Endotoxin Testing: Questions and Answers, June 2012” was directed at storing and handling of the final drug product samples prior to release testing. In addition, the guidance document does not address low endotoxin recovery.
- c) This is acceptable.
- d) It is acceptable to compare endotoxin recovery to the T_0 value over time. The worst-case hold time for the dulaglutide DS endotoxin sample (b) (4) should meet the (b) (4) acceptance criterion for endotoxin recovery in your hold time study using (b) (4) and three DS lots.
- e) Refer to comments (a) and (b) above. In addition, please identify the drug substance batches used to manufacture semi-finished syringe batches LYLA02, A970003, and A972065.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
04/16/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Wednesday, April 09, 2014 1:57 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: BLA 125469 (dulaglutide)

Importance: High

Dear Ken,

In our preliminary review of the dulaglutide BLA we note the following:

Based on the prespecified analysis of the primary study endpoint:

- Dulaglutide 1.5 mg achieved statistically significantly better HbA1c change than the active controls across the Phase 3 studies.
- Dulaglutide 0.75 mg achieved statistically significantly better HbA1c change than the active controls across multiple (but not all of the) Phase 3 studies. Dulaglutide 0.75 mg was non-inferior to active-controls across the phase 3 studies

Safety:

- Across the Phase 3 studies subjects in the high dose dulaglutide group were more likely to discontinue from the studies due to an adverse event than subjects in the low dose group.
- Gastrointestinal side effects were dose dependent and contributed to the higher discontinuation rate in the high dose dulaglutide group
- Pancreatic enzyme shifts seem to be dose-dependent (although the clinical significance is unknown)
- While there is no evident dose dependency in AEs for the moderate CKD subgroup, the sample is small and post-marketing reports of acute renal failure have been reported in the drug class secondary to nausea/vomiting.

Hence we have the following preliminary comments for the label. We may have additional recommendations after further review of the application

Labeling recommendations (Sections 6)

1. Update Tables, Figures, and text to include information on dulaglutide 0.75 mg.

Labeling recommendations (Sections 14)

1. Update Tables, Figures, and text to include information on dulaglutide 0.75 mg.
2. The findings for trial GBCF should be limited to subjects that were enrolled during Stage II of the study. Table 7 and the corresponding text should be updated accordingly.
3. Following the discussion from the midcycle communication, we request that the findings presented in Tables and text be based on the MMRM model that was prespecified in the protocol.
4. Update the x-axis in Figures 5 and 6 to include for each follow-up visit the number of subjects, for each treatment group, with HbA1c assessment. Please also include similar plots for Studies GBDC, GBDA, and GBDD

(b) (4)

Please update labeling and respond by COB April 18, 2014.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
04/09/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Tuesday, April 08, 2014 7:26 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: BLA 125469 (dulaglutide)

Dear Ken,

We have reviewed the risk analysis table you have proposed as a response to our additional information request on device hazards associated with the use of the (b) (4) pen.

The proposed response does not adequately address the request for the following reasons:

- 1 (b) (4)
 - 2
 - 3
 - 4
- 

Please respond to these deficiencies by April 24, 2014.

Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
04/08/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Monday, March 31, 2014 9:55 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: BLA 125469

Dear Ken

Please respond to the following request by April 16, 2014. We are continuing to consider the risk-benefit for both the 0.75 and 1.5 mg doses and may request an updated label.

1. Provide analysis similar to that performed in ISS.APP.113 with examination of the 0.75 mg and 1.5 mg doses, and including all comparator data for the AS7 dataset. Present the information by system organ class, high level term, and preferred term as shown below.

SOC	Dula 0.75 N(%)	Dula 1.5 N (%)	All Dula N(%)	All comp- arator N (%)	Odds ratio	p- value	CMH p- value
HLT							
PT							

2. Provide analysis similar to that performed in ISS.APP.92 with examination of the 0.75 mg and 1.5 mg doses, the pooled dulaglutide doses and all comparator for the AS7 dataset. Present the information by system organ class, high level term, and preferred term (see above).
3. Provide analysis similar to that performed in ISS.6.133 through 138 for the 0.75 mg and 1.5 mg doses, the pooled dulaglutide doses, and all comparator
4. Provide unblinded treatment information on all five cases of pancreatic cancer described in Table 27 of the 4 month safety update

Kindly acknowledge receipt of this email.

Regards, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
03/31/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, March 28, 2014 3:30 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: BLA 125469 (dulaglutide)

Dear Ken,
Please respond to the following by April 21, 2014:

Container Closure Integrity and Shipping

1. Please respond to the following comments regarding container closure integrity (CCI) testing of the SFS.
 - a. Indicate the positive control preparation requirement and the visual positive control dilution used (b) (4) 1.5 mg/ml dulaglutide CCI testing.
 - b. Compare the sensitivity of the dye ingress CCI test to microbial ingress testing in terms of the detectable defect size (b) (4).
 - c. Provide the method qualification report.
2. Please respond to the following comments regarding CCI testing of the PFS and SUP.
 - a. Describe the test methods, including preparation of the controls.
 - b. Compare the sensitivity of the dye ingress CCI tests to microbial ingress testing in terms of the detectable defect size (b) (4).
 - c. Provide the method qualification reports.
3. Please respond to the following comments regarding the stability testing schedules for CCI.
 - a. Indicate the number of SFS, PFS, and SUP stability samples that will be tested for CCI at each time point.
 - b. CCI testing for the SUP stability study is scheduled at 1 and 12 months (b) (4) and 6, 12, and 18 months (b) (4). It is not clear how these time points were chosen. Explain how this study was designed to demonstrate CCI of the SUP over the shelf life of the product.
4. Most of the CCI and transport studies in sections 3.2.P.2.4 and 3.2.P.3.5 do not indicate which container closure system was used (initial versus commercial). Therefore, it is not clear which studies should be reviewed. Please indicate which studies in sections 3.2.P.2.4.1.1 and 3.2.P.2.4.1.5 and tables 3.2.P.3.5.3-2 and 3.2.P.3.5.3-3 were done with the commercial container closure system (b) (4). Confirm that the planned studies in tables 3.2.P.3.5.3-2 and 3.2.P.3.5.3-3 will be done with the commercial container closure system.
5. Please respond to the following comments regarding shipping of the SFS, PFS, and SUP.
 - a. Explain how temperature is monitored during shipment of the SFS, PFS, and SUP. Indicate the allowable temperature excursions.

- b. Provide thermal qualification data (b) (4) used for the SFS, PFS, and SUP demonstrating temperature control under worst-case shipping conditions.
6. Please respond to the following comments regarding the SFS (b) (4) study.
- a. Clarify whether the study was performed with the commercial primary container closure system.
- (b) (4)
7. (b) (4)
- Please establish an (b) (4)
- (b) (4) and justify the limit using data from (b) (4) simulated shipping studies.
- The data should (b) (4)
- (b) (4) demonstrate maintenance of syringe integrity under worst-case conditions.
8. Please identify the batches of SUP used for the container closure integrity study shown in Table 3.2.R.5.3.6-1 (b) (4) and indicate whether this batch was manufactured with the commercial primary container closure system.
9. Table 3.2.R.6.3.6-1 lists LYL19A/C038888A as the batch of PFS used for a container closure integrity study, but C038888A is listed elsewhere as an SUP batch rather than a PFS batch. Please describe the PFS batch used for this study and indicate whether this batch was manufactured with the commercial primary container closure system.

Kindly acknowledge receipt of this email.

Regards, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
03/28/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Wednesday, March 26, 2014 3:01 PM
To: coffey_scott@lilly.com
Cc: Kenneth F Mace (mace_kenneth_f@lilly.com); Adeolu, Abolade
Subject: BLA 125469(dulaglutide)

Dear Scott,

Please respond by April 17, 2014, to the following with regards to DMF (b) (4) (Eli Lilly, dulaglutide):

1. Section D.7 of the DMF states that (b) (4)
taken (b) (4) Explain where these samples are
(b) (4) and justify their exclusion from the acceptance criteria

2. Indicate the limits, sampling methods, and sampling frequencies for nonviable particulates.

3. (b) (4)

Kindly acknowledge receipt of this email and let me know if you need further clarification.

Regards, Bola
Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
03/26/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Wednesday, March 26, 2014 2:57 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: BLA 125469 (dulaglutide)

Dear Ken,

Please respond by April 17, 2014, to the following:

Drug Product Manufacturing Process and Controls

1. Please clarify whether (b) (4) used for (b) (4) preparation and drug product formulation at Eli Lilly and (b) (4) are (b) (4).
2. Please clarify whether the (b) (4) bioburden sample is taken at (b) (4) during routine production of the drug product at Eli Lilly and (b) (4).
3. Because the drug product manufacturing process includes a (b) (4), the control strategy for drug product manufacturing should include (b) (4) endotoxin monitoring. Please establish endotoxin limits and implement routine (b) (4) testing for endotoxin (b) (4).
4. Please provide bioburden method qualification data from three different lots of (b) (4) drug product.
5. The processing and hold temperatures for the commercial manufacturing process are not clearly indicated. Please indicate the temperatures for the processing time limits shown in Table 3.2.P.3.4.2 for Eli Lilly and (b) (4). Indicate whether the same temperatures were used for commercial-scale hold time validation studies.
6. The (b) (4) (b) (4) for each of the (b) (4) process validation batches (Table 3.2.P.3.5.1-5) was (b) (4) the proposed (b) (4) of (b) (4). Therefore, additional information is needed to determine whether the (b) (4) has been adequately validated at (b) (4). Data from the full-scale development batches LYLA01 and LYLA02 may be used to support the (b) (4) if the (b) (4) conditions were the same as those for commercial production or worst-case compared to commercial production (b) (4). Please indicate the (b) (4) for these batches, as well as the (b) (4) the processing time samples taken at the end (b) (4).

- (b) (4)
7. Please respond to the following comments regarding the dulaglutide (b) (4) step performed at Eli Lilly and (b) (4).

- a. Describe the (b) (4) used for dulaglutide production.
- b. Please clarify whether post-use integrity testing (b) (4) may be performed with

(b) (4)

8. Please respond to the following comments regarding the microbial retention study (b) (4)

(b) (4)

- a. Provide the microbial retention study report for the (b) (4) drug product.
- b. Section 3.2.P.3.5.2.2 indicates that challenge levels of at least (b) (4) were used for the microbial retention study, but Table 2.3.P.3.5.2.2-1 indicates that the challenge levels at the end of the test were lower.

9. Environmental and personnel monitoring program information should be included in the drug product portion of the BLA rather than the appendix. Please move the environmental and personnel monitoring program information for (b) (4) to section P.3.5 of the application.

10. Please respond to the following comments regarding the process simulations performed to support dulaglutide production at (b) (4)

- a. (b) (4)
- b. (b) (4)
- c. (b) (4)
- d. (b) (4)
- e. (b) (4)
- f. (b) (4)
- g. (b) (4)

11. Please respond to the following comments regarding (b) (4) (b) (4)

- a. (b) (4)
- b. (b) (4)
- c. (b) (4)

12. Please respond to the following comments regarding the process simulations performed to support dulaglutide production at Eli Lilly (Table 3.2.P.3.5.2.4-1).

- a.
- b.
- c.
- d.
- e.
- f.
- g.

(b) (4)

Drug Product Testing

13. Please provide the (b) (4) test reports from the contract testing laboratory.

14. Please respond to the following comments regarding sterility test method qualification.

- a. (b) (4)
- b. Identify the (b) (4) drug product lot number corresponding to the material used for each of the three method qualification runs. Method qualification should be done with material sourced from three different (b) (4) drug product lots.

15. Please respond to the following comments regarding bacterial endotoxin test method qualification (USP <85>).

- a. Identify the (b) (4) drug product lot number corresponding to the material used for the method qualification studies summarized in Table 3.2.P.5.3.1.1-1.
- b. Indicate which sample dilutions of (b) (4) and 1.5 mg/ml dulaglutide drug product will be used for endotoxin release testing at Eli Lilly and (b) (4)

Please acknowledge receipt and let me know if you need any further clarifications.

Regards, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
03/26/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Thursday, March 13, 2014 9:00 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: FW: BLA 125469(dulaglutide): Deficiencies

Dear Ken,

1. We have completed our review of the documentation submitted in support of the (b) (4) single use pen. During our review we evaluated the documentation to determine if hazards associated with the use of this device are adequately addressed. There are hazardous situations that do not appear to be explicitly addressed in your submission:

Hazardous Situation	
Delivery Error	Device fluid path occlusion
	Incomplete drug delivery
	Unexpected separation of components
	Component failure
	Device insufficiently sealed to environment
	Insufficient / inadequate device activation
Contamination	Injection initiates prior to needle reaching the correct tissue depth of penetration.
	Device Reuse
Trauma	Device Body Breakage
	Needle Fracture / Remains Embedded in Subcutaneous Tissue
	Unexpected separation of components

Please provide a system level hazard analysis (e.g. fault tree analysis) identifying the causes of these hazardous situations for the (b) (4) single use pen injector. For each identified cause, provide the following:

- Describe the control method for each identified cause.
 - For each cause, provide an argument justifying the adequacy of the control to address the respective system hazard.
 - Provide evidence verifying the control method adequately addresses the respective cause / hazard.
2. Many of the design verification studies present the results in the following format:

Test Characteristic	Acceptance Criteria	Sample Size	Target K	Actual K	Pass / Fail
---------------------	---------------------	-------------	----------	----------	-------------

We are familiar with the use of tolerance limit factors when presenting design verification studies for pen injectors, and other delivery devices. However, the presentation of design verification results in your submission is not well understood. For example, we would generally expect to see results in the following format:

Test Characteristic	Acceptance Criteria	Sample Size	Mean, \bar{x}	Standard deviation, $\pm\sigma$	Lower / Upper Spec Limit, $x\pm k\sigma$	Pass / Fail
---------------------	---------------------	-------------	-----------------	---------------------------------	------------------------------------------	-------------

Please provide the derivation of tolerance limit factor, k, to the Target K value and explain how this corresponds to the device performance. Alternatively, reformat the results into the expected format, as specified in the second table.

3. There does not appear to be any performance evaluation on the needle to verify that the mechanical strength properties, patency, etc. are reliably achieved. Additionally, there does not appear to be information regarding manufacture of the needle and assurance that the manufacturing process reliably produces a needle that conforms to its specifications. Needle based hazards may be covered as part of the response to the hazardous situations, which is only related to the single use pen injector. However, please be sure to update the submission with specific information regarding the safe and effective use of the needle component of the prefilled syringe and single use pen injector.
4. Section 3.2.P.5 includes specifications for the device constituents. Many of the device acceptance criteria are identified only as "Pass". This is not sufficient. Update the specifications with the specific acceptability criteria that will be applied, as verified and validated. Additionally, the list of specifications is not complete. For example, specifications for injection depth, activation force, needle retraction time, injection force, locking mechanism override force, time between injection activation and injection initiation, etc. are not specified. Provide a complete list of device functional specifications with the corresponding acceptability criteria.
5. The break loose force and glide force testing (Section 3.2.P.5, Control of Drug Product, (b) (4)) for the semi-finished and prefilled syringe presentation appears to be a process capability test, rather than a design verification test. The acceptability criteria are not specified with respect to safety and effectiveness. Identify the design functional specifications on break loose force and glide force required for maintaining safe and effective drug delivery, and then provide the process capability testing demonstrating that the manufacturing process is producing the intended design.
6. The batch analysis results (Section 3.2.P.5.4) identifies tests, acceptance criteria, and results for the single use pen, prefilled syringe, and semi-finished syringe. Please address the following issues related to the device testing:
 - a. The visual inspection and functional inspection (manual operation) tests are not clearly described such that we understand what the tests entail. Further, the acceptance criteria are stated as "pass", which is not adequate. Update the table to include specifics of the visual and functional inspection tests and identify specific acceptance criteria.
 - b. Break loose force and glide force acceptance criteria are listed as an upper bound (e.g. NMT (b) (4) and NMT (b) (4), respectively) and no minimum force requirements are specified. Given the importance of balancing requirements for providing a microbial ingress barrier into the syringe and preventing leakage of the drug, against functional requirements for ease of use, it is clear that the force specifications must be (b) (4). Identify (b) (4) requirements for initiating and maintaining an injection and provide a justification for the acceptability criteria.
7. The shipping simulation testing results for the single use pen indicates on major defect following testing (Table 3.2.R.5.3.3-6). Please describe the observed defect, describe the impact to the patient from the defect and provide a risk assessment.
8. The (b) (4) single use pen instructions for use references the Medication Guide for complete information about proper storage; however, the Medication Guide does not appear to include any storage information. Please correct the discrepancy.

Kindly acknowledge receipt.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,

Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
03/13/2014



BLA125469/0

MID-CYCLE COMMUNICATION

Eli Lilly and Company
Attention: Kenneth Mace, PhD
Advisor, Global Regulatory Affairs-US Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Mace:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Trulicity (dulaglutide) injection.

We also refer to the teleconference between representatives of your firm and the FDA on June 2, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301)796-4264.

Sincerely,

{See appended electronic signature page}

Abolade (Bola) Adeolu, RPh, MS, MBA
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: March 3, 2014

Application Number: BLA 125469
Product Name: Trulicity (dulaglutide) injection
Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)
Applicant Name: Eli Lilly and Company

Meeting Chair: Jean-Marc Guettier, MD
Meeting Recorder: Abolade (Bola) Adeolu

FDA ATTENDEES

Mary Parks, MD - Deputy Director, Office of Drug Evaluation II
Jean-Marc Guettier, MD - Director (acting) Division of Metabolism & Endocrinology Products (DMEP)
Jennifer Pippins, MD, MPH – Division Director for Safety (Acting)
Ali Mohamadi, MD - Clinical Team Leader, DMEP
Suchitra Balakrishnan, MD - Clinical Reviewer, DMEP
Karen Davis-Bruno, PhD - Nonclinical Supervisor, DMEP
Tim Hummer, PhD - Nonclinical Reviewer, DMEP
Lokesh Jain, PhD - Clinical Pharmacology Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Sang Chung, PhD - Clinical Pharmacology Reviewer, DCPII, OCP
Mark Rothmann, PhD - Lead Mathematical Statistician, Division of Biometrics II (DBII)
Laurie Graham, MS - CMC/Product Quality Team Leader, Office of Biotechnology Products (OC), Division of Monoclonal Antibodies (DMA)
Joel Welch, PhD - CMC/Product Quality Reviewer, OBP, DMA
Nguyen, Quynh Nhu, MS - Combination Products Human Factors Specialist
Naomi Redd, PharmD - Risk Management Analyst, Division of Risk Management
LT. Lyle Canida, PharmD – Safety Regulatory Project Manager, Office of Surveillance & Epidemiology
Julie Van der Waag, MPH - Chief, Project Management Staff
Abolade (Bola) Adeolu, RPh, MS, MBA - Regulatory Project Manager

INDEPENDENT ASSESSOR

(b) (6) - Eastern Research Group

APPLICANT ATTENDEES

Elizabeth Bearby, Pharm D - Senior Director, Global Regulatory Affairs-US

Richard Byrd, MS - Research Advisor, Non-clinical Safety Assessment
Amparo De La Pena Motta, PhD - Research Advisor, Global PK/PD
John R. Dobbins, MS - Principal Research Scientist, Global Regulatory Affairs - CMC
Jessie Fahrback, MD - Medical Director, Global Diabetes Development
Pawel Fludzinski, PhD - Dulaglutide Global Brand Development Leader
Kristine D Harper, MD, MBA - Medical Fellow, Global Patient Safety
Robert Lew, MD - Senior Medical Director, Global Patient Safety
Kenneth F. Mace, PhD - Regulatory Advisor, Global Regulatory Affairs-US
Sherry Martin, MD - Senior Medical Director, Global Diabetes Development
Robert Metcalf, PhD - Vice President, Global Regulatory Affairs
Linda Shurzinske, MS - Research Advisor, Statistics
(b) (4) - Consultant, Global Regulatory Affairs-US
John Towns, PhD - Principal Fellow, Global Regulatory Affairs- Devices

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

Clinical and Statistics

- a) We are continuing to evaluate your plan to only market the 1.5mg dose. At this stage, neither efficacy nor the number of adverse events appears to be markedly different between the two doses. Our review is ongoing and a determination as to which dose is approvable has not been made up to this point.
- b) Information from the dulaglutide 0.75 mg dose was not presented in the package insert despite this dose achieving statistically significant better HbA1c change than multiple active controls. Including information in the package insert on both the 0.75 mg dose and the 1.5mg dose is being considered.
- c) (b) (4)
We have reconsidered this approach to missing data following publication of the 2010 report on missing data by the National Academy of Sciences, The Prevention and Treatment of Missing Data in Clinical Trials. We are considering

presenting results in this section based on an alternative statistical analysis, possibly your prespecified repeated measure analysis.

CMC Microbiology

Incomplete information is provided in modules 3.2.P and 3.2.R for several operations that directly impact drug product sterility assurance. The most significant issues are as follows:

- d) Additional information is needed in order to determine whether the microbial retention study [REDACTED] (b) (4) is adequate.
- e) Additional information is needed in order to determine whether [REDACTED] (b) (4) dulaglutide has been adequately validated [REDACTED] (b) (4)
- f) [REDACTED] (b) (4)
- g) Additional information is needed in order to determine whether the dye ingress test method for container closure integrity is adequate. It is not clear whether the dye ingress test is as sensitive as a rigorous microbial ingress test.
- h) It is not clear whether maintenance of container closure integrity during PFS and SUP assembly has been adequately validated from a drug product sterility assurance perspective.
- i) Additional information is needed to determine whether [REDACTED] (b) (4) [REDACTED] container closure integrity during shipping have been adequately assessed. [REDACTED] (b) (4)

CDRH Human Factor

- j) There was no differentiation study for the two strengths available with other competitor's products for both the pen and prefilled syringe configuration. Submit results of a study focusing on evaluating the differentiating aspects for both the pen and prefilled syringe configuration, and demonstrating that representative users can identify and select the correct product.
- k) Results of the pen and prefilled syringe human factors validation study showed multiple failures on critical tasks across different user groups and these failures could result in patient harm (needle stick injuries, injection into the intramuscular space, reduced drug efficacy, etc.) We believe that additional mitigations are necessary, and we need to review results demonstrating that the mitigations improve user's ability to use the device safely and effectively.

- i. For the prefilled syringe configuration, we are most concerned with failures to inspect the device and check expiration date, selecting improper injection site, failures to insert the needle at ^(b)₍₄₎ degrees, and disposing the product improperly.
- ii. For the pen configuration, we are most concerned with failures to check expiration date and ensure that the drug product is clear (not cloudy), reattaching the base cap, selecting improper injection site, and failures to press the button down to ensure full dose delivery.

3.0 INFORMATION REQUESTS

CMC Microbiology

The responses to the CMC microbiology questions provided in the amendment dated February 21, 2014, are still under review. Two additional CMC microbiology information requests regarding drug product manufacturing will be sent by March 7, 2014. One request will cover container closure integrity and shipping validation, and the other will cover all other topics.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

We are in general agreement with the REMS proposed, however major edits will be forthcoming via track changes.

5.0 ADVISORY COMMITTEE MEETING

None anticipated

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

Discussion of labeling/PMR/PMC/REMS will be initiated by May 31, 2014.

FDA's internal Wrap-Up meeting is scheduled for July 24, 2014.

The Late Cycle meeting with Eli Lilly and Company is scheduled for June 2, 2014 from 1:00 to 2:00 P.M.

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

/s/

ABOLADE ADEOLU
03/06/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, February 14, 2014 10:00 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: FW: BLA 1254699dulaglutide)

Importance: High

Dear Ken,

1. There was minimal information pertaining to 21 CFR 820.30 Design Controls.
2. Regarding compliance to 820.50, Purchasing Controls, information about agreements with suppliers or control of supplies was not adequate.
3. Information regarding compliance with 21 CFR 820.100, Corrective and Preventive Action,
4. 21 CFR 820.170, installation and 21 CFR 820.200, Servicing was inadequate.

If you consider that any of these regulations do not apply to your product, include an explanation of why they don't apply. You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocument>

<s/ucm070897.htm>

CDRH

Please acknowledge receipt.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA

Regulatory Project Manager,

CDER/OND

Office of Metabolism and Endocrinology Products

White Oak, Bldg 22, Rm 3239

10903 New Hampshire Avenue,

Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
02/14/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, February 07, 2014 11:45 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: BLA 125469 (dulaglutide): Information request

Importance: High

*Dear Ken,
Please respond to the following information request by February 28, 2014*

Characterization 3.2.S.3.1

(b) (4)

Manufacturers (3.2.S.2.1 and 3.2.P.3.1)

6. Section 3.2.S.2.1 and 3.2.P.3.1 should be updated to include the assays performed at each testing site.

DS Manufacturing 3.2.S.2

7.  . Provide information that your process validation activities are applicable 

(b) (4)

(b) (4)

8.

(b) (4)

Drug Substance Manufacturing Process Development 3.2.S.2.6

9. Inadequate information was provided to support the PK, safety, and immunogenicity assessments that were performed to determine CQAs. It is unclear, therefore, whether all CQAs have been identified. Specifically,

(b) (4)

10

11

12

13. There are concerns that the small scale equivalence studies and process characterization studies did not include the appropriate CQAs. For each unit operation, a justification is needed for the CQAs selected for inclusion in the small scale equivalency studies and in the process characterization studies. This justification should include consideration for the following:



14. Provide additional information to support that the practically significant thresholds used for the equivalency studies ^{(b) (4)} do not represent clinically meaningful differences.
15. With regard to the ^{(b) (4)} design of experiment (DoE) studies conducted ^{(b) (4)} provide summary results including values used for the practically significant calculations.
16. For process parameter studies, provide information to support the quality of the overall model fits (e.g. R² values for regression models)
17. Provide a justification that the CQAs that were included in the ^{(b) (4)} stability study. Provide summary ^{(b) (4)} results.
18. Additional information is needed with regard to the calculation of practically significant differences used to evaluate the process parameter characterization studies.
- Provide information on which full scale lots were used to determine the CT half range and CT mean results for each CQA. This should include information to support that these lots were all manufactured with a full scale process that uses the same set points as the small scale process and that the process has been shown to be equivalent to the small scale process.
 - Provide confirmation that the baseline CQA response represents the small scale process results run at the set-points of the proposed commercial process.

19. It does not appear that pre-determined critical quality attribute acceptance criteria were used in evaluating process characterization studies. It is unclear that the practically significant difference calculations provide sufficient assurance that CQA results in the small scale characterization studies will be within ranges that are not expected to impact safety and/or efficacy. For example, it would appear that small scale results could have significantly, and clinically meaningful, differences from the full scale process in terms of CQA values, but this difference would be considered acceptable if the small scale results had adequately decreased variability compared to the full scale process. (b) (4)
- (b) (4) please clarify if the process parameter characterization studies were evaluated in terms of the CQA results needing to be within defined CQA acceptance criteria. Provide the pre-determined CQA acceptance criteria, if any, which were in the process parameter characterization studies.
20. For the (b) (4) provide summary supportive data that this step would only be expected to impact (b) (4) capabilities and not other product quality attributes.
21. It appears that for multiple unit operations, process parameters that were statistically and practically significant were dismissed based upon the level of manufacturing control. (b) (4) It is unclear that the level of control over a process parameter is relevant to whether the parameter should be considered a critical process parameter. Provide a justification for this strategy, (b) (4).
22. For the DoE study performed on (b) (4) provide the statistical evaluation and the referenced practically significant calculations.
23. For certain unit operations, such as (b) (4), the initial process parameter risk assessment included classifying parameters as non-CPPs if the operating ranges are within vendor recommendations. It is unclear, however, that this provides sufficient assurance that the parameters are not CPPs. For example, it is unclear how the vendors evaluated the parameters to determine criticality. Provide additional information on how the vendor recommendations for parameters operating ranges were evaluated to determine process parameter criticality for dulaglutide.
24. To support your control strategy, provide available unit operation linkage information on the cumulative impact to each CQA if each unit operation was run under worst case conditions for that CQA.

Drug Substance (b) (4) 3.2.S.2.5

25. Provide product quality data supporting all of the (b) (4) listed in table 3.2.S.2.5.2.1.
26. Provide a justification for the CQAs evaluated to validate each (b) (4)
27. (b) (4)
28. (b) (4)

Validation of Analytical Methods 3.2.S.4.3

29. Specificity during assay validation was demonstrated in part by using unrelated Lilly products. Provide summary information regarding the nature of these products.

30. Your validation packages do not include protocols and raw data, such as values for individual recovery samples and chromatograms/electropherograms and acceptance criteria for robustness experiments. Provide this information.

31. For the Determination of Identity and Purity (b) (4)

- a. (b) (4) Provide additional data and justification demonstrating the validity of the method for quantitating additional impurities.
- b. References are made throughout the report to the "original" and "amended" protocol. Provide a description of any revisions made to the protocol and any failures observed.
- c. It is noted that the (b) (4) failed the precision reproducibility criteria and that this laboratory may not analyze drug product as a consequence. Provide additional information on the investigation into the failure and any corrective actions.
- d. Your robustness validation identified no additional (b) (4) become unavailable. Provide an additional justification and a risk assessment.

32. For the Determination of Identity and Purity (b) (4)

- a. The range assessed during validation for drug product (b) (4) is narrower than the ICH Q2 recommendation of evaluating from (b) (4) specification level. Provide a justification.
- b. The method is used to report the content (b) (4). However, these two impurity groups were not universally evaluated for each validation characteristic. Provide a justification for this approach.
- c. It is noted that the Kinsale laboratory failed the acceptance criterion for (b) (4). Provide additional information on the investigation including any potential corrective actions.
- d. It is noted that there was a failure to identify an additional (b) (4). Provide justification for their risk assessment to control these parameters.

33. For the Determination of (b) (4)

- a. It is noted that failure was observed for the accuracy parameter by the (b) (4) site. Please provide information on any investigation performed to evaluate the impact as well as any correction actions.
- b. Provide additional description for the aggregate sample used to validate this method.
- c. Provide an impact assessment for the lack of identification of (b) (4).

34. For the Determination of Purity by (b) (4)

- a. As noted in your validation, (b) (4) (b) (4) (b) (4). Please justify the lack of system suitability criterion for this resolution.
- b. Provide additional data and justification for parameters associated with sample preparation that were not considered as a part of robustness (b) (4)

35. For the Determination of (b) (4)

- a. Your correlation coefficient acceptance criteria for linearity are (b) (4), but are also different (b) (4). Provide justification.

- b. While the method quantitates basic variants, the parameters linearity, accuracy, and precision reproducibility did not consider basic variants. Provide rationale.
- c. The validation range for linearity is typically up to (b) (4) for an impurity per ICHQ2. The range you evaluated falls short (b) (4). Provide a justification.
- d. Wider acceptance criteria (b) (4) were established to evaluate precision (b) (4). Provide justification.
- e. Provide justification for the inclusion of only (b) (4) in your assessment of precision reproducibility.
- f. Your acceptance criteria for robustness parameter assessment is relatively broad (b) (4) and do not include criteria for (b) (4). Provide the observed (b) (4) results for conditions considered that were considered "passing" (b) (4).

36. For the Determination of (b) (4) Content

- a. Your specificity experiment states that neither process nor product related impurities interfere. Provide data justifying this conclusion.
- b. Provide solution stability results for drug product.
- c. Provide a summary for any experiment performed to identify an additional vendor for (b) (4)

Reference Standard

37. Identify all uses of the primary vs. secondary reference standards.

38. Update the BLA with the protocols for the primary and secondary reference standards (including manufacturing, qualification, and requalification).

39. Provide information on how the stability of the reference standards is monitored and update the BLA with available stability data.

40. Provide information on the conditions that would result in the need to replace a reference standard.

41. Provide summary information and data on the reference standards used prior to (b) (4)

42. The reference standards appear to have been qualified using only drug substance release methods. The reference standards should be characterized for a broad range of physicochemical and functional attributes such as the primary, secondary, tertiary and quaternary structure, charge variants, glycoforms, immunochemical properties, binding, potency, and stability. Provide a justification for your qualification strategy or update the BLA with additional reference standard characterization data.

Immunogenicity Assays (5.3.1.4)

43. Provide detailed methods for all of the immunogenicity assays (b) (4) used for clinical samples. In addition, provide detailed validation protocols for each of these assays along with the validation reports.

44. Provide clarification on whether (b) (4) assay positive results were subject to a confirmatory assay.

45. For the (b) (4) assay validation, clarify whether patient population treatment naïve samples were assessed with regard to confirming the assay cut-point.

46. For the (b) (4) assay, (b) (4) (b) (4). Provide a rational for this approach and additional data, if available, (b) (4).

47. Provide a justification for the use of a “(b) (4)” as the criterion to report treatment emergent anti-drug antibodies. Additionally, provide a numerical value for the number of patients who had ADA above baseline, but were reported as non-treatment emergent based on this criterion.
48. Your assays to detect neutralizing antibodies against GLP-1 appear to have both poor sensitivity and poor drug tolerance. This raises concerns that the neutralizing activity against native GLP-1 has been underestimated. Additional information is, therefore, needed to support the claimed rate of neutralizing antibodies against native GLP-1. This could include, for example, available data characterizing the cross-reactive antibodies to native GLP-1 to support that they are not neutralizing.

Let me know if you have additional questions/clarification.

Regards, Bola

Bola Adeolu, R.Ph., MS, MBA

Regulatory Project Manager,

CDER/OND

Office of Metabolism and Endocrinology Products

White Oak, Bldg 22, Rm 3239

10903 New Hampshire Avenue,

Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
02/07/2014



BLA 125469/0

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Eli Lilly and Company
Lilly Corporate Center
DC 2543
Indianapolis, IN 46285

Attention: Susan D. Sutton, PhD
Consultant, Global Regulatory Affairs – US

Dear Dr. Sutton:

Please refer to your Biologics License Application (BLA) dated September 17, 2013, received September 18, 2013, submitted under section 351(a) of the Public Health Service Act for Dulaglutide, 0.75 mg/0.5 mL and 1.5 mg/0.5 mL.

We also refer to your November 22, 2013, correspondence, received November 22, 2013, requesting review of your proposed proprietary name, Trulicity. We have completed our review of the proposed proprietary name, Trulicity, and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your November 22, 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 Bola Adeolu at (301) 796-4264.

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

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

/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
01/11/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125469/0

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Eli Lilly and Company
Lilly Corporate Center
DC 2543
Indianapolis, IN 46285

Attention: Susan D. Sutton, Ph.D.
Consultant, Global Regulatory Affairs - U.S.

Dear Dr. Sutton:

Please refer to your Biologics License Application (BLA) dated September 17, 2013, received September 18, 2013, submitted under section 351(a) of the Public Health Service Act, for Dulaglutide, 0.75 mg/0.5 mL and 1.5 mg/0.5 mL.

We acknowledge receipt of your November 22, 2013, correspondence, on November 22, 2013, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4). This proposed proprietary name request is considered withdrawn as of November 22, 2013.

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 Abolade Adeolu, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Margarita Tossa, M.S.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

MARGARITA V TOSSA
01/10/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Thursday, January 02, 2014 12:14 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: BLA 125469 (dulaglutide): Information request

Dear Ken;

Please respond to the following requests by January 10, 2014:

For Study H9X-MC-GBDA:

- Please provide the SAS program that includes data management for the MMRM analysis summarized in Table GBDA.14.18 of the Clinical Study Report (page 482).
- Please clarify why 28 patients in the ITT population with baseline information on estimated creatinine clearance were excluded from the baseline analysis; e.g., see Clinical Study Report pg. 3689.

For Study H9X-MC-GBCF:

- Please provide 1) the statistical analysis plan, and 2) the simulation report investigating the operational characteristics for the study's testing strategy. Neither document were accessible in the BLA submission.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
01/02/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Tuesday, December 10, 2013 12:12 PM
To: Kenneth F Mace (mace_kenneth_f@lilly.com)
Cc: Adeolu, Abolade
Subject: Dulaglutide: Information request

Dear Ken,

In order to justify the information in your proposed label about missed dose and changing the day of weekly administration, simulate mean PD (HbA1c, FPG) profiles of the following scenarios in addition to the simulated PK profiles:

Mean PD profile following once weekly dosing (100% Compliant)

Mean PD profile when dulaglutide is administered within 4 days of missed dose (Missed 1 dose, Dose taken at Day 4)

Mean PD profile following a missed dose (Skipped 1 dose)

Mean PD profile when the day of weekly administration is changed

Please submit this information by COB Dec 12, 2013.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
12/11/2013

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Tuesday, December 03, 2013 8:28 AM
To: Kenneth F Mace (mace_kenneth_f@lilly.com); Susan D Sutton (sutton_susan@lilly.com)
Cc: Adeolu, Abolade
Subject: BLA 125469

Dear Ken,

Please provide updated preliminary manufacturing schedule, including detailed (b) (4) schedule for Dulaglutide drug substance at Eli Lilly S.A. for the period between February 24, 2014 and March 18, 2014.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

/s/

ABOLADE ADEOLU
12/03/2013



BLA 125469

**FILING COMMUNICATION –
FILING REVIEW ISSUES IDENTIFIED**

Eli Lilly and Company
Attention: Kenneth Mace, PhD
Advisor, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Mace:

Please refer to your Biologics License Application (BLA) dated September 17, 2013, received September 18, 2013, submitted under section 351(a) of the Public Health Service Act for dulaglutide.

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 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is **September 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 post-marketing commitment requests by **May 31, 2014**.

In addition, the planned date for our internal mid-cycle review meeting is **February 13, 2014**. We have not determined our plan regarding an advisory committee meeting to discuss this application.

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

Labeling

1. Patient labeling materials should meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).
2. Patient labeling materials should utilize simple wording and clear concepts where possible and should be consistent with the Prescribing Information. Do not use complex medical terminology.
3. To enhance comprehension and readability, patient labeling materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.
 - a. The grade level of your proposed Medication Guide (MG) is 8.9 and the reading ease is 56.2%.
 - b. The grade level of your proposed Instructions for Use (IFU) is 6.4 and the reading ease is 68.9%.
4. Patient labeling materials should be in fonts such as Verdana, Arial or APFont at font size 11 or greater to make medical information more accessible for patients with vision loss. We recommend Verdana 11, point font.
5. Do not use underlining, italics, all capital letters or text boxes in patient labeling as it is difficult to read for patients with vision loss. Use bolded text instead to highlight important information.
6. Use bolding for headers and to highlight important text only. Overuse of bolding minimizes the importance of certain important information for the patient.

Comments specifically for the IFU:

7. We do not recommend using (b) (4), and recommend using only an IFU.



8. The IFU should be titled as such and appear at the end of the MG after the list of ingredients. The IFU may also be provided as a separate document.

9. IFUs are generally organized as follows:

- a. Standard header
- b. Bulleted list of all the supplies needed to complete the task, including an illustration of all supplies needed.
- c. Patient instructions that are not sequential should be bulleted.
- d. Patient instructions that are sequential should be labeled as “**Step 1, Step 2**” etc.
- e. Figures should accompany all numbered steps as appropriate and should be placed immediately adjacent to the related text. The figures should be labeled as “**Figure A, Figure B**” etc.
- f. Within the figures there should be detailed labeling for each part of any device that the patient expected to become familiar with.
- g. Refer to each figure at the end of each numbered step. For example, at the end of **Step 1**, say (**See Figure A**). If Figures are placed immediately adjacent to the corresponding step, it is not necessary to say, “See Figure X.”
- h. Storage information as stated in the Prescribing Information (PI) should appear at the end of the IFU if the IFU will be a separate document. If the Patient Information and IFU are combined, the storage information should appear in the Patient Information only.
- i. Disposal information. If needles, syringes or injectable Pens are used to prepare or deliver the drug, disposal language should be consistent with the FDA “Safe Sharps Disposal” website language.
- j. Other pertinent miscellaneous instructions to the patient
 - Manufacturer name and address
 - If the IFU is a stand-alone document, add the statement “These Instructions for Use have been approved by the U.S. Food and Drug Administration.”
 - If the IFU is attached to the PPI, add the statement, “This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.”
 - “Approved” or “Revised” Month/Year

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

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.

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), and Medication Guide. 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), and Medication Guide, and you believe the labeling is close to the final version.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

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

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

/s/

JEAN-MARC P GUETTIER
11/14/2013



BLA 125469

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Eli Lilly and Company
Lilly Corporate Center
DC 2543
Indianapolis, IN 46285

Attention: Kenneth F. Mace, PhD
Regulatory Advisor, Global Regulatory Affairs – US

Dear Dr. Mace:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for for Dulaglutide, 1.5 mg/0.5 mL.

We also refer to your September 17, 2013, correspondence, received September 18, 2013, requesting review of your proposed proprietary name, [REDACTED] (b) (4). We have completed our review of the proposed proprietary name, [REDACTED] (b) (4) and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your September 17, 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 Bola Adeolu at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

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

/s/

CAROL A HOLQUIST
10/21/2013



BLA 125469

BLA ACKNOWLEDGEMENT

Eli Lilly and Company
Attention: Kenneth Mace, PhD
Advisor, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Mace:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: dulaglutide

Date of Application: September 17, 2013

Date of Receipt: September 18, 2013

Our Secondary Tracking Number (STN): BLA 125469/0

Proposed Use: For improved glycemic control in patients with type 2 diabetes mellitus

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 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 BLA Submission Tracking 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 & 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.

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

If you have any questions, call me at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Abolade (Bola) Adeolu, RPh, MS, MBA
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

ABOLADE ADEOLU
09/23/2013



IND 070930

MEETING MINUTES

Eli Lilly and Company
Attention: Kenneth Mace, PhD
Advisor, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Mace:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for dulaglutide; compound LY2189265 injection.

We also refer to the meeting between representatives of your firm and the FDA on July 9, 2013. The purpose of the meeting was to discuss your proposed Biologics License Application (BLA) submission.

A copy of the official minutes of the July 9, 2013, 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 Abolade (Bola) Adeolu, Regulatory Project Manager at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: July 9, 2013 9:00 to 10:00 AM EDT
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, MD 20903

Application Number: 070930
Product Name: Dulaglutide
Indication: Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Eli Lilly and Company

Meeting Chair: Mary H. Parks, MD
Meeting Recorder: Abolade (Bola) Adeolu

FDA ATTENDEES

Division of Metabolism & Endocrinology Products

Mary H. Parks, MD - Director, Division of Metabolism & Endocrinology Products (DMEP)
Amy G. Egan, MD, MPH – Deputy Director for Safety, DMEP
Jean-Marc Guettier, MD - Clinical Team Leader
Karim Calis, PharmD, MPH - Clinical Reviewer
Karen Bruno-Davis, PhD - Nonclinical Supervisor
Tim Hummer, PhD – Nonclinical Reviewer
Julie Marchick, MPH - Chief, Project Management Staff
Abolade (Bola) Adeolu, RPh, MS, MBA - Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Sang Chung, PhD – Clinical Pharmacology Reviewer

Division of Biometrics II

Mark Rothmann, PhD – Statistical Team Leader
Lee-Ping Pian, PhD - Statistical Reviewer

Division of Biometrics VII

Mat Soukup, PhD- Team Leader
Janelle Charles, PhD- Statistical Safety Reviewer

Office of Biotechnology Products, Division of Therapeutic Proteins

Laurie Graham, PhD- Quality Team Leader
Joel Welch, PhD- Quality Reviewer

Office of Scientific Investigations, Division of Good Clinical Practice, Good Clinical Practice Assessment Branch

Cynthia Kleppinger, MD- Senior Medical Officer

Office of Surveillance and Epidemiology

Margarita Tossa, MS- Safety Regulatory Project Manager
Christian Hampp, PhD- Senior Staff Fellow/Epidemiologist, Division of Epidemiology
Reasol Agustin, PharmD - Safety Evaluator, Division of Medication Error Prevention and Analysis
Amarilys Vega, MD, MPH- Medical Officer, Division of Risk Management (DRISK)
Debra Ryan, PharmD- Safety Evaluator, Division of Pharmacovigilance

Center for Devices and Radiological Health

Carl Fischer, PhD – Chief, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance
LCDR Anne Stohr, RN, BSN – Regulatory Operations Officer, DOEA, OC, GHDB

Office of Compliance, Biotechnology Manufacturing Assessment Branch

Colleen Thomas, PhD – Product Quality Microbiology Reviewer
Candace Gomez-Broughton, PhD – Product Quality Microbiology Reviewer

Office of Business Informatics

Douglas Warfield, PhD - Interdisciplinary Scientist-Technical Lead, Division of Data Management Services & Solutions

Office of Strategic Programs

Kimberly Taylor, MBA, MPH – Operations Research Analyst

EASTERN RESEARCH GROUP ATTENDEE

 ^{(b) (6)} Independent Assessor

SPONSOR ATTENDEES

Elizabeth Bearby, Pharm D - Senior Director, Global Regulatory Affairs-US
John R. Dobbins, MS - Principal Research Scientist, Global Regulatory Affairs – CMC
Pawel Fludzinski, PhD - Dulaglutide Global Brand Development Leader

Kristine D Harper MD, MBA - Medical Fellow, Global Patient Safety
Kenneth F. Mace, PhD - Regulatory Advisor, Global Regulatory Affairs-US
Sherry Martin, MD - Senior Medical Director, Global Diabetes Development
Robert Metcalf, PhD - Vice President, Global Regulatory Affairs
Linda Shurzinske, MS - Research Advisor, Statistics
(b) (4) - Consultant, Global Regulatory Affairs-US
John Towns, PhD - Principal Fellow, Global Regulatory Affairs- Devices

1.0 BACKGROUND

Eli Lilly plans to submit a Biologics License Application (BLA) for dulaglutide in September 2013.

Dulaglutide is a New Molecular Entity (NME) that exhibits GLP-1 mediated effects, including glucose-dependent potentiation of insulin secretion, inhibition of glucagon secretion, delay of gastric emptying, and weight loss. The proposed indication for dulaglutide is an adjunct to diet and exercise for the treatment of type 2 diabetes mellitus (T2DM).

Based on safety and efficacy analyses of the Phase 3 data, Eli Lilly has determined that the 1.5 mg dose showed optimal benefit: risk ratio and will seek approval for this dose in the BLA submission as a drug/device combination product. The application will provide for both a pre-filled syringe device and a single use pen.

Since this is an NME, the BLA submission will be subject to “The Program” under PDUFA V.

Eli Lilly and Company submitted a Pre-Biologics License Application (BLA) meeting request on February 8, 2013. The Division agreed to a face-to-face meeting scheduled for May 2, 2013. The meeting was subsequently cancelled by the Division on April 30, 2013, because the background information provided was not sufficiently detailed to allow the Division to provide meaningful responses. The Division issued an Advice/Information request letter on May 2, 2013, responding to questions enclosed in the meeting package, and included additional comments/information requests.

Eli Lilly and Company submitted another Pre-BLA meeting request on May 13, 2013. The meeting was granted and meeting packages were received on June 10, 2013.

2. DISCUSSION

FDA’s preliminary responses to the questions in the June 10, 2013, meeting package were emailed to Eli Lilly on July 3, 2013. Eli Lilly’s questions are repeated below followed by FDA’s preliminary responses in **bold** print. A summary of the discussion at the meeting are shown in *italics*.

Question 1: Does FDA agree that the information related to BLA content provided in the Lilly briefing document submitted on 28 Mar 2013, combined with the information provided herein in response to FDA Advice-IR issued 03 May 2013, provides a complete application in support of registration of dulaglutide as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (see relevant discussion in section **Error! Reference source not found.**)?

FDA Response to Question 1: Please address the comments under “Additional Comments”. Provided you can address these satisfactorily, the proposal you outlined for dulaglutide appears to include all of the required elements of a biologics license application (BLA). However, until we review the specific content of your application after it has been submitted, we are not able to comment on whether it constitutes a complete application that can be filed. Additionally, your proposal to submit integrated datasets—using Lilly’s standard analysis dataset format—for the nine completed Phase 2 and 3 trials included in the meta-analysis for evaluation of cardiovascular risk appears acceptable.

APPEARS
THIS WAY
ON
ORIGINAL

Meeting Discussion: No discussion occurred.

Question 2: Does the FDA agree with Lilly’s proposal for the contents of the 4-Month Safety Update (see relevant discussion in section **Error! Reference source not found.**)?

Request for FDA Response: Lilly is seeking confirmation that our submission plans for the assembly validation data meets FDA’s expectations (see relevant discussion in section **Error! Reference source not found.**).

FDA Response to Question 2: We agree with the proposed August 2013 cut-off time frame for the 4-month safety update and with your proposal to include deaths, SAEs, discontinuations due to adverse events, and all events designated as “of special interest” as outlined in your briefing document. However, for these important event categories, unblinded data should be presented.

Meeting Discussion: Eli Lilly was informed by the FDA that they should be prepared to unblind 4 month safety update data related to specific adverse events should the need arise. Examples of such events were provided. The company was advised to develop internal processes (i.e., use of firewalls) to ensure trial integrity is maintained. The 4-month safety update will contain additional numbers of patients exposed and longer term exposure. This dataset will provide valuable information to better characterize safety signals identified in the original dataset.

Additional Comments

- 1. Notwithstanding your characterization of a “completed study” as defined in Section 4.1.2 on page 12 of your background document, identify the “ongoing” Phase 3 trials in which all enrolled subjects have already reached the pre-specified primary study endpoint.**

Meeting Discussion: Eli Lilly informed FDA that patient enrollment is still ongoing for some of these studies, that no trials are fully complete, and that no database lock has occurred for any of the trials key time points (e.g., partial trial up to efficacy assessment, complete trial including efficacy and safety extension phase)..

- 2. Confirm that the adjudication processes for pancreatic adverse events and cardiovascular events occurred in a blinded manner.**

Meeting Discussion: No discussion occurred.

- 3. Conventional units of measure for laboratory data should be provided in place of or in addition to SI units. Please clarify your intention.**

Meeting Discussion: Eli Lilly informed the FDA that most datasets will have laboratory data in both SI and conventional units. The integrated summary of safety (ISS) submission will include some laboratory data in SI units and other laboratory data in conventional units. FDA stated that providing data in conventional units facilitates the review process. If Eli Lilly chooses not to provide datasets and ISS in conventional units and extensive data conversion is needed during the review it may impact the review timeline. Eli Lilly stated that conventional units will be available for critical safety laboratory (e.g., creatinine) and agreed to provide FDA with a detailed list of laboratory test that will be presented in conventional units prior to their submission of the BLA.

- 4. Explain the apparent discrepancy in the number of major adverse cardiovascular events reported in the current briefing document (page 47) compared to the original briefing document (page 37) across the nine completed phase 2/3 trials.**

Meeting Discussion: No discussion occurred.

- 5. Include supportive integrated safety analyses and an integrated analysis dataset pooling trials ≥ 26 weeks in duration through the safety follow-up visit (i.e., All trials included in Analysis Set 5, dulaglutide doses combined and comparator data, through to follow-up visit). Currently you have no integrated comparative safety analyses or datasets for longer term dulaglutide exposure. We believe this pool comparing longer term dulaglutide exposure to comparators is important to help inform the safety profile of dulaglutide. Clarify how you intend to use “study-by-study” presentations by illustrating with an example. Clarify which sections of the ICS and ISS will rely on “study-by-study” presentation (e.g., deaths, SAEs, common AEs, AEs of special interest, laboratory parameters, vitals etc..?). Clarify how differences in exposure will be handled in your “study-by-study” presentation.**

Meeting Discussion: Eli Lilly clarified their pooling strategy and provided answers to the questions posed in the FDA preliminary response. Importantly, Lilly confirmed that the safety analyses will be comprehensive and include all trials (e.g., placebo and active controlled) and the full exposure duration (i.e., include data from controlled safety extension phases). For

specific events where the active control (e.g., GLP-1 agonist) has the potential to confound interpretability of the results (e.g., pancreatitis) data will be shown on a “study-by-study” basis. It was agreed that this was reasonable. FDA asked that analyses based on pooled data (placebo and active comparator) for events where no confounding is expected (i.e., death, serious AE other than for specific events). The clarifications provided were otherwise acceptable. .

- 6. For each subject enrolled in the Phase 2 part of study GBCF, please include in the Primary efficacy dataset for each arm the probability that the subject was to be randomized to that arm.**

Meeting Discussion: No discussion occurred.

- 7. The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the BLA submission.**

Meeting Discussion: Eli Lilly stated that they will provide analysis program, primary efficacy program for each study, and definition document as part of their BLA submission. The definition document will explain how derivations were implemented.

- 8. Any integrated efficacy analysis across the Phase 3 studies will be regarded as exploratory.**

Meeting Discussion: No discussion occurred.

- 9. From a (b) (4) perspective, the effect of (b) (4) processes on the maintenance of (b) (4) during assembly, and shipping should be demonstrated.**

Meeting Discussion: Eli Lilly agreed to provide container closure integrity validation data for both of the pen injector assembly lines in the initial BLA submission.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that Eli Lilly will include a Communication Plan REMS in their original submission as described in section 4.2 of the briefing document.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

PRESCRIBING INFORMATION

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

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.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

Eli Lilly will provide the FDA with a summary of the data to be provided in SI and conventional units before the submission of the BLA.

6.0 ATTACHMENTS AND HANDOUTS

Handout provided by sponsor

4 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

MARY H PARKS
07/23/2013

Executive CAC

Date of Meeting: January 25, 2011

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Linda Fossom, Ph.D., DPP, Alternate Member
Karen Davis-Bruno, Ph.D., DMEP Pharm/Tox Supervisor
Tim Hummer, Ph.D., DMEP, Presenting Reviewer

Author of Minutes: Tim Hummer

The following information reflects a brief summary of the Committee discussion and its recommendations.

The committee did not address the sponsor's proposed statistical evaluation for the carcinogen bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document.

IND #: 70,930

Drug Name: LY2189265

Sponsor: Eli Lilly

Background:

LY2189265 is a long-acting GLP-1 receptor agonist being developed for the treatment of type 2 diabetes. Two-week and 1-month dose range-finding studies were conducted in 001178-W mice, the corresponding wild-type mouse for the Tg.RasH2 strain, using twice weekly subcutaneous doses of 1, 10, and 100 mg/kg. In the 2-week study, one TK group female receiving 100 mg/kg was sacrificed moribund. No other treatment-related deaths occurred. There were no significant target organ toxicities. The key treatment related effect was decreased body weight gain that correlated with decreased food consumption, an expected pharmacological effect of GLP-1 receptor analogs. In the 4-week study, body weight gains were approximately 70% and 90% less than controls for the 10 and 100 mg/kg dose groups, respectively. The most noteworthy effect on body weight occurred during the first week of treatment, during which time mice tended to lose body weight at ≥ 10 mg/kg. After Week 1, body weight gains exceeded controls in the 2-week study but remained lower than controls in the 4-week study, with mean body weight gains being 38% and 57% less for male and female 10 mg/kg-group animals and 8% and 43% less for male and female 100 mg/kg-group animals, respectively.

Tg.RasH2 Transgenic Mouse Carcinogenicity Study Protocol and Dose Selection:

The sponsor proposed a 6-month carcinogenicity study in Tg.RasH2 mice (25/sex/group) using doses of 0 (vehicle), 0.1, 1, and 10 mg/kg LY2189265 twice weekly by subcutaneous injection in males and females. The vehicle will contain 10 mM citrate buffer (pH 6.5 ± 0.2), 4.7% mannitol (w/v), and 0.02% (w/v) polysorbate 80, prepared in sterile water for injection. High-dose selection was based on decreased body weight gain observed in the 4-week dose range-finding study. A positive control group receiving a single IP dose of 75 mg/kg MNU will also be included. Histopathology is planned to be conducted on all carcinogenicity group animals from all treatment groups. Immunohistochemistry of the thyroid is also planned.

Executive CAC Recommendations and Conclusions:

- The Committee recommended doses of 0 (vehicle control), 0 (saline control), 0.3, 1, and 3 mg/kg LY2189265 by twice weekly subcutaneous injection, based on MTD (excessively reduced body weight gain at 10 and 100 mg/kg in the 4-week study). Dose spacing was based on linear toxicokinetics.

David Jacobson Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DMEP
/Team leader, KDavis-Bruno, DMEP
/Reviewer, THummer, DMEP
/CSO/PM, RChiang, DMEP
/ASeifried, OND IO

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

/s/

ABIGAIL ABBY C C JACOBS
01/28/2011



IND 070930

MEETING MINUTES

Eli Lilly and Company
Attention: Sharon R. Myers, Ph.D., RAC
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Myers:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LY2189265 injection.

We also refer to the End-of-Phase 2 (EOP2) meeting between representatives of your firm and the FDA on November 10, 2009. The purpose of the meeting was to discuss the ongoing and proposed Phase 3 development plan for LY2189265 injection.

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

In addition, we have comments and requests for additional information, located at the end of the meeting minutes. Please note that these requests are not clinical hold issues. However, written response to them is requested.

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes from EOP2 meeting held on November 10, 2009

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Phase 2

Meeting Date and Time: November 10, 2009, 11:00 AM – 12:00 PM
Meeting Location: Building 22, White Oak Campus, Silver Spring, MD

Application Number: 070930
Product Name: LY2189265 injection
Indication: Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Eli Lilly and Company

Meeting Chair: Ilan Irony, M.D.
Meeting Recorder: Mehreen Hai, Ph.D.

FDA ATTENDEES

Mary Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Ilan Irony, M.D.	Diabetes Team Leader, DMEP
Karen Davis-Bruno, Ph.D.	Pharmacology/Toxicology Team Leader, DMEP
Tim Hummer, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Barbara Rellahan, Ph.D.	Team Leader, Division of Monoclonal Antibodies
Carla Lankford, M.D., Ph.D.	Product Quality Reviewer, Division of Monoclonal Antibodies
Jaya Vaidyanathan, Ph.D.	Reviewer, Division of Clinical Pharmacology II
Justin Earp, Ph.D.	Reviewer, Pharmacometrics Staff, Office of Clinical Pharmacology
Christoffer Tornoe, Ph.D.	Team Leader, Pharmacometrics Staff, Office of Clinical Pharmacology
Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II
Lee-Ping Pian, Ph.D.	Statistics Reviewer, Division of Biometrics II
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP

SPONSOR ATTENDEES

James Anderson, M.D.	Senior Director - Medical, GLP-Fc Team
Edward Bastyr, M.D.	Medical Fellow, GLP-Fc Team
Jenny Chien, Ph.D.	Research Advisor, PK/PD
Gregory Enas, Ph.D.	Senior Director, U.S. Regulatory Affairs
Pawel Fludzinski, Ph.D.	Global Development Leader, GLP-Fc Team

Mary Jane Geiger, M.D., Ph.D.	Senior Medical Advisor, GLP-Fc Team
Kristine Harper, M.D.	Medical Fellow, Global Patient Safety
Paul Hines, B.S., M.B.A.	Senior Advisor, Project Management, GLP-Fc Team
Corina Loghin, M.D.	Senior Research Scientist - Clinical, Clinical Pharmacology
Zvonko Milicevic, M.D., Ph.D.	Medical Fellow, GLP-Fc Team
LaRonda Morford, Ph.D.	Research Advisor, Toxicology
Sharon Myers, Ph.D.	Director, U.S. Regulatory Affairs
Zachary Skrivanek, Ph.D.	Senior Research Scientist, Statistics
John Vahle, D.V.M., Ph.D.	Research Fellow – Pathology, Toxicology

1.0 BACKGROUND

Eli Lilly submitted IND 70,930 for LY2189265 injection on August 4, 2005. On August 11, 2009, Lilly submitted an End-of-Phase 2 meeting request for this product. FDA has previously met with Lilly regarding this drug product, including a Pre-IND meeting and several guidance meetings.

LY2189265 injection is a long acting glucagon-like peptide (GLP-1) analog that is being developed for the treatment of type 2 diabetes mellitus (b) (4) Planned administration is once weekly as a subcutaneous injection.

LY2189265 is being developed as a Critical Path Initiative (CPI) pilot project, specifically using an adaptive randomization, seamless Phase 2/3 trial in clinical development.

The purpose of this meeting was to discuss the nonclinical and clinical data packages that are required for approval of LY2189265.

2. DISCUSSION

The Sponsor requested responses to the following questions. The questions are repeated below and the Division's preliminary responses provided to the Sponsor on November 9, 2009, follow in bold. A summary of the meeting discussion is indicated in italicized bold.

Section 1.2.1 TOXICOLOGY PLAN

Question 1: Does FDA agree that the nonclinical studies conducted to date, together with the additional proposed studies, will provide sufficient nonclinical safety information to support registration of LY2189265 in adults?

FDA Preliminary Response: The proposed non-clinical program for LY2189265 is consistent with the type and number of studies typically expected for a biotechnology-derived product intended for long-term clinical use. The adequacy of the non-clinical data in order to support product registration is a review issue and cannot be determined until the new drug application (NDA) has been submitted to the Agency. Please note that if unforeseen safety issues arise for LY2189265 or for other compounds in the same therapeutic class, additional non-clinical studies may be warranted before marketing or as a post-marketing requirement.

It should be noted that if the rat carcinogenicity study shows treatment-related thyroid C-cell tumors, a negative finding using Tg.rasH2 mice would likely not alleviate concerns regarding your product's potential to induce C-cell tumors in two rodent species based on the results of other GLP-1 receptor agonists tested in 2-year mouse bioassays.

***Meeting Discussion:** The Division confirmed that a transgenic mouse study is acceptable for submission in lieu of a 2-year mouse carcinogenicity study. However, the Division reiterated that a negative finding for thyroid C-cell tumors in the transgenic mouse carcinogenicity study would not be sufficient to distinguish LY2189265 from other GLP-1 agonists that induced thyroid c-cell tumors in 2-year bioassays in rodents.*

Section 1.2.2 CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS PLAN

Question 2: Does FDA agree that the clinical pharmacology/biopharmaceutics plan, including the types of studies, the proposed doses, and populations to be tested, is appropriate and sufficient to support registration of LY2189265?

FDA Preliminary Response: Your proposed clinical pharmacology plans are acceptable. You should consider conducting a hepatic impairment study since the impact of hepatic impairment on the exposure of GLP-1 analog appears to be unpredictable.

***Meeting Discussion:** Lilly explained that they do not plan to conduct a hepatic impairment study since they do not expect the pharmacokinetics of LY2189265 to be changed in patients with hepatic impairment, and provided their rationale for this expectation. The Division explained that the reason for their recommendation regarding a hepatic impairment study was due to the unpredictable response (e.g., increase or decrease in drug exposure) seen with similar GLP-1 receptor agonists, and may not be related to the mechanism of clearance of LY2189265. The Division also explained that the lack of data from different grades of impairment in liver function may affect labeling for this drug product.*

Section 1.2.3 PHASE 3 CLINICAL PLAN

Question 3: Does FDA agree that the designs of the proposed Phase 3 studies (including the patient populations to be enrolled, the choice and doses of background therapy, the endpoints,

the lead-in period, the time to the primary endpoint, the duration of the trials, the choice and doses of the comparators, and the plans for blinding) are acceptable to support registration of LY2189265?

FDA Preliminary Response: You indicate that, in addition to the studies listed under the Phase 3 development plan, you will conduct a 12- to 16-week hemodynamic safety study and an event-driven cardiovascular (CV) safety study (approximately 5 years and 10,000 subjects). It is unclear, however, where these two studies fit in your Phase 3 development plan for LY2189265. Please clarify this issue, noting that you will need to demonstrate that the CV risk associated with your investigational product does not exceed a hazard ratio of 1.8, prior to filing an NDA.

We note that your plan does not include studies of LY2189265 on a background of either a TZD or a sulfonylurea alone. Please justify your choice of studying the safety and efficacy of LY2189265 in subjects not controlled with a combination of metformin and one of these antidiabetic products. We recommend that you include stratified subsets of subjects under treatment with either a TZD or a sulfonylurea alone in your randomization for the CV safety study.

Some of the studies include a very short lead-in period, to account for adjustment of background therapies prior to randomization. Please note that while fasting plasma glucose may be stable after the short lead-in period, HbA1c may still be unstable and not reflective of a true baseline value for the subject.

Regarding the evidence for cardiovascular safety necessary for filing the NDA, it is not clear what proportion of events is expected from the dedicated CV safety study versus the meta-analysis of all Phase 3 studies and the Phase 2 studies lasting longer than 3 months.

From the Target Product Profile, it is not clear what the recommended dose will be for initiation of treatment and for maintenance. Please consider conducting trial(s) to investigate the effects of titration of the dose from 0.75 mg to 1.5 mg regarding safety, tolerability and efficacy.

Meeting Discussion: Lilly clarified that the hemodynamic study GBDN will be conducted along other Phase 3 studies, is expected to be completed in 2011 and will be submitted as part of the NDA. The CV safety study will be underway at the time of the NDA submission, and an interim analysis of that study will contribute the 2/3 to 4/5 of the total number of events (expected to be around 150 events) necessary to rule out the hazard ratio of 1.8 prior to filing. Lilly is not planning to study the effect of LY2189265 as add-on to a background of a TZD or sulfonylurea alone. The Division reminded Lilly that the label will contain relevant data only from the settings studied. Lilly also provided justification for the short lead-in period (2 weeks) in studies GBCD (monotherapy) and GBDD (combination with insulin), as being an acceptable approach to IRBs to reduce the exposure to prolonged pre-randomization hyperglycemia. Lilly acknowledged that HbA1c may not be reflective of a stable baseline period under these conditions. Lilly also provided justification on the decision to market a single dose, with a possible alternative lower dose. A Phase 2 study evaluated the effect of

dose titration on safety and tolerability, and concluded that dose titration would not be required or recommended.

Lilly clarified that 25-50 CV events out of the total of 150 events needed to have adequate power to rule out a relative risk of 1.8 will come from the phase 2/3 studies (i.e., not the dedicated CV study). Lilly is not proposing to conduct any interim analyses with respect to the 1.8 non-inferiority margin. The Division asked about a scenario in which the sponsor failed to show non-inferiority after 150 events with respect to the 1.8 margin. To address this scenario, the Division suggested that Lilly define a level of maximum information (i.e., number of events) that will apply to the 1.8 margin, and consider one or more interim analyses defined by the fraction of total information. The overall type 1 error would then need to be adjusted for any of these interim looks. Each non-inferiority margin (1.8 and 1.3) should be assigned a type 1 error of 2.5% (one-sided). Lilly will submit a protocol for the evaluation of CV safety for FDA review.

Question 4: Does FDA agree with Lilly's proposed routine safety monitoring plans in the Phase 3 trials, including assessments of vital signs, ECGs, immunogenicity assessment, hypoglycemia, and management of patients with persistent hyperglycemia?

FDA Preliminary Response: Your plans to conduct routine monitoring for cardiovascular (VS, ECG and biomarkers of CV risk), exocrine pancreatic, and thyroid safety are adequate. Similarly, your plans for assessment and treatment of hypoglycemia and hyperglycemia during the trials are adequate. However, your plan to monitor for LY2189265 potential immunogenicity is not clear: you state that only subjects with a treatment-emergent antibody response ≥ 4 -fold increase in titer from baseline will be tested for cross-reactivity to native GLP-1, and to assess the potential for neutralization of the LY2189265 and the endogenous GLP-1 effect. Please justify the threshold chosen.

Meeting Discussion: *The discussion evolved around a threshold to reduce the reporting of false positive samples and the Division agreed to Lilly's chosen threshold. The Division will examine the correlation between glycemic responses and antibody titers as well.*

Question 5: Does FDA agree with Lilly's proposal for the HbA1c margin of noninferiority for the mean treatment difference between LY2189265 and the active comparators in each of the 4 proposed pivotal Phase 3 trials?

FDA Preliminary Response: Yes, we agree. Additionally, for Study GBDA, we would like to see a direct test of 50% preservation of the control effect for week-26 HbA1c change from baseline that does not require use of a fixed margin. That is, construct the test statistic and hypotheses as follows:

$$H_0: (\mu_{\text{test}} - \mu_{\text{control}}) - \frac{1}{2} (\mu_{\text{placebo}} - \mu_{\text{control}}) \leq 0$$

$$H_1: (\mu_{\text{test}} - \mu_{\text{control}}) - \frac{1}{2} (\mu_{\text{placebo}} - \mu_{\text{control}}) > 0$$

Also, we expect to see general concordance between results in the ITT population and in the subset of completers, with respect to the non-inferiority margin.

Meeting Discussion: *The Division explained that the requested test would be a sensitivity analysis, and also noted the notation in the equation presented in the preliminary response was incorrect, and should actually be:*

$$H_0: (\mu_{\text{test}} - \mu_{\text{control}}) - \frac{1}{2} (\mu_{\text{placebo}} - \mu_{\text{control}}) \geq 0$$

$$H_1: (\mu_{\text{test}} - \mu_{\text{control}}) - \frac{1}{2} (\mu_{\text{placebo}} - \mu_{\text{control}}) < 0$$

Question 6: Does FDA agree that the tree-gatekeeping strategies for evaluating HbA_{1c} change from baseline proposed for the 4 pivotal Phase 3 registration studies will adequately control the Type I error rate, and that significant results under these testing strategies (b) (4) will lead to the inclusion of efficacy statements in the package insert (PI):

- a. For HbA_{1c} data collected at the time of the primary efficacy endpoint?
- b. For HbA_{1c} data collected at the completion of the trial (secondary efficacy endpoints)?

FDA Preliminary Response:

- a. **No, we do not agree. We think a sequential procedure starting with 1.5 mg poses risks (e.g., toxicity) that may cause this dose to fail to show efficacy (e.g., non-inferiority to the active control) and prevent the lower dose (0.75 mg) from being tested. We suggest using other procedures (e.g., Dennett's procedure) that will allow simultaneous testing of both doses as the first step in the testing procedure.**
- b. **Control of type 1 error rate for all endpoints intended for labeling is encouraged. However, labeling is ultimately a review issue and labeling of all statistically significant findings is not guaranteed,** (b) (4)

Meeting Discussion: *None.*

Question 7: Does FDA agree with the proposed population PK sampling design and PK/PD analysis strategies for the proposed pivotal Phase 3 studies?

FDA Preliminary Response: **Yes, we agree. We recommend that you collect the second point sample (24-96 hours) in a manner that best captures the C_{max} of the drug.**

In addition, an analysis correlating LY2189265 exposure to adverse events of pancreatitis and to increases in amylase and lipase is of interest, since we observe a narrow therapeutic window between the maximum proposed dose (1.5 mg) and a dose associated with such events in prior completed studies (3 mg).

Meeting Discussion: *The Division emphasized that it was important to capture the C_{max} of the drug and that a shorter sampling window may give better estimate of C_{max}. Lilly responded that the drug had a long half-life of elimination and that the broadly sloping nature of the peak concentrations would make this shorter sampling window have little effect on the estimation of C_{max}. The Division acknowledged this and agreed that their sampling schedule is reasonable. However, the Division pointed out the concern for underestimating C_{max} if too many samples were collected later in time.*

The Division also clarified that actual concentrations along with dose information may be used to identify signals for safety and effectiveness.

Question 8: Does FDA agree with Lilly's position, that (b) (4) are important concepts to measure in patients with type 2 diabetes who are obese, in order to demonstrate the efficacy of LY2189265?

FDA Preliminary Response: Response will be provided in writing at a later date.

Meeting Discussion: None.

Post-Meeting FDA Response: *No, we do not agree. The proposed indication for LY2189265 is an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.* (b) (4)

Question 9: Does FDA agree (b) (4)

FDA Preliminary Response: Response will be provided in writing at a later date.

Meeting Discussion: None.

Post-Meeting FDA Response: *No, we do not agree. As noted in our response to Question 8,* (b) (4)

Question 10: Does FDA agree that the proposed number of patients to be studied in Phase 2 and Phase 3 trials for the durations specified are adequate to support registration of LY2189265?

FDA Preliminary Response: The preamble to the question is unclear regarding the contribution of the CV safety study to the overall safety database. In order to satisfy the CV safety guidance, the expectation is that sponsors will greatly exceed the drug exposure (in person-years) in combined Phase 2 and Phase 3 trials previously recommended in the February 2008 guidance.

In addition, a substantial number of patients with different magnitudes of renal impairment need to be included, either in a dedicated study of diabetics with chronic renal insufficiency, or as subsets of the non-metformin Phase 3 studies and the CV safety study.

The NDA must be considered complete at the time of filing, so that no substantial information in support of the NDA will need to be reviewed at the 4-month safety update.

Meeting Discussion: *Lilly requested additional clarification regarding the need to include subjects with renal impairment. The Division explained that the concern relates to potential effects of the classes of GLP-1 agonists and DPP-4 inhibitors on renal function. The suggested guideline for exposure was 300 subjects exposed to the investigational drug for 6 months to 1 year, with about 2/3 of these in the category of moderate renal insufficiency and 100 in the category of severe renal insufficiency or end stage renal disease. This advice is consistent with recommendations given to other sponsors at their End-of-Phase 2 meetings.*

Question 11: Does FDA agree that the ongoing Study GBCF and the 4 proposed Phase 3 studies, supplemented with cardiovascular event data from other completed LY2189265 studies, and from an interim analysis of an ongoing cardiovascular safety study in high-risk patients, will in principle provide sufficient clinical safety and efficacy information to support registration of LY2189265?

FDA Preliminary Response: The amount of data necessary to support registration is unknown at this time. The review of the application will focus on the benefits provided by LY2189265 as weighted against the risks covered during the review of the application, including the known class risks of pancreatitis and the potential for medullary thyroid cancer.

Meeting Discussion: *None.*

Question 12: Does FDA agree with Lilly's proposal that Study GBDD and the cardiovascular safety study be considered for Special Protocol Assessment?

FDA Preliminary Response: The cardiovascular safety study does not qualify, because it is not an efficacy study. The issue regarding the merit of Study GBDD as a SPA will be discussed internally, as we have already reviewed one study (GBCF) very extensively under the Critical Path program.

Meeting Discussion: *The Division recommended that, instead of requesting a SPA for the review of their protocols, Lilly should submit their protocols under the IND to the Division with a standard request for feedback and include specific questions in their submission.*

Section 1.2.3 POTENTIAL DRUG OR THERAPEUTIC CLASS-RELATED SAFETY CONCERNS

Question 13: Does FDA agree with Lilly's proposed plan to assess the effects of LY2189265 on the exocrine pancreas?

FDA Preliminary Response: In order to further investigate the potential of LY2189265 to induce pancreatitis, we request that you conduct a 3-month study in an insulin resistant rodent model for type II diabetes (e.g., db/db mouse or zucker rat). The endpoints for this study should include pancreas/pancreatic ductal histopathology, assessment of pancreatic ductal proliferation (e.g., KI67), and serum amylase, lipase, insulin, and glucose.

Meeting Discussion: *The Division explained that a rodent model different from those suggested above, if relevant, would be acceptable for this study, and explained that a longer term study (i.e., 3 months) is preferred. The Division clarified that the recommended parameters stated in the initial response could be replaced by other relevant parameters, where justified. The Division recommended that this study be conducted per GLP regulations but recognized that this might not be possible for all aspects of the study (e.g., nonstandard assays that have not been validated). The Division agreed that an assessment for pancreatic cell proliferation could be evaluated at a single time point at the end of the dosing period and the study report could be submitted with the NDA submission. The Division agreed to review the protocol prior to the start of the study.*

Question 14a: Does FDA agree that the preclinical investigative approaches summarized in Section 7.2 are appropriate to further understand potential effects of LY2189265 and/or other GLP-1 agonists on the thyroid?

FDA Preliminary Response: We agree that there are a large number of approaches that could be taken to further investigate the role of GLP-1 receptor agonists on c-cell proliferation. The intention of the planned pre-clinical study focuses on a comparison of LY2189265 treatment with thyroid c-cell mass in rodents and primates in an effort to elucidate whether secretagogue-stimulated calcitonin is a dependable marker for thyroid c-cell preneoplastic findings across species including humans. Details of the experimental approach have not been determined. You have indicated that initial efforts will develop appropriate methods (e.g. calcitonin assays across species, calcitonin stimulation protocols, c-cell morphology). Should these studies suggest viable methods, a longitudinal time course

(young to old) has been suggested in rat to assess the response of rat c-cells to treatment with LY2189265 as well as a single long-term (duration not specified) assessment of secretagogue stimulated calcitonin over time with characterization of c-cell mass in monkey.

If the goal is to examine an interspecies difference in sensitivity, then the rat and monkey studies proposed here are unlikely to add significantly to the understanding of GLP-1 agonist activity, as other sponsors have performed similar assessments for other GLP-1 agonists. Time-course investigations in rat have demonstrated a modest, transient increase in calcitonin with chronic treatment of GLP-1 agonists. A similar long-term study in monkeys is not practical to perform. It may be useful to determine whether GLP-1 receptor expression correlates with the presence of hyperplasia and whether basal calcitonin levels correlate with the degree of stimulation and c-cell mass across a variety of species.

Other potential questions directed more toward the mechanism could include:

- 1) Is c-cell hyperplasia dependent on the GLP-1 receptor? This could be investigated by using a GLP-1 receptor knock-out mouse.
- 2) Is the GLP-1 receptor the only receptor on c-cells that is activated by GLP-1 receptor agonists?
- 3) If c-cell hyperplasia is dependent on the GLP-1 receptor, is GLP-1 receptor-mediated signaling in c-cells similar across species or is there a pathway(s) activated that could make rodents more susceptible to hyperplasia and tumor progression?

***Meeting Discussion:** Lilly clarified how their proposed nonclinical approach is different from that taken by other sponsors and that the information gained from the studies could lead to the development of methods useful for determining human risk. Although the Division feels that an approach aimed at elucidating the mechanism for c-cell proliferation and tumorigenesis in rodents would be more informative, the Division did not disagree with the sponsor's proposed approach, especially if it could lead to the development of methods that could be used reliably in humans.*

Question 14b: Does FDA agree with Lilly's proposed clinical assessment of the effects of LY2189265 on the thyroid?

FDA Preliminary Response: Yes, we agree.

***Meeting Discussion:** None.*

Question 15: Does FDA agree with the proposed clinical cardiovascular risk assessment plan, including the meta-analysis primary endpoint, methods of analysis, and studies to be included?

FDA Preliminary Response: Based on our current experience, we believe it is unlikely that a traditional Phase 3 program will meet the requirement to rule out a hazard ratio > 1.8,

through a meta-analysis of events accrued in the Phase 2 and Phase 3 studies. These events can be used to complement a dedicated CV study. The latter should be powered to collect sufficient numbers of adjudicated events, as the primary goal of the study.

The components listed are acceptable, as part of the composite primary endpoint.

The briefing package has not provided sufficient detail for review of the protocol for this dedicated study. In our experience, the important elements of the protocol and the statistical plan are: the power calculation, the CV risks used to enrich the patient population and the protection against inflation of the type 1 error through multiple looks at the data accrued over time. In addition, we would need to know your plans to demonstrate that the CV hazard ratio does not exceed the 1.3 goal post post-approval.

Meeting Discussion: *See Question 4.*

Additional Comments:

Statistical Analysis:

1. To be consistent with GBCF, the primary analysis method for studies GBDA, GBDB, GBDC and GBDD should be LOCF applied to the ITT population. As a sensitivity analysis to LOCF, you should conduct a MMRM analysis. We will examine the results of the repeated measures analysis in detail during the review. However, at this time we request that it serve as a secondary analysis.

Meeting Discussion: *The Division clarified the definition of LOCF in the presence of rescue, namely that Lilly should use the last observation prior to rescue.*

Manufacturing:

2. Your 2007 Annual Report indicates that a significant manufacturing change has been implemented (b) (4). Provide information on when material (b) (4) was introduced into the clinic. Include specific information on the trials that the new material has been used in and the number of patients in each study and dose level that received material from the original (b) (4) process compared to the new (b) (4) process. In addition, provide information on the immunogenicity rate and level observed with the (b) (4) derived product compared to the (b) (4) derived product. Significant manufacturing changes should be supported by comparability studies as outlined in the ICH guidance entitled "Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process" (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073476.pdf>). In the future, data from the comparability studies should be submitted to the Agency for review prior to clinical use of material made by the new process.

Meeting Discussion: *During the discussion Lilly indicated that the comparability study had been previously submitted to FDA, and agreed to provide information regarding the date on which the comparability information had been submitted. [Provided by Lilly via email on November 11, 2009.]*

Post-Meeting FDA Comments and Information Requests:

1. *Provide a detailed update on the current manufacturing and testing process for LY2189265. The update should include a detailed summary description of any significant process change made between the current process and that intended to be used to produce material for the proposed major efficacy trial. See comments 8, 11-14 and 20 below for additional information that should be included in the update.*
2. *Establish an acceptance criterion for (b) (4) that ensures that the amount of (b) (4) present in the maximum proposed dose will not exceed the World Health Organization's recommended limit of (b) (4).*
3. *An assay (b) (4) should be incorporated into the drug substance and drug product lot release and stability programs. Quantitative acceptance criteria that control for all (b) (4) should be included in the specification.*
4. *Provide information demonstrating that the mycoplasma testing method of the (b) (4) conforms to 21 CFR 610.30.*
5. *An assay for drug product excipients (b) (4) with acceptance criteria, should be incorporated to the drug product lot release program.*
6. *Where applicable (b) (4), quantitative acceptance criteria should be established for the drug substance and drug product stability program. For tests such as appearance, the acceptance criterion should include a description of the expected color, clarity, and visible particle presence that is deemed acceptable.*
7. *Revise the drug substance and drug product potency assay (s) acceptance criteria to directly reflect the activity of each lot as a percentage of the activity compared to that of the reference standard (i.e., (b) (4) of the reference standard).*
8. *Provide information on the strategy, with supportive data, for clearance of all process-related impurities including, but not limited to, (b) (4). All process related impurities must either be tested for during lot release or (b) (4) validated. This should include information on the level of (b) (4) which is present in the drug product. In addition, include a 'worst-case-estimate' for the amount of (b) (4) that could be present in a maximum dose. This estimate can take into consideration of (b) (4) steps that would be predicted to reduce the amount present in the drug product.*
9. *Provide a detailed description of the methodology and qualification/validation results of the assay that is being used for the detection of human anti-drug antibodies (ADA)*

or indicate when this information was submitted to the IND. The results should include data demonstrating that the assay is specific, sensitive and reproducible. The validated assay should be capable of sensitively detecting ADA responses in the presence of LY2189265 levels that are expected to be present at the time of patient sampling. In addition, provide information/data on the qualification of the assay being used to delineate neutralizing ADA responses. Until this assay has been reviewed by the Agency it is recommended that patient samples be banked under appropriate storage conditions.

10. Provide detailed information on tests and acceptance criteria used for qualification of the current reference standard.

11. Provide a detailed summary description of [REDACTED] (b) (4) conditions.

12. Provide a detailed summary description of [REDACTED] (b) (4) and results of all lots produced to date.

13. Provide a detailed summary description of the [REDACTED] (b) (4) controls, and descriptions of all materials (including the certificate of origin [REDACTED] (b) (4)) and all [REDACTED] (b) (4) hold steps, their duration, storage temperature and the bioburden testing performed before and after each hold intermediate during drug product manufacturing.

14. Provide a detailed description of, and justification/explanation of the need for, the [REDACTED] (b) (4) step. In addition, provide [REDACTED] (b) (4) controls and tests performed for this step.

15. [REDACTED] (b) (4) Provide a risk assessment, supported by data where available, on the ability of LY2189265 [REDACTED] (b) (4) s. If applicable, provide information on the strategy, with supportive data, in place to monitor [REDACTED] (b) (4)

16. The [REDACTED] (b) (4) assay needs to be qualified for its ability to detect potential [REDACTED] (b) (4) impurities. This data needs to include 2-dimensional SDS-PAGE gels of the range of [REDACTED] (b) (4) detected by a sensitive protein stain, such as silver stain, compared to the range detected by western blot analysis (or another similarly sensitive assay) using the [REDACTED] (b) (4) employed in the assay. It is the

Agency's experience that analysis of (b) (4) coverage by a 1-dimensional SDS-PAGE gel method is not sufficiently sensitive for this purpose.

17.

(b) (4)
It is recommended that in addition to <USP 788> particulate testing, smaller sub-visible particles (b) (4) be monitored at release and at regular intervals in the drug product stability program including under accelerated and/or stressed condition. Data from these characterization studies can be used to develop and provide support for an overall control strategy for particulate matter for the LY2189265 manufacturing process.

18. *Visible and/or sub-visible particle formation can represent a significant degradation pathway for monoclonal antibody products and impact product quality and safety. It is recommended that testing for visible and sub-visible particle be incorporated into the accelerated/stressed stability program to determine whether particulate formation is a component of the product's degradation pathway. This information can then be used to develop and support the testing interval used for particulate testing at the recommended storage temperature. It is recommended that testing for sub-visible particulates be performed at least on an annual basis in the drug product stability program.*

19. *Per the ICH Q5C Guideline for Industry entitled "Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products" (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073466.pdf>), drug product stability programs should include samples stored in both an upright and inverted position. Confirm these conditions are included in the current drug product stability program.*

20. *Provide information on the composition of the containers and the type of closure system (including vendor information) used for drug substance storage.*

21. *Prior to licensure, studies should be conducted to demonstrate/confirm (b) (4) (b) (4) may be required for release and stability testing.*

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

4.0 ACTION ITEMS

No action items.

5.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts for the meeting minutes.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-70930	GI-1	ELI LILLY AND CO	LY2189265 FOR INJECTION

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

/s/

MEHREEN HAI
01/19/2010

Executive CAC

Date of Meeting: August 4, 2009

Committee: David Jacobson Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND IO, Member
Todd Bourcier, Ph.D., DMEP, Alternate Member
Karen Davis-Bruno, Ph.D., DMEP Pharm/Tox Supervisor
Tim Hummer, Ph.D., DMEP, Presenting Reviewer

Author of Minutes: Tim Hummer

The following information reflects a brief summary of the Committee discussion and its recommendations.

The committee did not address the sponsor's proposed statistical evaluation for the carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document.

IND #: 70,930

Drug Name: LY2189265

Sponsor: Eli Lilly

Background:

LY2189265 is a long-acting GLP-1 receptor agonist. The sponsor primarily relied on the results from a 6-month toxicity study in rats as the basis for high-dose selection for the proposed rat carcinogenicity study. In the 6-month study, Sprague-Dawley rats were administered LY2189265 at doses of 0, 1.63 mg/kg, 4.89, and 16.29 mg/kg twice weekly by subcutaneous injection. There were no treatment-related deaths or significant target organ toxicities. The key treatment related effect was decreased body weight at all dose levels, which generally correlated with decreased food consumption. Final mean body weights were 7% to 18% (males) and 16% to 19% (females) less than control values.

Rat Carcinogenicity Study Protocol and Dose Selection

The sponsor proposed a standard 2-year carcinogenicity study in Sprague-Dawley rats (60/sex/group) using doses of 0, 0.05, 0.15, 1.5, and 5 mg/kg LY2189265 twice weekly by subcutaneous injection in males and females. High-dose selection was primarily based on decreased body weight ($\geq 10\%$) observed in males and females at the end of the 6-month study as well as predicted exposure multiples of the maximum clinical dose ($\geq 25X$). At the proposed high dose of 5 mg/kg (4.89 mg/kg in the 6-month study), males and females weighed 14% and 16% less than controls, respectively. Additionally, this dose level provided an exposure multiple of approximately 48X over the anticipated human exposure at the planned maximum clinical dose of 1.5 mg once weekly.

Executive CAC Recommendations and Conclusions:

Sponsor Question #1:

Does FDA agree with the design and dose selection of the 2-year carcinogenicity study in rats with LY2189265?

ECAC Response: The following protocol revisions are recommended:

- The Committee recommends doses of 0, 0.05, 0.5, 1.5, and 5 mg/kg by twice weekly subcutaneous injection, based on AUC ratios, raising the sponsor's proposed low mid-dose from 0.15 to 0.5 mg/kg.
- The Committee notes that if the clinical dose changes such that the ratio is no longer at least 25 fold above the clinical exposure, the study may not be acceptable.
- The Committee notes that if the sponsor prefers to use only three dose groups that the 0.05 mg/kg group may be dropped.
- The Committee recommends that body weights be measured before each dose administration (i.e., twice weekly rather than once weekly) as conducted in the 6-month study so that the durability of the distinct biweekly pattern of decreased body weight gain/weight loss can be tracked throughout the study. The Committee also recommends setting aside samples at the end of the study for possible future neutralizing antibody analysis, if necessary (e.g., if pharmacodynamic activity is not observed throughout the study).
- The Committee recommends the addition of a saline control group in addition to the planned vehicle control group.

Sponsor Question #2:

Does FDA agree with the plan to conduct a single carcinogenicity study in rats to support registration with LY2189265?

ECAC Response: No, as the sponsor indicated in their dose selection package, other long-acting GLP-1 receptor agonists have induced thyroid C-cell adenomas and carcinomas in both rats and mice, for which the relevance to humans is currently unknown. For LY2189265, the GLP-1 molecule has been significantly modified through the recombinant addition of a human IgG4 heavy chain. Therefore, it should not be assumed that the tumor-inducing properties, with regard to potency, species selectivity, or target tissue, will be the same as for other compounds in this class. Accordingly, a carcinogenicity study in both rats and mice will be required to fully assess the tumorigenic potential of LY2189265.

Additional Comments:

Although the sponsor's draft protocol for the rat carcinogenicity study currently states that histopathology will be performed on all main study group animals, please note that if the protocol is changed such that histological evaluation of tissues will only be conducted on control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:

- (a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups
- (b) for an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group
- (c) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level,
- (d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

David Jacobson Kram, Ph.D.
Chair, Executive CAC

cc:\

- /Division File, DMEP
- /Team leader, KDavis-Bruno, DMEP
- /Reviewer, THummer, DMEP
- /CSO/PM, LAIJuburi, DMEP
- /ASeifried, OND IO

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 70930	ORIG 1		LY2189265 FOR INJECTION
IND 70930	ORIG 1		LY2189265 FOR INJECTION

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

/s/

DAVID JACOBSON KRAM
08/05/2009

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 125469

LATE-CYCLE MEETING MINUTES

Eli Lilly and Company
Attention: Kenneth Mace, PhD
Advisor, Global Regulatory Affairs-US Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Mace:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Trulicity (dulaglutide) injection

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 2, 2014.

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

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

William Chong, MD
Clinical Team Leader (Acting)
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 2, 2014 from 1:00 to 2:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room Number: 1417
Silver Spring, MD 20903

Application Number: BLA 125469
Product Name: Trulicity (dulaglutide) injection
Applicant Name: Eli Lilly and Company

Meeting Chair: Jean-Marc Guettier, MD
Meeting Recorder: Abolade (Bola) Adeolu

FDA ATTENDEES

Mary Parks, MD - Deputy Director, Office of Drug Evaluation II
Jean-Marc Guettier, MD - Director, Division of Metabolism & Endocrinology Products (DMEP)
Jennifer Pippins, MD, MPH – Division Director for Safety (Acting)
William Chong, MD - Clinical Team Leader, DMEP
Suchitra Balakrishnan, MD, PhD. - Clinical Reviewer, DMEP
Karen Davis-Bruno, PhD - Nonclinical Supervisor, DMEP
Tim Hummer, PhD - Nonclinical Reviewer, DMEP
Lokesh Jain, PhD - Clinical Pharmacology Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Sang Chung, PhD - Clinical Pharmacology Reviewer, DCPII, OCP
Nitin Mehrotra, PhD – Team Lead, Division of Pharmacometrics, OCP
Lian Ma, PhD – Pharmacometrics Reviewer, OCP
Mark Rothmann, PhD - Lead Mathematical Statistician, Division of Biometrics II (DBII)
Brad McEvoy, PhD – Statistical Efficacy Reviewer, DBII
Janelle Charles, PhD – Statistical Safety Reviewer, DBVII
Laurie Graham, MS - CMC/Product Quality Team Leader, Office of Biotechnology Products (OC), Division of Monoclonal Antibodies (DMA)
Joel Welch, PhD - CMC/Product Quality Reviewer, OBP, DMA
Patricia Hughes, PhD – Quality Microbiology Team Leader
Colleen Thomas, PhD – Product Quality Microbiology Reviewer
Bo Chi, PhD- Product Quality Microbiology Reviewer
Shawna Hutchins, MPH, BSN, RN-Senior Patient Labeling Reviewer, Division of Medical Policy Programs (DMPP)
Nguyen, Quynh Nhu, MS - Combination Products Human Factors Specialist, Center for Devices and Radiological Health(CDRH)
LT Viky Verna, MSE, MSPharm – Biomedical Engineer, Office of Compliance, CDRH

Cynthia LaCivita, PharmD – Risk Management Team Leader, Division of Risk Management, Office of Surveillance & Epidemiology (OSE)
Naomi Redd, PharmD - Risk Management Analyst, Division of Risk Management, OSE
Julie Van der Waag, MPH - Chief, Project Management Staff
Mehreen Hai, PhD – Safety Project Manager
Abolade (Bola) Adeolu, RPh, MS, MBA - Regulatory Project Manage

EASTERN RESEARCH GROUP ATTENDEES

(b) (6) – Eastern Research Group

APPLICANT ATTENDEES

Elizabeth Bearby, Pharm D, Senior Director, Global Regulatory Affairs-US
Michael De Fellipis, PhD, Senior Research Fellow, Bioproduct Development-CMC
John R. Dobbins, MS, Principal Research Scientist, Global Regulatory Affairs – CMC
Jeff Emmick, MD-PhD, Vice President, Diabetes Development
Jessie Fahrback, MD, Medical Director, Global Diabetes Development
Pawel Fludzinski, PhD, Dulaglutide Global Brand Development Leader
Kristine D. Harper, MD, MBA, Medical Fellow, Global Patient Safety
John Kaiser, PharmD, Consultant, Global Regulatory Affairs-US
Kenneth F. Mace, PhD, Regulatory Advisor, Global Regulatory Affairs-US
Mark Marley, PharmD, Principal Research Scientist. Global Regulatory Affairs-Devices
Sherry Martin, MD, Senior Medical Director, Global Diabetes Development
Bruce Meiklejohn, PhD, Senior Research Fellow, Global Regulatory Affairs- CMC
Linda Shurzinske, MS, Research Advisor, Statistics
John Towns, PhD, Principal Fellow, Global Regulatory Affairs- Devices
John Vahle, PhD, Senior Research Fellow, Pathology

1.0 BACKGROUND

BLA 125469/0 for Trulicity (dulaglutide) injection as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus was submitted on September 17, 2014. The Prescription Drug User Fee Act (PDUFA) goal date for the application is September 18, 2014.

FDA issued a Background Package in preparation for this meeting on May 21, 2014.

2.0 DISCUSSION

1. Introductory Comments
2. Discussion of Substantive Review Issues

Clinical:

We have not identified any significant new safety issues with dulaglutide that are inconsistent with the drug class. We have identified a potentially substantive review issue with regards to dose. We continue to consider the risk-benefit profile of both the 0.75 mg and 1.5 mg doses and favor approval of both doses. We are considering your responses regarding dose selection dated April 22, 2014. Our review is ongoing.

Discussion:

FDA stated their opinion that both of the studied doses are approvable and should be labeled. Representatives of Eli Lilly stated that study GBCF was designed to select a dose of maximal clinical utility and that a second lower dose was selected for study as recommended by FDA in case an unforeseen safety signal was identified in the originally selected dose. Thus two doses were studied in the development program: 1.5 mg and 0.75 mg. While both doses demonstrated efficacy, the 1.5 mg dose was more efficacious than the 0.75 mg dose. As there were no unforeseen safety signals and out of concern that clinical inertia will prevent dose escalation, Eli Lilly is seeking approval of the 1.5 mg dose only. FDA outlined their position with regards to dose and their rationale for favoring approval of both doses. It was agreed that there will need to be further discussion of dosing after secondary and tertiary reviews are completed. Eli Lilly expressed concerns with regard to labelling language if both doses are approved as titration was not studied in the development program, but acknowledged FDA's position. Proposed labeling with both doses will be submitted by Eli Lilly for FDA review to assist in further labeling discussions while secondary and tertiary reviews are completed.

Nonclinical:

No substantive nonclinical review issues have been identified. Internal discussions are still ongoing. If it is decided that further investigation is warranted, additional mechanistic nonclinical studies to further evaluate the human relevance of thyroid C-cell tumors would be requested as PMRs.

Discussion:

No additional information was communicated

Product Quality Microbiology:

- A. There is uncertainty about the reliability of the endotoxin test release results for the drug substance and drug product (b) (4). The endotoxin hold-time study should be conducted using (b) (4) (b) (4) for endotoxin qualification studies.
- B. Review of the responses to the product quality microbiology information requests is still ongoing, and additional information will be requested.

Discussion:

It was agreed that a separate teleconference would be held with Eli Lilly to discuss the endotoxin spiking studies.

Product Quality CMC:

Review of the information request responses provided on April 29, 2014 is still ongoing.

Discussion:

FDA stated that the responses are under review and no significant issues have been identified to date.

3. REMS or Other Risk Management Actions

Discussion:

FDA stated that it was too preliminary to discuss a REMS at this time given the ongoing review and labeling discussions, beyond what was already communicated to Eli Lilly on May 30, 2014. A REMS similar to what has been required of other drugs-in-class could be expected. Further discussion of a REMS will be communicated to Eli Lilly as the review cycle progresses.

4. Postmarketing Requirements/Postmarketing Commitments

Discussion:

The FDA stated that post-marketing requirements in-line with what other drugs-in-class have received could be expected. This could include a requirement to complete the cardiovascular outcomes trial, study in pediatric patients, completion of study in renal impairment, and a medullary thyroid cancer registry. Additional postmarketing requirements may arise as the review proceeds. Further discussion of postmarketing requirements will be communicated to Eli Lilly as the review cycle progresses.

5. Review Plans

Discussion:

Primary reviews are being completed. This will be followed by secondary and tertiary reviews. No additional information requests are anticipated at this time. Additional information requests may be submitted if additional questions arise during the secondary and tertiary reviews.

6. Wrap-up and Action Items

Discussion:

Eli Lilly will submit updated labeling to include both the 1.5 mg and 0.75 mg dose.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/

WILLIAM H CHONG
06/12/2014