

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205692Orig1s000

CHEMISTRY REVIEW(S)

INDIA/BA - NDA-20562

NDA-205692-ORIG-1-RESUB-39

Project: [Project Details](#) | [Edit Project](#) | [Project Actions](#)

Task: **Complete** | Calendar: **On Target** | Planned Complete: **Dec 16, 2015** | [Refresh](#)

[Project Summary](#) | [Project Details](#) | [Application History](#) | **Inspection View** | [Tasks](#) | [Updates](#) | [More](#)

Inspection View

[Export](#) | [Details](#) | [Summary](#)

| Task Number | Task Name | Comments | Assignments | Planned Comp | Act Comp | Task Status | Actions | Additional Information |
|---|--|--|---|--------------|----------|-------------|----------------------------|---|
| Parent: Manufacturing Facility Inspections (2) | | | | | | | | |
| 7 | Application specific inspection criteria | If you are finished with this task, change the Task Status to Complete | Anita Chinnings | 11/1/15 | 11/27/15 | Complete | Go to Form | |
| 8 | Over all Manufacturing Inspection Recommendation | | Steven Herby Dr. Cliff Schaefer DAN RENNOLD | 12/15/15 | 12/09/15 | Complete | Go to Form | Recommendation Approved |

MEMO

From: Muthukumar Ramaswamy, Ph.D.,
Xavier Ysern, Ph.D.,
Office of New Drug Quality Assessment (ONDQA), CDER

To: File

Date: August 12, 2014

Subject: Final Quality Recommendation for NDA 205692 - Basaglar™ KwikPen™ 100 units/mL, 3 mL (insulin glargine [rDNA origin] injection)

This memo documents:

The Office of Compliance (OC) at CDRH has reassessed the need for inspection of facilities associated with pen injector and based on desk review the OC at CDRH has concluded that no facilities need to be inspected. For additional information, please refer to memo in DARRTS dated August 12, 2014.

The Office of Compliance (OC) at CDER has determined that the relevant facilities employed for the manufacture and testing of the drug substance, drug product are acceptable. A copy of the Establishment Evaluation Request Summary Report from OC is enclosed. Therefore, from both CMC perspective and Office of Compliance point of view, this NDA (205692) is recommended for approval.

CDRH's technical review of the pen injector found no quality-specific deficiency. For additional information, please refer to memo in DARRTS dated June 12, 2014.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

| | | | |
|-----------------------|----------------|---|---|
| Application: | NDA 205692/000 | Sponsor: | ELI LILLY AND CO |
| Org. Code: | 510 | | LILLY CORPORATE CENTER |
| Priority: | 5 | | INDIANAPOLIS, IN 46285 |
| Stamp Date: | 18-OCT-2013 | Brand Name: | ABASRIA KWIKPEN (INSULIN GLARGINE [RDNA |
| PDUFA Date: | 18-AUG-2014 | Estab. Name: | |
| Action Goal: | | Generic Name: | |
| District Goal: | 19-JUN-2014 | Product Number; Dosage Form; Ingredient; Strengths | 001; INJECTABLE; INSULIN GLARGINE; 300UNITS |

| | | | |
|----------------------|------------------|------------------------------|------------|
| FDA Contacts: | M. RAMASWAMY | Prod Qual Reviewer | 3017961676 |
| | P. KUMAR | Product Quality PM (HFD-800) | 2404023722 |
| | C. CAPPIEL-LYNCH | Regulatory Project Mgr | 3017968436 |
| | S. TRAN | Team Leader | 3017961764 |

| | | | | | |
|--------------------------------|------------|----------------|-------------|-----------|------------|
| Overall Recommendation: | ACCEPTABLE | on 12-AUG-2014 | by S. HERTZ | (HFD-320) | 3017963203 |
| | PENDING | on 01-NOV-2013 | by EES_PROD | | |
| | PENDING | on 28-OCT-2013 | by EES_PROD | | |
| | PENDING | on 28-OCT-2013 | by EES_PROD | | |

| | | | |
|-----------------------|-------------|-------------|---------|
| Establishment: | CFN: | FEL: | (b) (4) |
| | | | (b) (4) |

| | | | |
|--------------------------|-------------------------------|--------------------|------|
| DMF No: | | AADA: | |
| Responsibilities: | DRUG SUBSTANCE RELEASE TESTER | | |
| Profile: | CONTROL TESTING LABORATORY | OAI Status: | NONE |
| Last Milestone: | OC RECOMMENDATION | | |
| Milestone Date: | 01-DEC-2013 | | |
| Decision: | ACCEPTABLE | | |
| Reason: | DISTRICT RECOMMENDATION | | |

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 1819470 FEI: 1819470
ELI LILLY AND COMPANY

DMF No: INDIANAPOLIS, , UNITED STATES 462850001 **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-NOV-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 28-OCT-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 12-AUG-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

Last Milestone: DRUGS
OC RECOMMENDATION

Milestone Date: 05-NOV-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: 3004525072
LILLY DEL CARIBE INC

CAROLINA, , UNITED STATES 00986

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 9610945 FEI: 3002807475
LILLY FRANCE SAS
RUE DE COLONEL LILLY B.P. 10
FEGERSEIM, , FRANCE

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 28-OCT-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-NOV-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

MUTHUKUMAR RAMASWAMY
08/12/2014

XAVIER J YSERN
08/12/2014

SUONG T TRAN
08/12/2014

NDA 205-692

**Basaglar™ KwikPen™ 100 units/mL, 3 mL
(insulin glargine [rDNA origin] injection)**

Eli Lilly and Company

Muthukumar Ramaswamy PhD

Xavier Ysern, PhD

ONDQA/ DNDQA III/ Branch VII

(Clinical Review Division: DMEP)

Table of Contents

| | |
|---|-----|
| Table of Contents..... | 2 |
| Chemistry Review Data Sheet..... | 3 |
| The Executive Summary..... | 5 |
| I. Recommendations..... | 5 |
| A. Recommendation and Conclusion on Approvability..... | 5 |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 5 |
| II. Summary of Chemistry Assessments..... | 5 |
| A. Description of the Drug Product(s) and Drug Substance(s)..... | 5 |
| B. Description of How the Drug Product is Intended to be Used..... | 8 |
| C. Basis for Approvability or Not-Approval Recommendation..... | 9 |
| III. Administrative..... | |
| A. Reviewer’s Signature..... | 9 |
| B. Endorsement Block..... | 9 |
| C. CC Block..... | 9 |
| Chemistry Assessment..... | 10 |
| I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data..... | 10 |
| S Drug Substance [LY2963016 Insulin Glargine]..... | 10 |
| P Drug Product [Name, Dosage form]..... | 62 |
| A Appendices..... | 135 |
| R Regional Information..... | 135 |
| II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1..... | 147 |
| A. Labeling & Package Insert..... | 147 |
| B. Environmental Assessment Or Claim Of Categorical Exclusion..... | 148 |
| C. Establishment Inspection..... | 149 |
| III. List of Deficiencies To Be Communicated <i>None</i> | 149 |
| Attached | |

Chemistry Review Data Sheet

1. **NDA:** 205-692
2. **Review #:** 1
3. **Review Date:** 17-Jul-2014
4. **Reviewers:** Muthukumar Ramaswany, PhD, (Drug Product) and Xavier Ysern, PhD, (Drug Substance)

5. **Previous Documents:**

| <u>Previous Documents</u> | <u>Document Date</u> |
|---------------------------|----------------------|
| -- | -- |

6. **Submission(s) Being Reviewed:**

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|-------------------------------|----------------------|
| Original | 17-Oct-2013 |
| Amendment (SDN 020, eCTD 019) | 22-Apr-2014 |
| Amendment (SDN 024, eCTD 023) | 15-May-2014 |
| Amendment (SDN 029, eCTD 029) | 13-Jun-2014 |
| Amendment (SDN 030, eCTD 028) | 23-Jun-2014 |
| Amendment (SND 032, eCTD 031) | 10-Jul-2014 |
| Amendment (SND 034, eCTD 033) | 14-Jul-2014 |

7. **Name and Address of Applicant:**

Name: Eli Lilly and Company
Address: Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.
Representative: Joerg Pfefier, PhD, Advisor, US Regulatory Affairs
Telephone: (317) 276-2146

8. **Drug Product Name/Code/Type:**

- a) Proprietary Name: Basaglar™ (Acceptable 17-Jan-2014)
- b) Non-Proprietary Name (USAN): Insulin glargine
- c) Code Name: LY2963016
- d) Chem. Type/Submission Priority: Chem Type: 5 (new manufacturer) / Submission Priority: S

9. **Legal Basis For Submission:** 505(b)(2) The proposed PI relies on FDA's finding of safety and effectiveness for LANTUS® and LANTUS® SoloSTAR® (NDA 21081).

10. **Pharmacological Category:** Hormone. Long-acting human insulin analog indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

11. **Dosage Form:** Injectable [Solution for injection]

12. **Strength/Potency:** 100 units/mL

13. **Route of Administration:** Subcutaneous (sc)

14. **Rx/OTC Dispensed:** Rx

The Chemistry Review for NDA 205-692

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From a CMC perspective, the Applicant has resolved all CMC issues satisfactorily identified during the Review cycle. There is no pending issue specific to the CMC review.

At this time, the Quality final recommendation is pending the recommendations from CDRH for the acceptability of the (b) (4) injector. In addition, OMPQ has not issued an overall recommendation for the commercial manufacturing and testing facilities listed in the NDA.

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

None.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)****· Drug Substance LY296306 (Insulin glargine)**

The drug substance, LY2963016, is Lilly's insulin glargine obtained by recombinant DNA technology using the production strain *E. coli* K12 (b) (4). Insulin glargine is an insulin analog that differs from human insulin (b) (4)

Therefore, insulin glargine precipitates in the subcutaneous milieu after injection, stabilizing insulin hexamers, delaying their dissociation and allowing for slow, consistent absorption into the systemic circulation.

The drug substance LY2963016 is expressed as the (b) (4)

LY2963016 drug substance' specifications include identity (HPLC, peptide mapping, and biological), physical appearance (visual), assay by HPLC (b) (4)

(b) (4)

The provided drug substance stability data supports the requested 30 month expiry period when stored at not more than (b) (4) °C in amber glass containers (long-term storage condition).

Drug Product LY296306 (Basaglar™ KwikPen™ 100 U/mL 3 mL)

The drug product, Basaglar (Insulin Glargine) injection, is a long acting insulin, intended for once daily use by subcutaneous administration. Basaglar injection contains 100 units of insulin Glargine per mL filled in a 3 mL glass cartridge pre-assembled in Basaglar™ KwikPen™. (b) (4)

. Basaglar injection is a sterile, clear, and colorless aqueous solution containing 600 nmol of insulin glargine, 17.0 mg glycerol (b) (4) 2.70 mg metacresol (b) (4), and 30.0 µg zinc (b) (4) and water for injection. Hydrochloric acid or sodium hydroxide is added to adjust pH to approximately 4.0. The potency of the proposed formulation is 100 Units/mL and is based on mass (3.6378 mg of insulin glargine per mL of product). The proposed final formulation is the same as the one used in development and Phase 3 clinical studies.

The proposed formulation is optimized to confer chemical and physical stability of the formulation. The Applicant is proposing to use monograph grade excipients in the final formulation, which is acceptable. The finished product will be marketed as 5 x 3 mL prefilled pens in cartons. The proposed product is light sensitive and therefore secondary packaging is critical to assure the stability of the product.

The drug product, insulin glargine 100 U/mL, is manufactured b (b) (4)

The drug product is (b) (4)

During development, the Applicant has defined Quality Target Product Profile (QTPP), used design of experiment (DOE) to optimum range for formulation components, used risk assessment techniques to define critical quality attributes (CQAs), and critical process parameters. The proposed CQAs for the drug products include identity, insulin content of each active ingredient, glide force, and dosing accuracy (for measuring device performance), purity (total impurities, (b) (4) closure integrity (b) (4) endotoxin levels, appearance, particulate load, and pH.

The Applicant's developmental work, process evaluation studies were targeted to ensuring the proposed process parameters are adequate to ensure complete dissolution of excipients and active ingredients, attainment of correct pH, and assurance of sterility.

The NDA contains batch formula and a description of the proposed commercial process. Together with the information provided in the master batch record, the available information in the NDA is adequate to support the proposed commercial process. The NDA contains process control information for manufacturing the proposed product. The proposed critical process parameters (in-process tests) include assay, pH of final bulk, verification of (b) (4)

The drug product will be manufactured at (b) (4) Lilly France. The applicant has performed adequate studies (analytical comparability studies) to support the comparability of these batches.

The NDA contains batch analysis data from development through commercial scale to support the manufacturability of the proposed product. The NDA contains adequate information on the release specification used for controlling for quality of the drug product. The Applicant has proposed general tests typically expected for a parenteral product, and product-specific tests. The proposed general tests include pH, endotoxin limit, and sterility, and particulate matter. The product-specific tests include identity, insulin content, (b) (4) product related impurities (b) (4) individual largest specified, and unspecified impurity and total product related impurities (b) (4). In addition, the applicant is proposing to monitor the dose accuracy, and glide force of the pen-injector. The proposed limits for monitoring the individual insulin glargine related substances and impurities are acceptable.

CMC review team performed risk assessment on the factors that can impact product quality and concluded that the potential risk to overall product quality is low (See table below for an executive summary of the risk assessment)

| Executive Summary Risk Assessment | | | | | |
|---|---|--------------|--|--|---|
| From Initial Quality Assessment | | | Review Assessment | | |
| Product attribute/ CQA | Factors that can impact the CQA | Risk Ranking | Risk Mitigation approach | Risk evaluation Not acceptable or acceptable | Life cycle considerations/ comments |
| Assay (protein) | Formulation Container closure Raw materials Process parameters Scale/ equipment Site | L | Drug product final weight is linked to assay and is controlled with an in-process specification. Applicant's batch release and validation data indicate that assay values controlled tightly. (b) (4) (b) (4) parameters are adequate. Hence dissolution is not an issue. | Acceptable (Low risk) | Potency is based on mass based assay. 3.6378mg = 100U |
| Assay (preservative) | | M | (b) (4) parameters are adequate. Hence dissolution is not an issue. Validation and stability data indicates that (b) (4) content is tightly controlled during (b) (4) | Acceptable (Low risk) | |
| Product-related size variants – Soluble aggregates, (b) (4) | | H | Drug product is sensitive to heat (high rate of (b) (4) at 30 C compared to 5 C storage). Lot release data show manufacturing consistency lots contained a max. of (b) (4) % (b) (4). The (b) (4) content is controlled through proper storage condition and specification (Limit of (b) (4) %). | Acceptable (Low risk) | (b) (4) has the potential to be immunogenic |
| Other product-related variants | | H | Insulin glargine is sensitive to heat. Drug product deamidates at a rate of (b) (4) % per mo. when stored at 30 C. The impurity levels are controlled through proper storage condition and through appropriate impurity limit of (b) (4) %. As a worst-case, potency loss by (b) (4) % is within acceptable assay limits | Acceptable (Low risk) | |
| Sterility | | H | The components used in manufacturing are either (b) (4) | Acceptable (Low risk) | |
| Endotoxin | | L | (b) (4) procedures are adequately validated. | | |

| | | | | |
|--------------------------|---|---|-----------------------|--|
| | | The bulk product is (b) (4) End-product testing, in-process controls, and validated data provide assurance that it is a low risk | | |
| Appearance | L | Existing process control and stability data support the notion that product appearance is maintained during storage and handling | Acceptable (Low risk) | |
| Uniformity of dose | L | Dose accuracy is part of specification for pen injector | Acceptable (Low risk) | |
| Particulate matter | M | Existing process control and component control assures the quality. Tested per USP <788> | Acceptable (Low risk) | |
| Leachables/ extractables | L | Components used in manufacturing are appropriately characterized. | Acceptable (Low risk) | |
| pH | L | Adequate in-process controls in place to control pH. | Acceptable (Low risk) | |

The applicant's risk evaluation has identified drug substance (b) (4)

[Redacted]

The applicant has provided 18-24 month real time and 6 month accelerated stability data for six batches of the drug product manufactured at (b) (4) scale (3mL cartridge) (b) (4)

[Redacted] The stability studies were performed on the drug product packaged in 3 mL cartridge. Insulin glargine is light sensitive, and hence the Applicant's proposal to package the (b) (4) packaged in carton and store at 2-8 °C away from excessive light exposure is appropriate.

- Based on the long term and accelerated stability data evaluated in this document, a shelf life of 24 months at 5 °C ± 3 °C is recommended for Insulin glargine injection, 100 U/mL, filled 3mL glass cartridge and (b) (4) rubber seal and plunger.
- Based on the in-use stability data evaluated in this document, an in-use period of 28 days at up to 30 °C is recommended for BASAGLAR Kwikpen injection, 100 U/mL.

The NDA contains a post-approval stability protocol and commitment to place 6 full scale batches on stability and continue to update information on existing stability studies. The Applicant should update their stability protocol and post-approval stability protocol to include limits for individual product related substances and impurities.

B. Description of How the Drug Product is Intended to be Used

Basaglar™ (insulin glargine [rDNA origin] injection) 100 units/mL, available as 3 mL Basaglar™ prefilled KwikPen™, is a long-acting human insulin analog intended for subcutaneous administration once daily to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. It should not be administered intravenously or via an insulin pump. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. Basaglar™ is not supposed to be diluted or mix with any other insulin or solution.

Drug product delivery system and appropriate storage are adequately described in both package insert and patient package insert. Drug product shelf-life is 24 months at 2 ° - 8 °C, protected from light. In-use shelf-life period is 28 days at temperatures not exceeding 30 °C.

C. Basis for Approvability or Not-Approval Recommendation

The information on the quality of the drug substance and drug product, including additional information requested by the Agency, has been adequately provided. Based on the evaluation of the submitted information, from a CMC perspective the NDA is recommended for Approval. There are no pending CMC issues.

At this time, the Quality final recommendation is pending the recommendations from CDRH for the acceptability of the Penfill injector (Basaglar™'s KwikPen™) for the proposed use. In addition, OMPQ has not issued an overall recommendation for the commercial manufacturing and testing facilities listed in the NDA.

III. Administrative

- | | | |
|--------------------------------|---|--|
| A. Reviewer's Signature | Muthukumar Ramaswany, PhD Xavier Ysem, PhD | Chemist/ CDER/ ONDQA/ DNDQA III/ Branch VII Chemist/ CDER/ ONDQA/ DNDQA III/ Branch VII |
| B. Endorsement Block | Danae Christodoulou, PhD | Acting Branch Chief/ ONDQA/ DNDQA III/ Branch VII |
| C. CC Block | Callie CappelLynch | Project Manager/ CDER/ OND/ ODE II/ DMEP |

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

Chemistry Assessment

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling, Package Insert and Patient Package Insert *Pending*

1. Physician Package Insert (PI)

Although the Physician Package Insert (PI) is still under negotiation (several disciplines involved), the two sections of the PI that rely in Chemistry input, "Description" and "How Supplied" sections, appear adequately described.

Dosage Forms And Strengths - Adequate - No change recommended.

The following information provided under DOSAGE FORMS AND STRENGTHS is consistent with information provided under drug product section:

Basaglar injection 100 units/mL is available as: 3 mL BASAGLAR™ KwikPen™(prefilled)

Section 11 Description

The following drug product information provided under (Section 11 Description of the Drug product) is consistent with information provided in drug product 3.2.P.1.

Section 16.1 How Supplied Adequate.

Basaglar™ injection 100 units per mL is available as: 5 x 3 mL Basaglar™ KwikPen™ (prefilled)

Section 16.2 Recommended storage condition:

Unopened (unused) Basaglar™ KwikPen should be stored in a refrigerator, (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use Basaglar™ if it has been frozen.

In-use (opened) Basaglar™ should be stored at room temperature, below 86 °F (30 °C) and must be used within 28days or be discarded even if they still contain Basaglar™. Protect from direct heat and light.

After initial use, Basaglar™ KwikPen may be used for up to 28 days (4 weeks) if it is kept at room temperature, below 30 °C (86 °F). In-use Basaglar™ should not be stored in a refrigerator. This is important because some patients may be used to storing their insulin at 4 °C (39 °F). Basaglar™ must NOT be stored with the needle in place. Keep all BASAGLAR away from direct heat and light.

Not in-use (unopened) Basaglar™ can be used until the expiration date printed on the label if they are stored in a refrigerator.

| | Not In-Use (Unopened) Refrigerated | Not In-Use (Unopened) Room Temperature (Below 86 F [30 C]) | In-Use (Opened) Room Temperature, (Below 86 F [30 C]) |
|-------------------------------------|------------------------------------|--|---|
| 3 mL Basaglar™ KwikPen™ (prefilled) | Until expiration date | 28-days | 28 days, Do not refrigerate. |

2. Patient Package Insert (PPI or Patient Information)

Review of the Patient Package Insert is also multidisciplinary and still ongoing.

3. Container and Carton Labeling

The review of the Container and Carton Labeling is still ongoing (multidisciplinary review). A a copy of the draft container and carton label is shown below:

Chemistry Assessment

(b) (4)

B. Environmental Assessment or Claim of Categorical Exclusion *Adequate*

The use of LY2963016 is not expected to result in any environmental exposure to intact insulin larginine. The end degradation products of LY2963016, amino acids, occur naturally in the environment and the use of LY2963016 will not alter their distribution in the environment. Therefore, Eli Lilly and Company claims a categorical exclusion for this supplemental application pursuant to 21 CFR 25.15 (d) based on the exclusion allowed by 21 CFR 25.31 (c).

As described in the submission, the insulin analog LY2963016 is similar to insulin it is likely to be cleared like insulin. The in vivo degradation of insulin has been studied following subcutaneous and intravenous injections (Duckworth 1988; Duckworth et al. 1998)⁶. The uptake and degradation of insulin occurs predominantly in liver, kidney, muscle, and adipocytes, with the liver being the major organ involved in the clearance of insulin. In liver, muscle, and adipocytes, insulin binds to the cell surface either via insulin receptors or other less specific sites. Binding is followed by degradation on the cell surface or cellular uptake and subsequent degradation. It has also been shown that some insulin can be internalized, then cycle back to the cell surface where it is released, apparently intact. Metabolism by the kidney is predominated by glomerular filtration, followed by proximal tubular reabsorption and intracellular degradation. Less than 1 % of filtered insulin is excreted intact in urine. Therefore, rather than being excreted intact from the body, LY2963016 will predominantly be eliminated by degradation to smaller peptides and amino acids by a variety of proteolytic processes in the cells following receptor-mediated endocytosis. The small amount of LY2963016 that might be excreted intact would be discharged to a municipal sewage treatment facility or a septic system prior to entering the environment. In either case, the protein would be subject to degradation, which would also result in metabolic products of smaller proteins and amino acids. The end degradation products of LY2963016, amino acids, are the same as those of any other protein.

⁶ Duckworth WC. 1988. Insulin degradation: mechanisms, products, and significance. *Endocrine Reviews* 9(3):319-345.

Duckworth WC, Bennett RG, Hamel FG. 1998. Insulin Degradation: Progress and Potential. *Endocrine Reviews* 19(5):608-624.

Chemistry Assessment

Furthermore, even if LY2963016 were to be excreted from humans intact and was resistant to degradation in sewage treatment, the anticipated annual sales of LY2963016 would result in far less than 1 ppb of LY2963016 at the point of entry to the aquatic environment. For new drug applications, concentrations below this level are not considered to be an environmental risk and are categorically excluded from the environmental assessment requirement. Eli Lilly and Company knows of no extraordinary circumstances that exist that could require an environmental assessment.

Comment: Eli Lilly and Company's claim for a categorical exclusion for this application pursuant to 21 CFR 25.15 (d) based on the exclusion allowed by 21 CFR 25.31 (c) fulfills the requirements and it is deemed acceptable.

C. Establishment Inspections *Pending*

The sites involved in the manufacture, testing and packaging of the drug substance and drug product were requested for inspection. The recommendation for those sites by the Office of Compliance (OC) is still pending (EER summary report dated 15-Jul-2014 is attached).

III. List of Deficiencies to Be Communicated:

None

ATTACHED:

| | |
|--|--------------------|
| EER Summary Report dated 15-Jul-2014 (4 Pages) | <u>Page</u> 150 |
|--|--------------------|



CHEMISTRY REVIEW



Chemistry Assessment

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

| | | | |
|-----------------------|----------------|---|---|
| Application: | NDA 205692/000 | Sponsor: | ELI LILLY AND CO |
| Org. Code: | 510 | | LILLY CORPORATE CENTER |
| Priority: | 5 | | INDIANAPOLIS, IN 46285 |
| Stamp Date: | 18-OCT-2013 | Brand Name: | ABASRIA KWIKPEN (INSULIN GLARGINE [RDNA |
| PDUFA Date: | 18-AUG-2014 | Estab. Name: | |
| Action Goal: | | Generic Name: | |
| District Goal: | 19-JUN-2014 | Product Number; Dosage Form; Ingredient; Strengths | 001; INJECTABLE; INSULIN GLARGINE; 300UNITS |

| | | | |
|----------------------|-----------------|------------------------|----------------------|
| FDA Contacts: | M. RAMASWAMY | Prod Qual Reviewer | 3017961676 |
| | P. KUMAR | Product Quality PM | (HFD-800) 2404023722 |
| | C. CAPPEL-LYNCH | Regulatory Project Mgr | 3017968436 |
| | S. TRAN | Team Leader | 3017961764 |

| | | | |
|--------------------------------|---------|----------------|-------------|
| Overall Recommendation: | PENDING | on 01-NOV-2013 | by EES_PROD |
| | PENDING | on 28-OCT-2013 | by EES_PROD |
| | PENDING | on 28-OCT-2013 | by EES_PROD |

| | | | |
|--------------------------|-------------------------------|--------------------|---------|
| Establishment: | CFN: | FEI: | (b) (4) |
| | | | (b) (4) |
| DMF No: | | AADA: | |
| Responsibilities: | DRUG SUBSTANCE RELEASE TESTER | | |
| Profile: | CONTROL TESTING LABORATORY | OAI Status: | NONE |
| Last Milestone: | OC RECOMMENDATION | | |
| Milestone Date: | 01-DEC-2013 | | |
| Decision: | ACCEPTABLE | | |
| Reason: | DISTRICT RECOMMENDATION | | |

Chemistry Assessment

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: CFN: 1819470 FEI: 1819470
ELI LILLY AND COMPANY

DMF No: INDIANAPOLIS, , UNITED STATES 462850001 **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-NOV-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 28-OCT-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

Last Milestone: SUBMITTED TO OC

Milestone Date: 28-OCT-2013

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

Last Milestone: DRUGS
OC RECOMMENDATION

Milestone Date: 05-NOV-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Chemistry Assessment

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
HOSPIRA INC

DMF No: (b) (4) AADA:

Responsibilities: (b) (4)

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: 3004525072
LILLY DEL CARIBE INC

DMF No: CAROLINA, , UNITED STATES 00986 AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: (b) (4) (b) (4) DERIVED API (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-MAR-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Chemistry Assessment

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

| | | |
|--------------------------|---|-------------------------|
| Establishment: | CFN: 9610945 FEI: 3002607475 | |
| | LILLY FRANCE SAS RUE DE COLONEL LILLY B.P. 10 FEGERSHEIM, FRANCE | |
| DMF No: | | AADA: |
| Responsibilities: | DRUG SUBSTANCE RELEASE TESTER FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE RELEASE TESTER | |
| Profile: | CONTROL TESTING LABORATORY | OAI Status: NONE |
| Last Milestone: | OC RECOMMENDATION | |
| Milestone Date: | 28-OCT-2013 | |
| Decision: | ACCEPTABLE | |
| Reason: | BASED ON PROFILE | |
| Profile: | (b) (4) DRUGS | OAI Status: NONE |
| Last Milestone: | OC RECOMMENDATION | |
| Milestone Date: | 07-NOV-2013 | |
| Decision: | ACCEPTABLE | |
| Reason: | DISTRICT RECOMMENDATION | |

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

/s/

XAVIER J YSERN
07/21/2014

MUTHUKUMAR RAMASWAMY
07/21/2014

SUONG T TRAN
07/21/2014

ERIC P DUFFY
07/21/2014

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 205692
2. DATES AND GOALS:

| | |
|---|--|
| Letter Date: 17-OCT-2013 | Submission Received Date : 18-OCT-2013 |
| PDUFA Goal Date: 18-AUG-2014 (NDA is NOT in "The Program") | |

3. PRODUCT PROPERTIES:

| | |
|---|------------------------|
| Trade or Proprietary Name: | Proposed name: (b) (4) |
| Established or Non-Proprietary Name (USAN): | Insulin glargine |
| Dosage Form: | Sterile solution |
| Route of Administration | Subcutaneous injection |
| Strength/Potency | 100 units/mL |
| Rx/OTC Dispensed: | Rx |

4. INDICATION: Treatment of type 1 and type 2 diabetes

5. DRUG SUBSTANCE STRUCTURAL FORMULA:

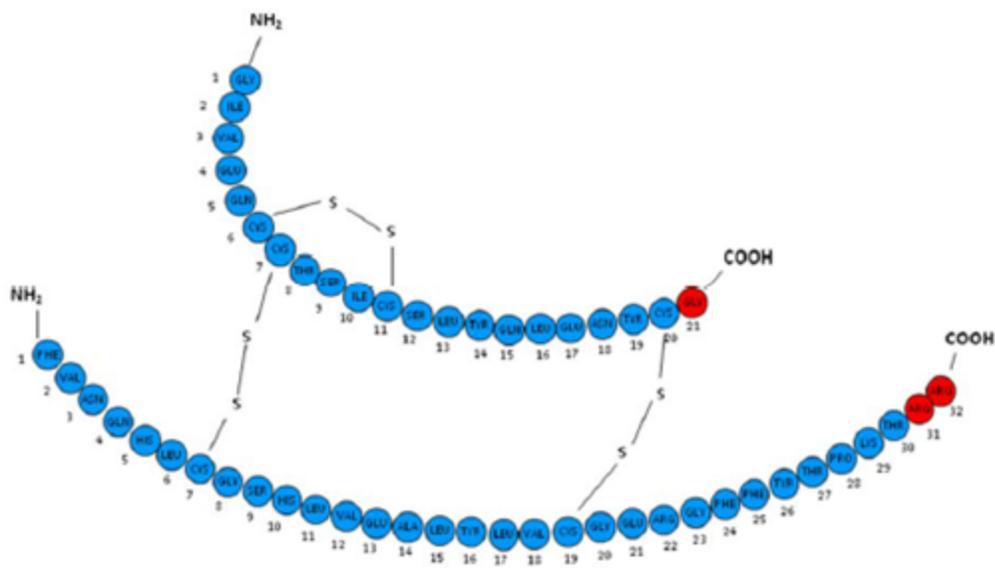
Molecular Formula: C₂₆₇H₄₀₄N₇₂O₇₈S₆

Molecular Weight: 6063 Da

Structural Formula: The protein sequence for LY2963016 is provided in Figure 2.3.S.1.2-1.

LY2963016 is a 2-chain peptide containing 53 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 32 amino acids. As in human insulin, LY2963016 contains 2 interchain disulfide bonds and one intrachain disulfide bond. LY2963016 differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and 2 arginines are added to the C-terminus of the B-chain.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**



6. NAME OF APPLICANT (as indicated on Form 356h): Eli Lilly

7. SUBMISSION PROPERTIES:

| | |
|--|--|
| Review Priority (select one) | Standard |
| Submission Classification (Chemical Classification Code) | 5 |
| Application Type | 505(b)(2) |
| Breakthrough Therapy | No |
| Responsible Organization (Clinical Division) | Division of Metabolism and Endocrinology Products CMC Lead: Suong (Su) Tran |

8. CONSULTS:

| CONSULT | YES | NO | COMMENTS: |
|--|-----|----|--|
| Biometrics | | x | |
| Clinical Pharmacology | | x | |
| Establishment Evaluation Request (EER) | x | | To be sent by ONDQA-PM |
| Pharmacology/Toxicology | x | | To review the toxicological limits on leachables and qualification of one process impurity |
| Methods Validation | | | To be determined by Primary Reviewer |
| Environmental Assessment | | | Categorical exclusion request to be reviewed by Primary Reviewer |
| CDRH | x | | Sent by the OND PM |
| Other | | | |

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

Overall Filing Conclusions and Recommendations

CMC:

| |
|---|
| Is the Product Quality Section of the application fileable from a CMC perspective? Yes |
| Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? No |

Biopharmaceutics: Not applicable

From: [Ghosh, Tapash](#)
To: [Tran, Suong T](#); [Christodoulou, Danae D](#); [Kumar, Priyanka](#); [CDER OPS TO MICRO](#)
Cc: [Cappell Lynch, Callie](#); [Ghosh, Tapash](#)
Subject: RE: please send assignments FW: NEW NDA 205692 Lilly's (b) (4) KwikPen (insulin glargine [rDNA origin] for injection)
Date: Wednesday, October 23, 2013 9:40:17 AM

No Biopharm consult needed. Thanks,

Microbiology:

| |
|--|
| Is the Product Quality Section of the application fileable from a Microbiology perspective? See Microbiology Filing Review for details and for any potential Microbiology review issues. |
| Microbiology Filing Issues: See Microbiology Filing Review for details and for any potential Microbiology review issues. |

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

Summary of Initial Quality Assessment

| Does the submission contain any of the following elements? | | | |
|--|--------------|-----|-----------------------|
| Nanotechnology | QbD Elements | PET | Other, please explain |
| | | | |

| Is a team review recommended? | Yes |
|---|-----|
| Suggested expertise for team: “Recombinant protein” drug substance and “sterile injectable solution” drug product | |

Summary of Critical Issues and Complexities

The NDA is a 505(b)(2) for Insulin Glargine, with the approved Lantus as referenced product.

(b) (4)

Note: the new product has zinc oxide while Lantus has zinc chloride, with the same zinc ion content for both products.

(b) (4)

| Ingredient | Function | New product Quantity/mL | Lantus Quantity/mL |
|------------------------|----------------|----------------------------|-----------------------|
| Insulin glargine | Drug substance | 100 units (3.6378 mg) | 100 units (3.6378 mg) |
| Glycerin | (b) (4) | 17 mg | 17 mg |
| Metacresol | | 2.7 mg | 2.7 mg |
| Zinc ²⁺ ion | | | (b) (4) |
| HCl/NaOH | pH adjustment | pH 3.5-4.5 | pH 3.5-4.5 |
| Water for Injection | Diluent | q.s. to 1 mL | q.s. to 1 mL |

In support of the 505(b)(2) aspect of the application and per previous agreement with FDA, the NDA includes a study report on the analytical comparison of both drug substance and drug product:

- between the U.S.- Lantus (five batches) and the E.U.- Lantus (three batches): the applicant claims both to be sufficiently similar, which will be evaluated by the reviewer.
- between the new product (14 batches) and Lantus (U.S. and E.U., same batches used to compare U.S.- and E.U.- Lantus): the applicant found two differences and claim both to be minor, which will be evaluated by the reviewer. The first difference is the presence of a process impurity (b) (4) in the new product. Up to (b) (4)% of this impurity was present in clinical batches, and a level of (b) (4)% was qualified in the rat toxicology study 8259267. The second difference is the higher rate of formation of the (b) (4) on accelerated stability of the new product, but this difference was not observed in the long term stability study.

The comparison between the new product and Lantus (U.S. and E.U.) includes analysis of the secondary structure by (b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**



In addition to the analytical comparison of the new product and the referenced product relied upon Lantus, a stand-alone characterization of the new product (commercial-scale product batch A805787 and primary reference standard PRS0843) was conducted. A comparability study report is also included in the NDA for the comparison between the product manufactured at Lilly France and the product manufactured at the contractor (b) (4).

- The primary structure of insulin glargine was confirmed by using standard protein analyses such as amino acid sequence by N-terminal sequencing, amino acid composition analysis, molecular mass by mass spectrometry, peptide mapping (reduced and non-reduced Glu-C digestion with RP-HPLC and MS detection), and isoelectric point. Higher-order structures were also confirmed: secondary structure by far-UV CD and FT-IR, tertiary structure by near-UV CD, and quaternary structure by static and dynamic light scattering.
- The biological activity (potency) of the new product was characterized by several in vitro binding assays as well as an in vivo rabbit assay. The in vitro assays used the drug product process validation batches manufactured at Lilly France and the contractor (b) (4). The in vivo assay used the commercial-scale product batch A805787.
- Characterization of impurities/degradants was conducted with the drug substance process validation batches (same scale and manufacturing site as for the clinical and stability batches). Information is provided on both the product related impurities/substances and process related impurities.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

Initial Quality Assessment

Previous quality-related meeting between FDA and the sponsor:

From the meeting dated 20-JUL-2012:

Question 9: The proposed cell-based bioidentity method, in place of the rabbit bioassay method, is under review by FDA (IND 105,423 Seq 0010, 06 March 2012, page 10 of document in IND Section 1.11.1). Lilly requests feedback related to the method and validation documents previously submitted.

FDA Response: The proposed cell-based bioidentity method, Method B12968, appears adequate, but its acceptability is a review issue.

Discussion: No discussion occurred; see attached email dated July 20, 2012.

Question 10: Lilly provided additional comparative data for US- and EU-approved Lantus in IND 105,423 Seq 0010 (06 March 2012, page 1 of document in IND Section 1.11.1). Lilly requests any feedback regarding the adequacy of the data submitted in response to FDA request.

FDA Response: Your commitment to provide a similarity package between the two comparators (US-approved Lantus and EU-approved insulin glargine) that is equal in extent to the similarity package between LY2963016 injection and Lantus, the listed drug relied upon, is acceptable.

Discussion: No discussion occurred; see attached email dated July 20, 2012.

Question 11: Lilly proposes that the quality biosimilar data package for LY2963016 and Lantus be provided in a standalone regional section (3.2.R) of the common technical document (CTD) structure. Lilly requests feedback regarding the proposal.

FDA Response: Your proposal for the quality data package for LY2963016 and Lantus, to be provided in a standalone regional section (3.2.R), is acceptable. See Additional Regulatory Comments.

ONDQA Initial Quality Assessment (IQA) and Filing Review For new NDAs

Discussion: With respect to Lilly's reference to the "quality biosimilar data package" in its question, FDA stated that LY2963016 is not a proposed biosimilar product; rather Lilly is proposing to seek approval for LY2963016 through the 505(b)(2) pathway under the FD&C Act. FDA explained that the 351(k) pathway for biosimilar products under the Public Health Service Act and the 505(b)(2) pathway under the FD&C Act are two separate regulatory schemes.

Question 12: Lilly proposes to submit an amendment with updated stability data no later than 3 months before the PDUFA date. Is this proposal acceptable to FDA?

FDA Response: No, we do not agree with your proposal to submit the primary long-term stability data in an amendment after the initial NDA submission. In accordance with Good Review Management Principles and Practices (GRMPP) timelines, a complete NDA should be submitted for filing. Therefore, all the stability data necessary for establishing a long-term expiry will be required in the initial NDA submission for our filing determination.

Discussion: No significant discussion occurred.

From the meeting dated 28-AUG-2013:

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

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

Discussion: No discussion occurred.

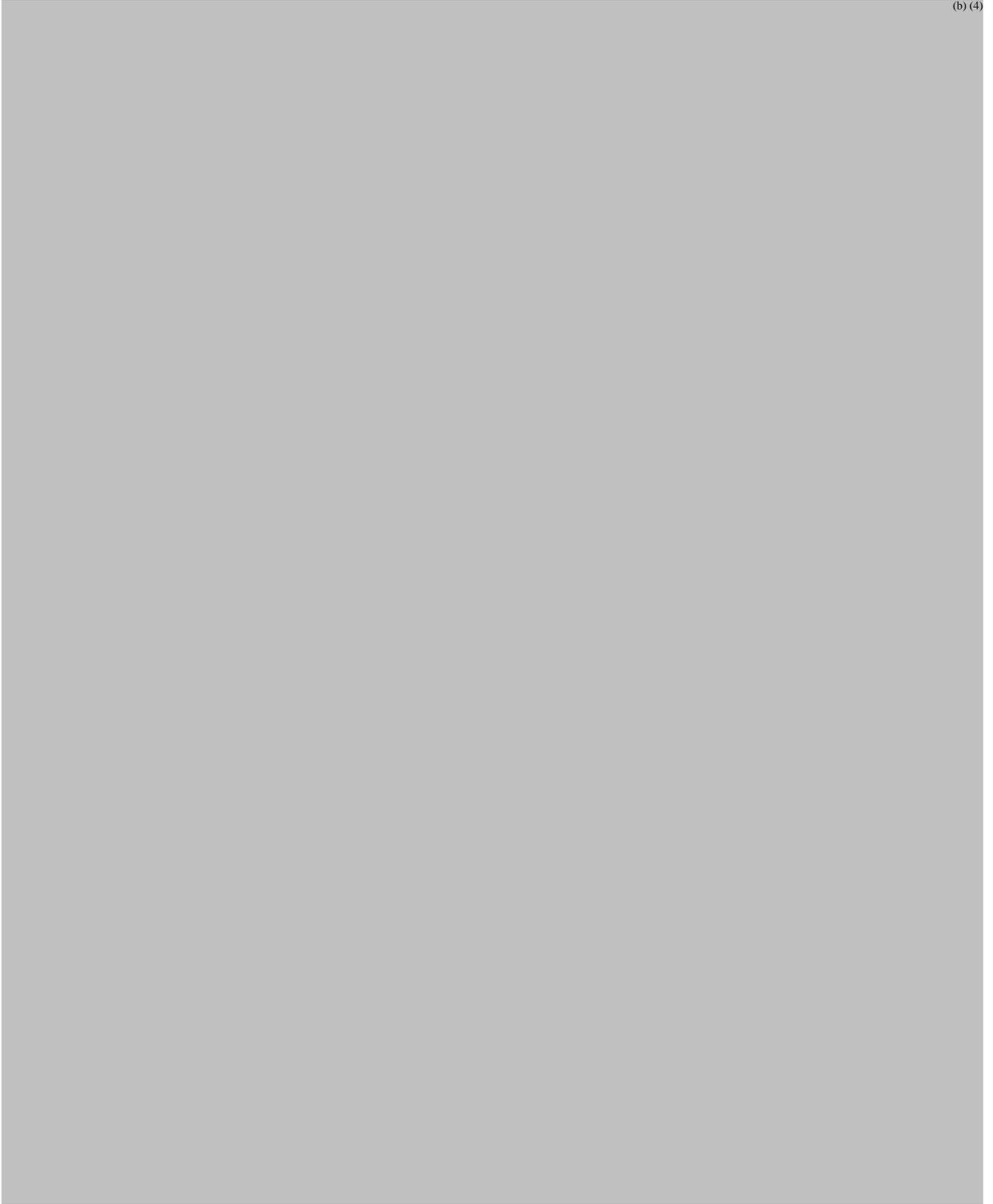
Drug Substance.

Insulin glargine has 53 amino acid residues in two chains: chain A has 21 residues and chain B has 32 residues. As in human insulin, the drug substance has two interchain disulfide bonds and one intrachain disulfide bond. It differs from human insulin by the addition of two Arginine residues to the C-terminus of the B-chain and by the replacement of Asparagine at A21 with Glycine. These changes result in a shift in the isoelectric point so that the analog is less soluble at neutral physiological pH, causing it precipitate at the SC injection site, delaying absorption and prolonging the duration of action.

Manufacture of the drug substance. (b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

(b) (4)



**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

(b) (4)

Drug Product

The product is a clear solution for injection, 100 units/mL, available in a 3 mL cartridge pre-assembled in a pen injector.

Composition. (see the copied composition table at the end of this review) As stated earlier in this review, the NDA is a 505(b)(2) for Insulin Glargine, with the approved Lantus as referenced product. (b) (4)

(b) (4) The NDA includes information on the Design of Experiments used for formulation characterization, but the applicant's main goal was to match the formulation of Lantus. There is no overage used in the new product.

Overfill. To ensure the delivery of the minimum 3 mL volume, each cartridge has an overfill of (b) (4), which should be adequate per USP<1151> Excess Volumes in Injections.

Comparability of the product used in the clinical studies, stability studies, and commercial

ONDQA Initial Quality Assessment (IQA) and Filing Review For new NDAs

product. The same product formulation was used in the pivotal clinical studies, primary stability studies, and to be used in the commercial product. The commercial primary container closure system (cartridge, to be used with a pen injector) was used in the clinical studies in addition to the vial packaging system (not proposed for marketing). The clinical and primary stability batches were produced at the commercial site Lilly France at the commercial scale ((b) (4)). Primary stability batches were produced the commercial site and contractor (b) (4) at the commercial scale ((b) (4)). Process validation was completed and reports are provided in the NDA for both sites at commercial scale ((b) (4) at Lilly France, and (b) (4)). Comparability and stability data are included in the NDA to bridge the two sites and scales.

Product manufacture. The product manufacturing process is (b) (4)

Drug product specification. (see the copied specification at the end of this review)

The drug product specification does not include testing for biological activity. As indicated earlier in this review, the potency/mass correlation in support of the assay test method was part of the product characterization study. The drug product specification (b) (4)

(b) (4) Dose accuracy is part of the pen injector specification and will be evaluated as part of the CDRH review. Same as in the drug substance specification, no specified degradant is included in the drug product specification; instead, the applicant proposes to include all the possible degradants in the limit of (b) (4) % on Total Impurities. There is a separate of (b) (4) % on (b) (4) . The reviewer will determine whether any of the degradants discussed in the characterization and stability reports should be individually listed with limits in the drug product specification. Batch analysis results are provided for validation, clinical, and stability batches. As per ICH Q6B, acceptance criteria or limits on impurities/degradants should be based on actual data from nonclinical, clinical, and stability batches.

Container closure systems. The drug product is packaged in a 3-mL clear type I glass cartridge sealed with a (b) (4) plunger and a (b) (4) crimp seal. Primary stability batches were stored in this container closure system. The applicant states that the packaging components meet requirements of USP<660> Glass and (b) (4) Closures. The NDA includes information on leachables , and the information will be assessed by the reviewer, with input from the PharmTox team on the toxicological limits. The pen injector device will be evaluated by CDRH.

Stability. Sufficient stability data are provided in the submission for filing. The primary reviewer will determine the final expiry based on all available data and per ICH Q5C guideline. The unopened product is stored under refrigeration, 2-8 °C. The NDA includes data from three primary stability batches manufactured at Lilly France (commercial site, process, and scale) and three primary stability batches manufactured at the contractor (b) (4) (commercial site, process, and scale). For Lilly France, the data include 18-month long term at 5 °C and 6-month accelerated at 30 °C, and for (b) (4) , the data include 9-month long term at 5 °C and 6-month accelerated at 30 °C. It is noted that the accelerated temperature 30 °C is higher than the usually recommended 25 °C, but the change is acceptable because it represents a worse stress case.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

Supporting stability data include photostability and in-use studies. The in-use study simulated actual patient use and was conducted with two product batches, each 14-month old, stored for 32 days at 30 C in support of the labeled in-use period of 28 days at room temperature.

Comparability protocol. The NDA includes one comparability protocol for the post-approval change of (b) (4)

Input from the Post-Marketing Branch may be obtained.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

| A. GENERAL | | | | |
|-------------------|--|------------|-----------|----------------|
| | Parameter | Yes | No | Comment |
| 1. | Is the CMC section organized adequately? | x | | |
| 2. | Is the CMC section indexed and paginated (including all PDF files) adequately? | x | | |
| 3. | Are all the pages in the CMC section legible? | x | | |
| 4. | Has all information requested during the IND phase, and at the pre-NDA meetings been included? | x | | |

| B. FACILITIES* | | | | |
|--|---|------------|-----------|----------------|
| * If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a potential filing issue or a potential review issue. | | | | |
| | Parameter | Yes | No | Comment |
| 5. | Is a single, comprehensive list of all involved facilities available in one location in the application? | x | | |
| 6. | For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API. | x | | |

| | Parameter | Yes | No | Comment |
|--|------------------|------------|-----------|----------------|
|--|------------------|------------|-----------|----------------|

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

| | | | | |
|----|--|---|--|--|
| 7. | <p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) | x | | |
| 8. | <p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) | x | | |

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

| | Parameter | Yes | No | Comment |
|-----|--|------------|-----------|----------------|
| 9. | <p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) | x | | |
| 10. | Is a statement provided that all facilities are ready for GMP inspection at the time of submission? | x | | |

| C. ENVIRONMENTAL ASSESMENT | | | | |
|-----------------------------------|--|------------|-----------|----------------|
| | Parameter | Yes | No | Comment |
| 11. | Has an environmental assessment or claim of categorical exclusion been provided? | x | | |

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

| D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API) | | | | |
|--|--|------------|-----------|----------------|
| | Parameter | Yes | No | Comment |
| 12. | Does the section contain a description of the DS manufacturing process? | x | | |
| 13. | Does the section contain identification and controls of critical steps and intermediates of the DS | x | | |
| 14. | Does the section contain information regarding the characterization of the DS? | x | | |
| 15. | Does the section contain controls for the DS? | x | | |
| 16. | Has stability data and analysis been provided for the drug substance? | x | | |
| 17. | Does the application contain Quality by Design (QbD) information regarding the DS? | | x | |
| 18. | Does the application contain Process Analytical Technology (PAT) information regarding the DS? | | x | |

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

| E. DRUG PRODUCT (DP) | | | | |
|-----------------------------|---|------------|-----------|----------------|
| | Parameter | Yes | No | Comment |
| 19. | Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging? | x | | |
| 20. | Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable? | x | | |
| 21. | Is there a batch production record and a proposed master batch record? | x | | |
| 22. | Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product? | x | | |
| 23. | Have any biowaivers been requested? | | x | |
| 24. | Does the section contain description of to-be-marketed container/closure system and presentations? | x | | |
| 25. | Does the section contain controls of the final drug product? | x | | |
| 26. | Has stability data and analysis been provided to support the requested expiration date? | x | | |
| 27. | Does the application contain Quality by Design (QbD) information regarding the DP? | | x | |
| 28. | Does the application contain Process Analytical Technology (PAT) information regarding the DP? | | x | |

| F. METHODS VALIDATION (MV) | | | | |
|-----------------------------------|--|------------|-----------|----------------|
| | Parameter | Yes | No | Comment |
| 29. | Is there a methods validation package? | x | | |

| G. MICROBIOLOGY | | | | |
|------------------------|------------------|------------|-----------|----------------|
| | Parameter | Yes | No | Comment |

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

| | | | | |
|-----|---|--|--|-------------------------------------|
| 30. | If appropriate, is a separate microbiological section included assuring sterility of the drug product | | | See the Microbiology filing review. |
|-----|---|--|--|-------------------------------------|

| H. MASTER FILES (DMF/MAF) | | | | |
|----------------------------------|---|------------|-----------|----------------|
| | Parameter | Yes | No | Comment |
| 31. | Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete? | x | | |

| DMF # (b) (4) | TYPE | HOLDER | ITEM REFERENCED (b) (4) | LOA DATE | COMMENTS |
|------------------|------|--------|----------------------------|-------------|----------|
| | III | | | 05-JUL-2012 | |
| | III | | | 16-JUL-2012 | |
| | III | | | 03-JUL-2012 | |
| | III | | | 13-JUL-2012 | |

| I. LABELING | | | | |
|--------------------|---|------------|-----------|----------------|
| | Parameter | Yes | No | Comment |
| 32. | Has the draft package insert been provided? | x | | |
| 33. | Have the immediate container and carton labels been provided? | x | | |

See appended electronic signature page.

NAME
CMC-Lead
Office of New Drug Quality Assessment

{See appended electronic signature page}

NAME
Branch Chief or Designee
Office of New Drug Quality Assessment

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

Appendix 1. Composition of Drug Product

Table 2.3.P.1-1 Unit Formula for LY2963016 Injection, 3 mL Cartridges

| Ingredient | Quantity/mL | Function | Reference to Standards |
|--------------------------------------|--|---------------|------------------------|
| Active Ingredient | | | |
| LY2963016 | 100 Units (3.6378 mg ¹) | Active | In-house |
| Other Ingredients² | | | |
| Glycerin | 17 mg | (b) (4) | USP-NF/Ph.Eur. |
| Metacresol | 2.7 mg | (b) (4) | USP-NF/Ph.Eur. |
| Zinc Oxide ³ | (b) (4) | (b) (4) | USP-NF/Ph.Eur. |
| Hydrochloric Acid | -- ⁴ | pH adjustment | In-house ⁴ |
| Sodium Hydroxide | -- ⁴ | pH adjustment | In-house ⁴ |
| Water for Injection | q. s. to 1 mL | (b) (4) | USP-NF/Ph.Eur. |
| (b) (4) | | | |

ONDQA Initial Quality Assessment (IQA) and Filing Review For new NDAs

Appendix 2. Drug Product Specification

Table 2.3.P.5.1-1 Specifications for LY2963016 Injection

| Test | Analytical Procedure | Acceptance Criteria |
|----------------------------------|---------------------------------------|---|
| Identification Test | | |
| Identity | B12882/HPLC | The retention time of the main peak compares with that of the reference standard. |
| Potency Tests | | |
| Assay | B12882/HPLC | Not less than 95.0% and not more than 105.0% of the label claim ¹ |
| (b) (4) | B03996/HPLC | Not less than (b) (4)% and not more than (b) (4)% of label claim (b) (4) |
| Purity Tests | | |
| Impurities: Total | B12883/HPLC | Not more than (b) (4)% |
| (b) (4) | B03622/(b) (4)-HPLC | Not more than (b) (4)% |
| Other Tests | | |
| Physical Appearance ² | Visual | Clear, colorless solution |
| (b) (4) | B09980/Atomic Absorption Spectroscopy | Not less than (b) (4)/100 U and not more than (b) (4)/100 U |
| Sterility | USP <71> Ph.Eur. 2.6.1 | Meets test |
| Bacterial Endotoxins | USP <85> Ph.Eur. 2.6.14 | Not more than (b) (4)/100 U |
| Particulate Matter | USP <788> Ph.Eur. 2.9.19 | Meets test |
| pH | USP <791> Ph.Eur. 2.2.3 | Not less than 3.5 and not more than 4.5 |
| Color | Ph.Eur. 2.2.2 | Colorless (not more intensely colored than reference solution B9) |
| Clarity | Ph.Eur. 2.2.1 | Clear (opalescence not more pronounced than reference suspension I) |

¹ The limit of (b) (4)% of the label is equivalent to (b) (4)

² "Physical Appearance" is equivalent to the ICH term "Description."

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

Table 2.3.P.5.1-2 Specifications for Pen-Injector

| Test | Analytical Procedure | Acceptance Criteria |
|-------------------|--|---|
| Visual Inspection | Visual Examination | No missing parts No cracked or broken cartridges Proper alignment of numbers in dose window Good print quality Correct label information Correct cartridge identity (Alternate Method - HPLC Identity) |
| Functional Test | Manual Operation in Accordance with Instructions for Use | Verify pen dials properly Verify pen returns to zero when dialed or dosed Verify button function Verify cap can be removed and attached |
| Dose Accuracy | Dose Accuracy Test | Passes Test |
| Glide Force | Glide Force Test | Passes Test |

ONDQA Initial Quality Assessment (IQA) and Filing Review For new NDAs

Appendix 3. Drug Substance Specification

| Test | Analytical Procedure | Acceptance Criteria |
|----------------------------------|---|--|
| Identification Test | | |
| Identity | B12882/ HPLC | The retention time of the main peak compares with that of the reference standard. |
| Identity | B12976/ HPLC-Peptide Map | Conforms to reference standard |
| Biological Identity | B12968/ (b) (4) | Identity is confirmed when the bioresponse of the sample is not less than (b) (4) % potency relative to the potency of the reference standard. |
| Potency Test | | |
| Assay | B12882/ HPLC | Not less than 95.0% and not more than 105.0% (Not less than (b) (4) and not more than (b) (4) on a (b) (4) |
| Purity Tests | | |
| Impurities: Total | B12883/ HPLC | Not more than (b) (4) % |
| (b) (4) | B03622/ (b) (4) HPLC | Not more than (b) (4) % |
| Other Tests | | |
| Physical Appearance ¹ | Visual | White or almost white solid |
| (b) (4) | B09980/ Atomic Absorption Spectroscopy | Not less than (b) (4) % and not more than (b) (4) % |
| Loss on Drying | USP <731> Ph.Eur. 2.2.32 | Not more than (b) (4) % |
| (b) (4) | G1324/ Immunoassay | Not more than (b) (4) |
| | B12977/ Immunoassay | Not more than (b) (4) |
| | B05416/ Atomic Absorption Spectroscopy | Not more than (b) (4) |

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDAs**

| Test | Analytical Procedure | Acceptance Criteria |
|---|----------------------------|-------------------------|
| Bacterial Endotoxins | USP <85> Ph.Eur. 2.6.14 | Not more than (b) (4) |
| Bioburden (Total Aerobic Microbial Count) | USP <61> Ph.Eur. 2.6.12 | Not more than (b) (4) |
| (b) (4) | B05054/ (b) (4) | Not more than (b) (4) % |

“Physical Appearance” is equivalent to the ICH term “Description”.

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

/s/

SUONG T TRAN
11/20/2013

DANAE D CHRISTODOULOU
11/20/2013