CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125469Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	BLA125469/000	**Action Goal:**	
Rp Date:	08-NOV-2012	**District Goal:**	20-JUL-2014
Regulatory:	18-SEP-2014		
Applicant:	SHELTON PHCY	**Brand Name:**	
		Estab. Name:	
	, ,	**Generic Name:**	
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	510	001; INJECTION, SOLUTION; DULAGLUTIDE; 1.5MG	

Application Comment: NEW BLA (on 22-AUG-2014 by T. WILSON () 2404024226)

FDA Contacts:	J. WELCH	Prod Qual Reviewer	3017962017
	L. CANIDA	Regulatory Project Mgr	3017961637

Overall Recommendation:	ACCEPTABLE	on 18-SEP-2014	by C. CAPACCI-DANIEL	()	3017963532
	PENDING	on 15-SEP-2014	by EES_PROD		
	PENDING	on 29-AUG-2014	by EES_PROD		
	PENDING	on 28-AUG-2014	by EES_PROD		
	PENDING	on 28-APR-2014	by EES_PROD		

Reference ID: 3630085

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** [redacted] (b) (4) **FEI:** [redacted] (b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: DRUG SUBSTANCE RELEASE TESTING (on 22-AUG-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
SUBMITTED TO OC	28-APR-2014				WILSONT
OC RECOMMENDATION	24-JUN-2014			ACCEPTABLE	WILSONT
SUBMITTED TO DO	28-AUG-2014	10-Day Letter			CAPACCIDANIC
DO RECOMMENDATION	29-AUG-2014			ACCEPTABLE	MROSE
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	CAPACCIDANIC

Milestone Name: SUBMITTED TO OC — Milestone Date: 28-APR-2014 — Creator: WILSONT

Milestone Name: OC RECOMMENDATION — Milestone Date: 24-JUN-2014 — Decision: ACCEPTABLE — Creator: WILSONT

Comment: BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY IOG [redacted] (b) (4) AND CLASSIFIED AS VAI. THIS WAS A ROUTINE GMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG SUBSTANCE TESTING OPERATIONS. THE CTX PROFILE WAS UPDATED AND IS ACCEPTABLE.

Milestone Name: SUBMITTED TO DO — Milestone Date: 28-AUG-2014 — Request Type: 10-Day Letter — Creator: CAPACCIDANIC

Comment: CTL STATUS IS INITIAL
PDUFA IS 18-SEP-2014

Milestone Name: DO RECOMMENDATION — Milestone Date: 29-AUG-2014 — Decision: ACCEPTABLE — Creator: MROSE

Comment: BASED ON EXPEDITED REVEIW RE: CMS WORK [redacted] (b) (4)

Milestone Name: OC RECOMMENDATION — Milestone Date: 29-AUG-2014 — Decision: ACCEPTABLE — Creator: CAPACCIDANIC

Comment: BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY IOG [redacted] (b) (4) AND CLASSIFIED AS NAI. THIS WAS A ROUTINE GMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG SUBSTANCE TESTING OPERATIONS. THE CTX PROFILE WAS UPDATED AND IS ACCEPTABLE PER DO REVIEW (CMS [redacted] (b) (4).

Reference ID: 3630003

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: DRUG SUBSTANCE RELEASE TESTING (on 22-AUG-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	28-APR-2014				WILSONT
OC RECOMMENDATION	24-JUN-2014			ACCEPTABLE	WILSONT

BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY (b)-DO FROM (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE GMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG SUBSTANCE TESTING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCEPTABLE.

Reference ID: 3630003

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

FINISHED DOSAGE OTHER TESTER

Establishment Comment: DRUG SUBSTANCE AND DRUG PRODUCT RELEASE AND STABILITY TESTING (on 22-AUG-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	28-APR-2014				WILSONT
OC RECOMMENDATION	24-JUN-2014			ACCEPTABLE	WILSONT

BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED VAI. THIS WAS A ROUTINE GMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG SUBSTANCE TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.

Reference ID: 3630085

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 1819470 **FEI:** 1819470

ELI LILLY AND COMPANY

1555 S. HARDING/LILLY CORPORATE CENTER
INDIANAPOLIS, IN 462850001

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURE, DEVICE ASSEMBLY, PACKAGING AND LABELING, DRUG PRODUCT RELEASE AND STABILITY TESTING (on 22-AUG-2014 by T. WILSON () 2404024226)
DRUG PRODUCT MANUFACTURE, DEVICE ASSEMBLY, PACKAGING AND LABELING, DRUG PRODUCT RELEASE AND STABILITY TESTING (on 22-AUG-2014 by T. WILSON () 2404024226)

Profile: DEVICE KIT ASSEMBLER **OAI Status:** NONE

(b) (4) NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	22-AUG-2014				WILSONT
RECOMMENDATION	29-AUG-2014			ACCEPTABLE	CAPACCIDANIC
CDRH RECOMMENDS APPROVAL OF THIS FACIILTY FOR THIS APPLICATION PER MEMO DATED MAY 8, 2014 FROM VIKY VERNA IN DARRTS.					
SUBMITTED TO OC	28-APR-2014				WILSONT
OC RECOMMENDATION	24-JUN-2014			ACCEPTABLE	WILSONT
BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY DET-DO FROM 4/15/2013 ¿ 4/19/2013 AND CLASSIFIED VAI. THIS WAS A ROUTINE GMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG PRODUCT MANUFACTURING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCEPTABLE.					
INSPECTION PERFORMED	25-JUL-2014		25-JUL-2014		PRABHAKARAR
EIR RECEIVED BY OC	03-SEP-2014				PRABHAKARAR
SUBMITTED TO BMR	15-SEP-2014	Request BMR Evaluation			PRABHAKARAR
PLI NEEDED IN SUPPORT OF 125469?					
ASSIGNED INSPECTION TO BMR	15-SEP-2014	Product Specific and GMP Inspection			PRABHAKARAR
PLI WILL BE REQUIRED BEFORE APPROVAL OF BLA 125469					
INSPECTION SCHEDULED	15-SEP-2014		25-JUL-2014		PRABHAKARAR

Reference ID: 3630003

OC RECOMMENDATION 16-SEP-2014 ACCEPTABLE PRABHAKARAR

THIS SITE WAS INSPECTED BY CDER-OMPQ (BMAB) FROM JULY 21-25, 2014 AND INITIALLY CLASSIFIED NAI. BASED ON DISCUSSION WITH THE INVESTIGATOR AND A REVIEW OF THE EIR, THIS SITE HAS BEEN FOUND ACCEPTABLE FOR THE MANUFACTURING RESPONSIBILITIES LISTED IN THIS BLA. FACTS WILL BE UPDATED ACCORDINGLY. PLEASE REFER TO CMS WA (b) (4).

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9611006 **FEI:** 3002806888

ELI LILLY SA IRISH BRANCH

DUNDERROW
KINSALE, COUNTY CORK, , IRELAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE OTHER TESTER

Establishment Comment: DRUG SUBSTANCE MANUFACTURE AND STORAGE, DRUG SUBSTANCE RELEASE AND STABILITY TESTING (on 22-AUG-2014 by T. WILSON () 2404024226)

Profile: BIOTECHNOLOGY DERIVED API (STERILE & NON-STERILE) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
INSPECTION PERFORMED ACCEPTABLE	18-MAR-2014		18-MAR-2014		QIUZ
SUBMITTED TO OC	28-APR-2014				WILSONT
SUBMITTED TO BMR	24-JUN-2014	Request BMR Evaluation			WILSONT
BLA BACKFILL ONLY - THERE IS NO FDA INSPECTIONAL HISTORY FOR BIOTECH DRUG SUBSTANCE MANUFACTURING AT THIS SITE. BMAB (WITH THE INPUT OF OBP) WILL DETERMINE WHETHER THIS SITE REQUIRES A PLI FOR THIS BLA. PLEASE RESUBMIT THIS TB-EER 15-30 DAYS PRIOR TO THE PLANNED ACTION DATE FOR AN UPDATED COMPLIANCE EVALUATION.					
ASSIGNED INSPECTION TO BMR	14-JUL-2014	Product-Specific Inspection			QIUZ
BMAB DETERMINED A PAI IS NEEDED					
INSPECTION SCHEDULED	14-JUL-2014		18-MAR-2014		QIUZ
BMR RECOMMENDATION	14-JUL-2014			ACCEPTABLE	QIUZ
BMAB FINDS THIS SITE IS ACCEPTABLE FOR THIS BLA.					
SUBMITTED TO DO	14-JUL-2014	10-Day Letter			PRABHAKARAR
BLA PILOT - GMP STATUS IS INITIAL.					
UNDER REVIEW	01-AUG-2014				MROSE
DO RECOMMENDATION	18-SEP-2014			ACCEPTABLE	MROSE
EMAIL FROM A. ALDRIDGE STATING VAI CLASSIFICATION (PENDING FIRM'S RESPONSE)THIS BLA IS ACCEPTABLE.					
OC RECOMMENDATION	18-SEP-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY CDER-OMPQ FROM 3/10/2014 ¿ 3/18/2014 AND INITIALLY CLASSIFIED VAI. THIS WAS A PRE-LICENSE INSPECTION COVERING DULAGLUTIDE (BLA 125469) DRUG SUBSTANCE MANUFACTURING OPERATIONS (b) (4) PROFILE). DIDQ DOES NOT OPPOSE APPROVAL OF THIS SUPPLEMENT FROM A GMP PERSPECTIVE. HOWEVER, THE APPROVAL OF THIS SUPPLEMENT DOES NOT					

Reference ID: 3630085

PRECLUDE THE FDA FROM OTHER ACTIONS RELATED TO THE ONGOING EVALUATION OF THIS SITE.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: VISUAL INSPECTION (on 22-AUG-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
SUBMITTED TO OC	28-APR-2014				WILSONT
OC RECOMMENDATION	24-JUN-2014			ACCEPTABLE	WILSONT

Comment

OAI Submit To OC

Request to Extend Re-eval Date To

Extension Request Comment

Reason

BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY IOG (b) (4) AND CLASSIFIED AS NAI. THIS WAS A ROUTINE GMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG PRODUCT MANUFACTURING, SPECIFICALLY VISUAL INSPECTION OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.

Reference ID: 3630085

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: VISUAL INSPECTION, DRUG PRODUCT NRELEASE AND STABILITY TESTING (on 22-AUG-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	28-APR-2014				WILSONT
OC RECOMMENDATION	24-JUN-2014			ACCEPTABLE	WILSONT

BLA BACKFILL ONLY - THIS SITE WAS INSPECTED (b) (4) AND FOUND TO BE VAI. THIS WAS A ROUTINE GMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG PRODUCT MANUFACTURING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCEPTABLE.

Reference ID: 3630085

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURE, RELEASE AND STABILITY TESTING (on 22-AUG-2014 by T. WILSON () 2404024226)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	28-APR-2014				WILSONT
OC RECOMMENDATION	24-JUN-2014			ACCEPTABLE	WILSONT

BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED AS VAI. THIS WAS A ROUTINE GMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG PRODUCT MANUFACTURING OPERATIONS. THE (b) (4) AND (b) (4) PROFILES WERE UPDATED AND ARE ACCEPTABLE.

Reference ID: 3630085

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: DRUG PRODUCT RELEASE AND STABILITY TESTING (on 22-AUG-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	28-APR-2014				WILSONT
OC RECOMMENDATION	24-JUN-2014			ACCEPTABLE	WILSONT

BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE GMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG PRODUCT TESTING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCEPTABLE.

OC RECOMMENDATION 29-AUG-2014 ACCEPTABLE CAPACCIDANIC

BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE GMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG PRODUCT MANUFACTURING AND TESTING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCEPTABLE.

Reference ID: 3630085

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

Establishment Comment: DEVICE ASSEMBLY, PACKAGING AND LABELING, DRUG PRODUCT RELEASE AND STABILITY TESTING (on 22-AUG-2014 by T. WILSON () 2404024226)
DEVICE ASSEMBLY, PACKAGING AND LABELING, DRUG PRODUCT RELEASE AND STABILITY TESTING (on 22-AUG-2014 by T. WILSON () 2404024226)

Profile: DEVICE KIT ASSEMBLER **OAI Status:** NONE

(b) (4) NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	22-AUG-2014				WILSONT
RECOMMENDATION	29-AUG-2014			ACCEPTABLE	CAPACCIDANIC
CDRH RECOMMENDS APPROVAL OF THIS FACIILTY FOR THIS APPLICATION PER MEMO DATED MAY 8, 2014 FROM VIKY VERNA IN DARRTS.					
SUBMITTED TO OC	28-APR-2014				WILSONT
OC RECOMMENDATION	24-JUN-2014			ACCEPTABLE	WILSONT
BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY IOG (b) (4) AND CLASSIFIED AS NAI. THIS WAS A ROUTINE GMP SURVEILLANCE INSPECTION COVERING (b) (4) DRUG PRODUCT MANUFACTURE AND TESTING, AND ADDITIONALLY COVERED BIOTECH DRUG PRODUCT MANUFACTURING OPERATIONS. THE (b) () PROFILE WAS UPDATED AND IS ACCEPTABLE.					
SUBMITTED TO DO	29-AUG-2014	10-Day Letter			CAPACCIDANIC
(b) PROFILE *PDUFA IS 18-SEP-2014*					
DO RECOMMENDATION	29-AUG-2014			ACCEPTABLE	MROSE
OC RECOMMENDATION	29-AUG-2014			ACCEPTABLE	CAPACCIDANIC
THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED AS NAI. THIS WAS A ROUTINE GMP SURVEILLANCE INSPECTION COVERING (b) (4) DRUG PRODUCT MANUFACTURE AND TESTING, AND ADDITIONALLY COVERED BIOTECH DRUG PRODUCT MANUFACTURING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCEPTABLE.					

Reference ID: 3630085

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

/s/

CHRISTINA A CAPACCI-DANIEL
09/18/2014

OBP CMC Review Data Sheet

1. **BLA#:** STN 125469
   Applicant: Eli Lilly and Company
   Product: Dulaglutide
   Indication: Type II diabetes
   Proprietary Name: Trulicity

2. **APPLICATION INFORMATION:**
   Application Number: 125469/0, 0.11, 0.20, 0.25, and 0.29
   eCTD Sequence Number: 000, 0011, 20, 25, and 29
   CBER Receipt Date: STN 0- September 17, 2013, STN 11-February 28, 2014, STN 20- April 29, 2014, STN 25 May 30, 2014, STN 29 June 11, 2014

3. **REVIEW DATE:** 125469/0, 0.11, and 0.20 - May 30, 2014
   125469/0.25 and 125469/0.29 – August 26, 2014

4. **PRIMARY REVIEW TEAM:**
   Medical Officer: Suchitra Balakrishan
   Pharm/Tox: Tim Hummer
   Product Quality: Joel Welch
   BMAB or Facilities: Bo Chi (Drug Substance) / Colleen Thomas (Drug Product)
   Clinical Pharmacology: Sang Chung
   Statistics: Janelle Charles
   OBP Labeling: Jibril Abdus-Samad
   RPM: Abolade Adeolu

5. **MAJOR GRMP DEADLINES:**
   Filing Meeting: October 31, 2013
   Mid-Cycle Meeting: February 10, 2014
   Wrap-Up Meeting: July 24, 2014
   Primary Review Due: May 30, 2014
   Secondary Review Due: June 6, 2014
   PDUFA Action Date: September 18, 2014

Recommendation:
From a quality perspective, approval of the submission is recommended.

Submission
The primary quality review for dulaglutide was finalized on May 30, 2014. There were two quality submissions after the primary review was finalized:

125469/0.25:
The primary CMC review recommended approval from a quality perspective, and included proposed specifications and agreements based on the outcome of teleconferences held on May 15, 2014, and May 22, 2014. The sponsor's

agreements in the teleconferences and email communications were considered sufficient to recommend approval. The sponsor did subsequently update the BLA with the required, agreed upon information. These updates were the subject of this quality amendment.

125469/0.29: The Agency sent an information request to the sponsor on June 6, 2014 and had a teleconference with the sponsor on June 11, 2014 to discuss their email responses. This amendment contained the sponsor's official responses to the information request.

These 2 amendments are summarized in more detail below.

1. **125469/0.25**

On May 30, 2014 the sponsor submitted an additional quality submission (eCTD #0025) which included the following items:

A. The responses provided by email previously to facilitate the May 15 and May 22 teleconferences were included in section 1.11.1.

1.11.1 Quality Information Amendment
Quality Responses to Questions from May 14, 2014
Quality Responses to Question from May 20, 2014

B. 3.2.S.2.2 Manufacturing Process Description
Updated to remove the phrase [redacted] (b) (4) as agreed to in the response to Q14, May 14, 2014.Updated to reflect the agreed upon [redacted] (b) (4) cycles for the [redacted] (b) (4) agreed to in the May 22, 2014 FDA / Lilly teleconference.

C. 3.2.S.2.4., Control of Critical Steps and Intermediates
Updated to reflect the agreed upon [redacted] (b) (4) cycles for the [redacted] (b) (4) [redacted] agreed to in the 22 May 2014 FDA / Lilly teleconference.

D. 3.2.S.4.1 Specification
The drug substance specification has been updated to reflect agreements from the May 15, 2014 and May 22, 2014 teleconferences.

Table 3.2.S.4.1-1 Specifications for Dulaglutide Drug Substance

Test	Analytical Procedure	Acceptance Criteria
Identification Test		
Identity	(b) (4)	
Identity		
Quantity Test		
Quantity		
Potency Test		
Potency		
Purity Tests		
Dulaglutide (b) (4) Purity		
Related Substances/Impurities: (b) (4		

Table 3.2.S.4.1-1 (continued) Specifications for Dulaglutide Drug Substance

Test	Analytical Procedure	Acceptance Criteria
Purity Tests, continued		
(b) (4)		(b) (4)
Other Tests		
(b) (4)		
Physical Appearance[1]	Visual	
Color	Ph.Eur. 2.2.2	
Clarity	Ph.Eur. 2.2.1	
Bacterial Endotoxins (b) (4)	USP <85>	
Bioburden (b) (4)	USP <61>	
pH	USP <791>	

[1] "Physical Appearance" is equivalent to the ICH term "Description."

Reviewer Comment:
The sponsor has revised the specification acceptance criteria for Potency, Dulaglutide Main Peak Purity, Total Related Substances/Impurities, (b) (4), (b) (4) *as requested. The specification is considered acceptable.*

E. 3.2.S.4.5 Justification of Specifications

The justification of specifications has been updated to include the revised specification acceptance criteria. ***Reviewer Comment****: There is no additional action required.*

F. 3.2.S.7.1. Stability Summary and Conclusion

Updated to add study durations for ongoing stability studies and a commitment to complete these studies. ***Reviewer Comment****: There is no additional action required.*

G. 3.2.P.5.1 Specification

The drug product specification has been updated to reflect agreements from the May 22, 2014 teleconference.

Test	Analytical Procedure	Release Acceptance Criteria	End of Shelf Life Acceptance Criteria
Potency Test			
Potency	Bioassay	(b) (4)	
Purity Tests			
Dulaglutide (b) (4) Purity	(b) (4)		
Related Substances/Impurities: (b) (4			

Test	Analytical Procedure	Release Acceptance Criteria	End of Shelf Life Acceptance Criteria
Other Tests			
(b) (4)			(b) (4)
Physical Appearance[1]	USP <1>		
Bacterial Endotoxins	USP <85>		
Particulate Matter: ≥25 micron	USP <788>		
Particulate Matter: ≥10 micron	USP <788>		
Sterility	USP <71>		
pH	USP <791>		
Osmolality	USP <785>		
Color	Ph.Eur. 2.2.2		
Clarity	Ph.Eur. 2.2.1		

Test	Analytical Procedure	Release Acceptance Criteria	End of Shelf Life Acceptance Criteria
Other Tests, continued			
(b) (4)			

[1] "Physical Appearance" is equivalent to the ICH term "Description."

Reviewer Comment:

The sponsor has revised the specification to include separate sections for release and stability. Changes in acceptance criteria for Potency, Dulaglutide Main Peak Purity, Total Related Substances/Impurities, (b) (4) *as agreed in the May 22, 2014 teleconference. Additionally, they changed the* (b) (4) *release specification,* (b) (4) *and leaving the stability (end of shelf life) specification as* (b) (4)*. The* (b) (4) *have also been specified at release and on stability* (b) (4) *to be more transparent. There is no additional action required.*

H. 3.2.P.5.6, Justification of Specifications
Updated to reflect the specification limits agreed to during the May 22 2014 teleconference. ***Reviewer Comment***: *There is no additional action required.*

I. 3.2.P.8.1, Stability Summary and Conclusion
Updated to add study durations for the ongoing stability studies and a commitment to complete these studies. ***Reviewer Comment***: *There is no additional action required.*

J. 3.8.P.8.2., Post-Approval Stability Protocol and Stability Commitment
This section of the BLA was updated to add the end of shelf life stability study protocol. ***Reviewer Comment***: *There is no additional action required.*

2. 125469/0.29 (response to Agency IR dated June 10, 2014)

A. The sponsor updated the BLA with the [redacted] (b) (4) potency results for the primary stability data for DS. This data had previously been requested by the Agency in an IR dated May 14, 2014. The sponsor provided an IR response with the data on May 30, 2014 in 125469/0.25. However, the Agency had to request on June 10, 2014 that the BLA be updated with the additional stability data.

B. The sponsor was asked to revise the DS and DP specifications to include acceptance criteria of no new peak compared to reference for the [redacted] (b) (4) assay. The sponsor indicated that the method, rather than specifications, was being revised to include control of new peaks.

Reviewer Comment: *In the context of the overall control strategy, this was determined to be acceptable.*

C. The sponsor was asked to provide clarification on an IR response of February 28, 2014 regarding reference standard qualification. Specifically, in the original BLA, secondary reference standard qualification included reporting potency of [redacted] (b) (4) if the results were [redacted] (b) (4) compared to the primary reference standard. This information appeared to be deleted in the proposed updates to reference standard qualification. In addition, there was information to suggest that future secondary reference standards would only need to meet potency results of [redacted] (b) (4). The sponsor was asked to provide clarification [redacted] (b) (4) The sponsor indicated that future secondary reference standards would need to meet [redacted] (b) (4) potency criteria. The sponsor provided an updated 3.2.S.5. It is noted that the sponsor also monitors curve parameters of the potency assay [redacted] (b) (4).

Reviewer Comment: *The information provided is acceptable. No further action is required at this time.*

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/s/

JOEL T WELCH
08/26/2014

LAURIE J GRAHAM
08/27/2014

First Approval for Indication

Recommendation: Approval

BLA 125469
Review 1
May 30, 2014

Drug Name/Dosage Form	**Trulicity for injection**
Strength/Potency	**1.5 mg and 0.75 mg**
Route of Administration	**subcutaneous**
Rx/OTC Dispensed	**Rx**
Indication	**Improve glycemic control in Type 2 diabetes as an adjunct to diet and exercise**
Applicant/Sponsor	**Eli Lilly and Company**
US agent, if applicable	**Not applicable**

Communications with Sponsor	Date
Pre-BLA Meeting	July 9, 2013
Filing Date	November 17, 2013
Information Request #1	February 9, 2014
Midcycle Telecon	March 3, 2014
Information Request #2	April 15, 2014
Information Request #3	May 12 2014
CMC telecon with sponsor	May 15, 2014
CMC telecon with sponsor	May 22, 2014
Late Cycle Meeting	June 2, 2014

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original Submission	September 18, 2013
Amendment 11	February 28, 2014
Amendment 20	April 29, 2014
Amendment 21	May 5, 2014
Amendment 25	May 30, 2014

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joel Welch	OBP/DMA
Drug Product	Joel Welch	OBP/DMA
Immunogenicity	Joel Welch	OBP/DMA
Labeling	Joel Welch	OBP/DMA and OPE/DMEPA
Facility and Microbiology	Bo Chi for DS Colleen Thomas for DP	OC/OMPQ/DGMPA/BMAB

Reference ID: 3603246

Secondary Reviewer	Laurie Graham	OBP/DMA
Tertiary Reviewer	Sarah Kennett	OBP/DMA

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Abolade Adeolu	ODEII/DMEP
Cross-disciplinary Team Lead	William Chong	ODEII/DMEP
Medical Officer	Suchitra Balakrishan	ODEII/DMEP
Pharm/Tox	Tim Hummer	ODEII/DMEP
Clinical Pharmacology	Sang Chung	OCP/DCPII
Statistics	Janelle Charles	OB/DBVII

Reference ID: 3603246

Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION: 351(a)**

2. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
[redacted]	[redacted]	[redacted] (b) (4)	Yes	Adequate information in BLA, not reviewed
[redacted]	[redacted]	[redacted]	Yes	Adequate information in BLA, not reviewed
[redacted]	[redacted]	[redacted]	Yes	Review dated September 19, 2012 is adequate
[redacted]	[redacted]	[redacted]	Yes	Review dated March 22, 2013 is adequate.
[redacted]	[redacted]	[redacted]	Yes	[redacted] (b) (4) is reviewed by BMAB

B. Other Documents: None

3. **CONSULTS:**
The only consult requested by OBP was with the non-clinical review team to evaluate the raw material leachable/extractable risk assessments. This was an email request on May 6, 2014. The requested material was evaluated and found to be acceptable.

Reference ID: 3603246

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation –

The Office of Biotechnology Products, OPS, CDER, recommends approval of STN 125469 for Trulicity manufactured by Eli Lilly and Company pending acceptable compliance checks. The data submitted in this application are adequate to support the conclusion that the manufacture of Trulicity is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert.

b. Approval action letter language

- Manufacturing location:
  - Drug substance – Eli Lilly S.A, Kinsale, Ireland (FEI number 3002806888)
  - Drug product –Eli Lilly and Company, Indianapolis, IN (FEI number 1819470) and (b) (4) [redacted] manufacture the semi-finished syringes. The semi-finished syringes are assembled into pre-filled syringes at (b) (4) [redacted] The semi-finished syringes are assembled into pre-filled pens at Eli Lilly and Company, Indianapolis, IN (FEI number 1819470).

- Fill size and dosage form – 1.5 mg/0.5 mL and 0.75 mg/0.5 mL single use pre-filled syringes and pre-filled pens.

  Reviewer Comment: *In the original BLA, the sponsor was seeking approval of only the 1.5 mg/0.5 mL dose. However, during the course of the BLA review, the clinical team suggested to the sponsor that both the 1.5 mg/0.5 mL and 0.75 mg/0.5 mL dosage strengths should be considered by the Agency. This issue had not been resolved at the time of this review. However, the sponsor provided CMC information to support both dosage strengths. From a CMC perspective, therefore, both dosage strengths have been reviewed for approvability.*

- Dating period:
  - Drug product: 24 months at 2-8 °C and 2 weeks at 30°C

Reference ID: 3603246

- Drug substance : (b) (4) months at (b) (4) C

- Exempt from lot release
  - Yes
  - Rationale if exempted – exempt per 601.2a (specified product)

c. Benefit/Risk Considerations
Trulicity is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

There were a number of issues identified with the dulaglutide control strategy, the most significant of which include:

- The sponsor did not appropriately classify all critical quality attributes for the product. In particular, the PK assessment provided was not acceptable, given that the product was specifically designed to include an Fc region (b) (4), yet the PK assessment excluded consideration of the Fc region of the product. However, the BLA did contain a list of the different Fc modifications, a summary of the current understanding of the manufacturing process and stability data with regard to these modifications, and an assessment of the current analytics to detect these modifications. This information was considered adequate for approval. However, because Fc modifications were considered low risk by the sponsor, results from analytics that could specifically detect, quantify, and assess the PK impact of Fc modifications were not included in the BLA. To address this issue, there will be a PMC to re-assess the dulaglutide control strategy with regard to the Fc region and its impact on PK. This will include an assessment of neonatal FcR binding.

- Process characterization studies used to determine the regulatory commitments in the BLA, including the process parameters and in-process controls were inadequate. These studies relied upon the use of small scale models that were not appropriately qualified. For example, the qualifications did not include all CQAs relevant to the unit operations, and the criteria used to evaluate the models were not sufficient. In addition, the process characterization studies themselves were not adequate. For example, all relevant CQAs were not included, and the process parameter ranges studied were, in some cases, too narrow. To address this issue, at the request of the Agency, the sponsor updated sections 3.2.S.2.2, 3.2.S.2.4, 3.2.P.3.3, and 3.2.S.P.3.4 of the BLA with additional regulatory commitments.

- The dulaglutide control strategy did not include an adequate assessment of raw materials and leachables/extractables. During the course of the

review, the sponsor updated the BLA to include a more detailed description of the raw material and leachable/extractable risk assessments that were performed for both drug substance and drug product. The results of these risk assessments were evaluated by the non-clinical review team and found to be adequate. However, it was noted on inspection of the drug substance manufacturing facility in Kinsale, Ireland, (b) (4) (b) (4) (b) (4) The DS manufacturing facility did provide, on inspection, information from extractable studies conducted (b) (4) . These studies were conducted by the (b) (4) vendor. This "worst case" study cited by the sponsor appears to have been performed (b) (4). One extractable has (b) (4) . A toxicology and total exposure assessment was completed during the inspection. However, because no (b) (4) extractable/leachable studies have been performed, (b) (4) there is residual risk that the dulaglutide (b) (4) conditions, including the drug product and/or drug substance (b) (4) might result in increased leachable levels compared to the studies conducted by the (b) (4) vendor. To address this risk, there will be a PMC to conduct product specific (b) (4) leachable/extractable studies and, if needed, to optimize the (b) (4) steps in DS and DP manufacturing.

The risks associated with the dulaglutide control strategy have been adequately addressed. Therefore, we recommend approval of this product with the four post-marketing commitments described below.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

1. To re-evaluate dulaglutide drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process.

2. To re-evaluate dulaglutide drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process.

3. To conduct drug substance and drug product specific leachable and extractable studies on the (b) (4) used during manufacturing. The drug substance and drug product manufacturing processes will be optimized, as needed, based on the results.

4. To reassess the dulaglutide drug substance and drug product control strategy, and the reference standard qualification/requalification programs, with regards to Fc region modifications and their impact on PK, including neonatal Fc binding.

II. Summary of Quality Assessments

The dulaglutide control strategy for both drug substance and drug product was based upon three components that are briefly summarized below.

- A risk ranking of quality attributes that involved scoring attributes with regard to impact on activity, PK/PD, immunogenicity, and safety. This scoring system also considered the strengths and weaknesses of the knowledge source.

  Reviewer's comment: *There are concerns that the sponsor did not identify all high risk quality attributes. For example, as previously noted, the sponsor did not consider the Fc modifications with regard to their potential impact on PK. In addition, in some cases, the sponsor's risk assessment used the levels of attributes observed in drug substance or drug product, which is not acceptable. Levels are not relevant to determining criticality of an attribute, but rather to process understanding and the final control strategy. In addition, it appears that, for the assessments of safety and immunogenicity, the sponsor relied upon clinical data in which certain variants were present at low levels. The clinical studies were not designed to assess clinical impact of low levels variants.*

- An evaluation of how the manufacturing process impacts the identified high risk quality attributes. These studies were used to identify critical process parameters. These studies relied upon the use of small scale studies.

  Reviewer's comment: *As previously indicated, there were concerns that the qualifications of the small scale models and the process characterization studies were not adequate (see benefit/risk considerations).*

- An evaluation of the analytics or detectability. This is based on method capability and how the assay will be used in the final control strategy (e.g., release, stability, in-process, non-routine, etc.). Methods are ranked high or low. Method capability is determined based on specificity and precision.

  Reviewer's comment: *In the analytical scoring system, a method with low capability can still be used for lot release and stability testing. It is the overall score (CQA severity, process capability, and analytics) that determines the overall risk score for an attribute with regard to the adequacy of the control strategy. Because the sponsor appears to have inappropriately categorized some attributes as low risk, all high risk attributes might not have assays with acceptable specificity and precision.*

Reference ID: 3603246

A. Active Pharmaceutical Ingrediant[1] Intrinsic CQA Identification, Risk and Lifecycle Knowledge Management

The table below provides a summary of product related critical quality attributes and are relevant to both drug substance and drug product. The table includes the identification of the various attributes along with their risk management.

Identification of other CQAs associated with just drug substance (e.g., process related impurities, adventitious agents, pH, appearance, etc.) or drug product are described in separate risk tables in section B, Drug Substance Quality Summary and section C, Drug Product Quality Summary.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA	Risk	Introduction	Control Strategy	Other
			(b) (4)	

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Reference ID: 3603246

	(b) (4)			

B. Drug Substance [Dulaglutide] Quality Summary

The table below provides a summary of the identification and risk management for process related impurities and general drug substance attributes. It is noted that during the BLA review, the sponsor documented raw material and leachable/extractable risk assessments for dulaglutide drug substance manufacturing. These assessments were found to be adequate for approval.

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA	Source	Risk	Introduction	Control Strategy	
				(b) (4)	

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/s/

LAURIE J GRAHAM
08/01/2014

SARAH B KENNETT
08/01/2014

KATHLEEN A CLOUSE STREBEL
08/01/2014

BLA STN 125469

Dulaglutide

Eli Lilly and Company

Joel Welch, Ph.D.
Laurie Graham, M.S.
Division of Monoclonal Antibodies

OBP CMC Review Data Sheet

1. **BLA#:** STN 125469

2. **REVIEW DATE: May 30, 2014**

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Suchitra Balakrishan
Pharm/Tox: Tim Hummer
Product Quality Team: Joel Welch
BMAB or Facilities: Bo Chi (Drug Substance) / Colleen Thomas (Drug Product)
Clinical Pharmacology: Sang Chung
Statistics: Janelle Charles
OBP Labeling: Joel Welch
RPM: Abolade Adeolu

4. **MAJOR GRMP DEADLINES**

Filing Meeting: October 31, 2014
Mid-Cycle Meeting: February 10, 2014
Wrap-Up Meeting: July 24, 2014
Primary Review Due: May 30, 2014
Secondary Review Due: June 6, 2014
PDUFA Action Date: September 18, 2014

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Pre-BLA Meeting	July 9, 2013
Filing Date	November 17, 2013
Information Request #1	February 9, 2014
Midcycle Telecon	March 3, 2014
Information Request #2	April 15, 2014
Information Request #3	May 12 2014
CMC telecon with sponsor	May 15, 2014
CMC telecon with sponsor	May 22, 2014
Late Cycle Meeting	June 2, 2014

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN 125469/0	September 18, 2013	Yes
STN 125469/10	February 28, 2014	Yes
STN 125469/20	April 29, 2014	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Trulicity™
   b. Trade Name: dulaglutide
   c. Non-Proprietary/USAN: dulaglutide
   d. CAS name: 923950-08-7
   e. Common name: TBD
   f. INN Name: TBD
   g. Compendial Name: TBD
   h. OBP systematic name: OBP systematic name: FUS:MABFRAG HUMAN (IGG4 FC); RPROT P01275 (GLUC_HUMAN |98-126) [LY2189265]
   i. Other Names: GLP-1 analog IV-Fc, GLP-Fc

8. **PHARMACOLOGICAL CATEGORY:** GLP-1 receptor agonist, incretin fusion protein

9. **DOSAGE FORM:** Pre-Filled Syringe and pen

10. **STRENGTH/POTENCY:**
   (i) 1.5 mg/0.5 mL and 0.75 mg/0.5 mL
   (ii) Type of potency assay (s): Cell-based bioassay measuring activation of GLP-1 receptor

Reviewer Comment:
In the original BLA, the sponsor was seeking approval of only the 1.5 mg/0.5 mL dose. However, during the course of the BLA review, the clinical team suggested to the sponsor that both the 1.5 mg/0.5 mL and 0.75 mg/0.5 mL dosage strengths should be considered by the Agency. This issue had not been resolved at the time of this review. However, the sponsor provided CMC information to support both dosage strengths. From a CMC perspective, therefore, both dosage strengths have been reviewed for approvability.

11. **ROUTE OF ADMINISTRATION:** Subcutaneous injection

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
		(b) (4)	Yes	Adequate information in BLA, not reviewed
			Yes	Adequate information in BLA, not reviewed
			Yes	Review is adequate

(b) (4)		September 19, 2012
	Yes	Review March 22, 2013 is adequate.
	Yes	(b) (4) is reviewed by BMAB

13. INSPECTIONAL ACTIVITIES

During the period of March 10, 2014 to March 18, 2014 an inspection was performed of the Eli Lilly S.A. – Irish Branch located in Dunderrow, Kinsale, in County Cork, in Ireland. This is the commercial drug substance manufacturing facility. Four CDER officials attended the inspection: Dr. Lakshmi Rani Narasimhan and Dr. Bo Chi from the Biotechnology Manufacturing Assessment Branch in the Office of Compliance, and Dr. Joel Welch and Ms. Laurie Graham from the Division of Monoclonal Antibodies in the Office of Biotechnology Products. Seven observations were noted in the 483. The observations are stated below as well as a summary of the sponsor's response. From an OBP perspective, none of these issues preclude approval.

(b) (4)

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(b) (4)

[redacted]

14. CONSULTS REQUESTED BY OBP

There was only one consult requested, to the toxicology reviewer by email on May 6, 2014 to review risk assessments for raw materials; consumables; and extractables and leachables.

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment / Risk Management

	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

The sponsor includes a control strategy informed by a formal risk assessment to identify critical quality attributes followed by process characterization studies. This approach is used for both drug substance and drug product.

Specifically, the overall control strategy reflects the assignment of three risk values. The first, severity, reflects an attributes ability to affect the quality of the product. The second, occurrence assesses the process capability and relies on process knowledge gathered throughout development. The final component is detectability and describes the capability of analytical methods to detect and quantify the attribute. The product of the multiplication of these three scores becomes a risk priority number. The risk priority number determines the risk associated with the control strategy for each CQA.

16. PRECEDENTS

There are no precedents set by the review of this application.

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Laurie Graham, M.S. Team Leader, Division of Monoclonal Antibodies	See appended electronic signature
Joel Welch, Ph.D. Primary Reviewer (s) Division of Monoclonal Antibodies	See appended electronic signature

B. CC Block

Recipient	Date
Abolade Adeolu	Provided Electronically

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/s/

JOEL T WELCH
05/30/2014

LAURIE J GRAHAM
05/30/2014

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number:	Applicant:	Stamp Date:
125469	Eli Lilly and Company	September 17, 2013

Established/Proper Name:	BLA/NDA Type:
Dulaglutide	BLA

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	***Y*** N	
Form 356h completed	***Y*** N	
❑ including list of all establishment sites and their registration numbers	***Y*** N	
Comprehensive Table of Contents	***Y*** N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	***Y*** N	
Labeling:	***Y*** N	A separate diluent not proposed.
❑ PI –non-annotated	***Y*** N	
❑ PI –annotated	***Y*** N	
❑ PI (electronic)	***Y*** N	
❑ Medication Guide	***Y*** N	
❑ Patient Insert	***Y*** N	
❑ package and container	***Y*** N	
❑ diluent	Y ***N***	
❑ other components	***Y*** N	
❑ established name (e.g. USAN)	***Y*** N	
❑ proprietary name (for review)	***Y*** N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	***Y*** N	
❑ legible	***Y*** N	
❑ English (or translated into English)	***Y*** N	
❑ compatible file formats	***Y*** N	
❑ navigable hyper-links	***Y*** N	
❑ interpretable data tabulations (line listings) & graphical displays	***Y*** N	
❑ summary reports reference the location of individual data and records	***Y*** N	
❑ all electronic submission components usable (e.g. conforms to published guidance)	***Y*** N	
Companion application received if a shared or divided manufacturing	Y ***N***	No shared or divided manufacturing arrangement is included. No companion

Reference ID: 3405057

Examples of Filing Issues	Yes?	If not, justification, action & status
arrangement		application required.

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	***Y*** N	
Introduction to the summary documents (1 page) [2.2]	***Y*** N	
Quality overall summary [2.3]	***Y*** N	No comparability protocols are proposed.
❑ Drug Substance	***Y*** N	
❑ Drug Product	***Y*** N	
❑ Facilities and Equipment	***Y*** N	
❑ Adventitious Agents Safety Evaluation	***Y*** N	
❑ Novel Excipients	***Y*** N	
❑ Executed Batch Records	***Y*** N	
❑ Method Validation Package	***Y*** N	
❑ Comparability Protocols	Y ***N***	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	***Y*** N	
Drug Substance [3.2.S]		
❑ general info	***Y*** N	
○ nomenclature		
○ structure (e.g. sequence, glycosylation sites)		
○ properties		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	***Y*** N	
❑ description of manufacturing process and process control	***Y*** N	
○ batch numbering and pooling scheme		
○ cell culture and harvest		
○ purification		
○ filling, storage and shipping		
❑ control of materials		
○ raw materials and reagents	***Y*** N	
○ biological source and starting materials		
○ cell substrate: source, history, and generation		
○ cell banking system, characterization, and testing		
❑ control of critical steps and intermediates	***Y*** N	
○ justification of specifications		

Reference ID: 3405057

CTD Module 3 Contents	Present?	If not, justification, action & status
○ stability		
❑ process validation (prospective plan, results, analysis, and conclusions)	***Y*** N	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	***Y*** N	
❑ characterization of drug substance	***Y*** N	
❑ control of drug substance	***Y*** N	
○ specifications		
○ justification of specs.		
○ analytical procedures		
○ analytical method validation		
○ batch analyses		
❑ reference standards	***Y*** N	
❑ container closure system	***Y*** N	
❑ stability		
❑ summary	***Y*** N	
❑ post-approval protocol and commitment	***Y*** N	
❑ pre-approval	***Y*** N	
○ protocol		
○ results		
○ method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	***Y*** N	
❑ pharmaceutical development	***Y*** N	
○ preservative effectiveness		
○ container-closure integrity		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	***Y*** N	
❑ batch formula	***Y*** N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	***Y*** N	
❑ controls of critical steps and intermediates	***Y*** N	
❑ process validation including aseptic processing & sterility assurance:	***Y*** N	
○ Filter validation		
○ Component, container, closure depyrogenation and sterilization validation		
○ Validation of aseptic		

Reference ID: 3405057

CTD Module 3 Contents	Present?	If not, justification, action & status
processing (media simulations) ○ Environmental Monitoring Program ○ Lyophilizer validation ○ Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	***Y*** N	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	***Y*** N	
❑ reference standards or materials	***Y*** N	
❑ container closure system [3.2.P.7] ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ○ administration device(s)	***Y*** N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	***Y*** N	
Diluent (vials or filled syringes) [3.2P′]		A separate diluent is not proposed.
❑ description and composition of diluent	Y ***N***	
❑ pharmaceutical development ○ preservative effectiveness ○ container-closure integrity	Y ***N***	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y ***N***	
❑ batch formula	Y ***N***	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y ***N***	
❑ controls of critical steps and intermediates	Y ***N***	
❑ process validation including aseptic	Y ***N***	

Reference ID: 3405057

CTD Module 3 Contents	Present?	If not, justification, action & status
processing & sterility assurance: ○ Filter validation ○ Component, container, closure depyrogenation and sterilization validation ○ Validation of aseptic processing (media simulations) ○ Environmental Monitoring Program ○ Lyophilizer sterilization validation ○ Other needed validation data (hold times) ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) ❑ reference standards ❑ container closure system ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results	Y ***N*** Y ***N*** Y ***N*** Y ***N*** Y ***N*** Y ***N*** Y ***N*** Y ***N*** Y ***N*** Y ***N***	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	 Y ***N*** Y ***N***	No other components are included.
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility	 ***Y*** N	

Reference ID: 3405057

CTD Module 3 Contents	Present?	If not, justification, action & status
○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production	***Y*** N	
❑ novel excipients	Y ***N***	No novel excipients are included.
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 ***Y*** N ***Y*** N Y ***N***	No comparability protocols are proposed.
Literature references and copies [3.3]	***Y*** N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	***Y*** N	
Includes data demonstrating consistency of manufacture	***Y*** N	
Includes complete description of product lots and manufacturing process utilized for clinical studies	***Y*** N	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	***Y*** N	
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	***Y*** N	
Certification that all facilities are ready for inspection	***Y*** N	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test	***Y*** N	

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Examples of Filing Issues	Yes?	If not, justification, action & status
methods used and time intervals for product assessment.		
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	***Y*** N ***Y*** N ***Y*** N ***Y*** N	
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	***Y*** N	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	***Y*** N	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	***Y*** N	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? ***Yes*** No

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Product Quality Reviewer(s) Date

Branch Chief/Team Leader/Supervisor Date

Division Director Date

Reference ID: 3405057

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

/s/

JOEL T WELCH
11/12/2013

LAURIE J GRAHAM
11/13/2013

KATHLEEN A CLOUSE STREBEL
11/13/2013