

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205692Orig1s000**

**MICROBIOLOGY/VIROLOGY REVIEW(S)**

# Product Quality Microbiology Review

28 FEB 2014

**NDA:** 205-692

**Drug Product Name**

**Proprietary:** (b) (4) (proposed)

**Non-proprietary:** Insulin glargine

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

Submit	Received	Review Request	Assigned to Reviewer
17 OCT 2013	18 OCT 2013	23 OCT 2013	23 OCT 2013
06 DEC 2013	06 DEC 2013	N/A	N/A
22 JAN 2014	22 JAN 2014	N/A	N/A
25 FEB 2014	25 FEB 2014	N/A	N/A

**Applicant/Sponsor**

**Name:** Eli Lilly and Company

**Address:** Lilly Corporate Center  
Drop Code 2543  
Indianapolis, IN 46285

**Representative:** Jorge Pfeifer, PhD

**Telephone:** 317-276-2146

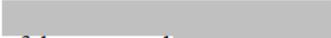
**Name of Reviewer:** Jessica G. Cole, PhD

**Conclusion:** Recommended for Approval

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## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** 505(b)(2) NDA
  2. **SUBMISSION PROVIDES FOR:** New drug product
  3. **MANUFACTURING SITES:**  
Drug Product:  
Lilly France  
2 rue du Colonel Lilly  
67640 Fegersheim, France  
FEI/DUNS: 3002807475/ 395346919  
  
 (b) (4)
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
    - Sterile, preserved solution in a multi-dose pen injector
    - 100 units/mL in a 3 mL cartridge
    - Subcutaneous injection
  5. **METHOD(S) OF STERILIZATION:**  (b) (4)
  6. **PHARMACOLOGICAL CATEGORY:** Improved glycemic control in adults and children with Type 1 diabetes mellitus and in adults with type 2 diabetes mellitus
- B. **SUPPORTING/RELATED DOCUMENTS:** Microbiology review of DMF 16307 dated 21 January 2014. This DMF review covered a complete update to DMF  (b) (4) operations dated  (b) (4) and found the data adequate to support  (b) (4) manufacturing activities for 3 mL cartridges  (b) (4).
- C. **REMARKS:** This NDA is in the eCTD format. The following information request was sent to the applicant on 21 November 2013 and a response was received on 06 December 2013.

The NDA does not contain the  (b) (4)  
 (b) (4) Lilly commercial manufacturing sites. Please submit a description of the proposed  (b) (4)  
 drug product. For more information on the data to be submitted please

refer to the following Guidance: (b) (4) Current Good Manufacturing Practice  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances> (b) (4))

The following information request was sent to the applicant on 31 December 2013 and a response was received on 22 January 2014.

Please provide the following information or a reference to its location in the NDA or DMF.

1. DMF (b) (4) does not contain a letter of authorization for NDA 205-692. We note inclusion of the letter of authorization dated (b) (4) in the NDA but the DMF does not include similar authorization. Please have the DMF holder submit a copy of the authorization letter to the DMF.
2. The container-closure integrity studies described in Module 3.2.P.2.4.1.3 do not contain sufficient details to evaluate the test method and results. Provide the following information for the dye ingress test method.

- a. The concentration of (b) (4) used.
- b. The test conditions. Include the duration of (b) (4) used.
- c. The inspection method (i.e., visual or spectrophotometric)
- d. A description of the positive control and/or the limit of detection for the assay

3. The proposed manufacturing process at (b) (4) includes collection of a bioburden sample after (b) (4) thus has minimal microbial value. Revise the bioburden step to (b) (4)

4. Minimal information was provided on (b) (4) site. Provide a summary of the validation results for (b) (4) process. Alternately, provide the incoming endotoxin specification if components are received (b) (4)

5. The (b) (4) validation summaries provided in the (b) (4) validation package did not provided sufficient detail on the proposed (b) (4) Provide the following information. (b) (4)

6. We note that the (b) (4) and Lilly sites propose (b) (4) drug product stored at 2-8°C. Justify the proposal to allow for an (b) (4) storage of the drug product.

7. We note your 06 December 2013 submission in response to our 21 November 2013 information request regarding the (b) (4) Lilly manufacturing sites. Your submission did not contain sufficient detail to allow for evaluation of the proposed (b) (4) at each facility. Submit the (b) (4) reports or a more detailed description of the studies conducted. The following information is required: (b) (4)

(b) (4)

The following information request was sent to the applicant on 03 February 2014 and a response was received on 25 February 2014.

1. We refer to the (b) (4) validation studies conducted to support manufacture at the (b) (4) site. The submitted validation studies did not include the establishment of (b) (4) product. We note the inclusion of results from (b) (4). Please provide data to support the proposed in process (b) (4).
2. (b) (4)
3. We refer to the dye ingress test described in the 22 January 2014 submission that was part of the pharmaceutical development program to support the proposed container-closure system. We also refer to the container-closure test proposed (b) (4).
4. We refer to the 22 January 2014 response regarding the (b) (4) studies conducted in 2011, 2012, and 2013. Confirm that the proposed (b) (4) no new worst case products were required to support the proposed manufacturing process.

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## **Executive Summary**

### **I. Recommendations**

- A. Recommendation on Approvability** - Recommended for Approval
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable

### **II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – This is a preserved, sterile drug product [REDACTED]<sup>(b) (4)</sup> at two drug product manufacturing sites. There is adequate information on the preservative effectiveness [REDACTED]<sup>(b) (4)</sup> manufacturing process for this drug product.
- B. Brief Description of Microbiology Deficiencies** – Not applicable
- C. Assessment of Risk Due to Microbiology Deficiencies** – Not applicable
- D. Contains Potential Precedent Decision(s)-**  Yes  No

### **III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
Jessica G. Cole, PhD
- B. Endorsement Block** \_\_\_\_\_  
Bryan Riley, PhD  
Microbiology Team Leader
- C. CC Block**  
In DARRTS

**Product Quality Microbiology Assessment**

**1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)  
MODULE 3.2: BODY OF DATA**

**S DRUG SUBSTANCE** The LY2963016 drug substance is produced by (b) (4). The drug substance is non-sterile solid with a microbial specification of NMT (b) (4) and NMT (b) (4).

REVIEWER COMMENT: The drug substance is produced (b) (4) and thus viral clearance data are not required. See Section A.2 of this review for more information.

**P DRUG PRODUCT**

**P.1 Description of the Composition of the Drug Product**

- **Description of drug product** – Sterile, preserved drug product in a glass cartridge in a pen injector (KwikPen). Each pen contains 300 units (3 mL) of LY2963016 and is intended for use over 28 days.
- **Drug product composition** –

**Table 1-** Drug product composition (Sponsor Table 3.2.P.1-1)

Ingredient	Quantity/mL	Function	Reference to Standards
<b>Active Ingredient</b>			
LY2963016	100 Units (3.6378 mg <sup>1</sup> )	Active	In-house
<b>Other Ingredients<sup>2</sup></b>			
Glycerin	17 mg	(b) (4)	USP-NF/Ph.Eur.
Metacresol	2.7 mg	(b) (4)	USP-NF/Ph.Eur.
Zinc Oxide <sup>3</sup>	(b) (4)	(b) (4)	USP-NF/Ph.Eur.
Hydrochloric Acid (b) (4)	- - <sup>4</sup>	pH adjustment	In-house <sup>4</sup>
Sodium Hydroxide (b) (4)	- - <sup>4</sup>	pH adjustment	In-house <sup>4</sup>
Water for Injection	q.s. to 1 mL	(b) (4)	USP-NF/Ph.Eur.
(b) (4)			

- **Description of container closure system** – The drug product is filled into a 3 mL cartridge that is then loaded into a pen injector. The pen injector is similar to that approved for Humalog but has been modified

slightly to improve the patient experience. See Section P.7 of this review for more information on the pen. The cartridge will be supplied by (b) (4), the disc seal and plunger are supplied by (b) (4)

**Table 2-** Drug product container closure system (Sponsor Table 3.2.P.7.2-1)

Drug Product Strength (U/mL)	Cartridge Size	Packaging Components and Identification
100	3 mL	<p data-bbox="573 478 764 506"><u>Primary Components</u></p> <p data-bbox="573 527 837 554">Cartridge: Type I clear glass.</p> <p data-bbox="573 569 1149 688">(b) (4)</p> <p data-bbox="573 695 1149 751">Plunger: (b) (4)</p>

**P.2 Pharmaceutical Development**

**P.2.5 Microbiological Attributes**

- Container-Closure and Package integrity** – Microbial and dye ingress tests were used to confirm the integrity of the cartridge and the test results from both studies were acceptable. No additional information will be provided regarding the *Brevundimonas diminuta* microbial ingress test as only one test is required. 60 cartridges from Fegersheim and 60 cartridges from (b) (4) were tested and no dye ingress was observed.

31 December 2013 information request

The container-closure integrity studies described in Module 3.2.P.2.4.1.3 do not contain sufficient details to evaluate the test method and results. Provide the following information for the dye ingress test method.

- The concentration of (b) (4) used.
- The test conditions. Include the duration of (b) (4) used.
- The inspection method (i.e., visual or spectrophotometric)
- A description of the positive control and/or the limit of detection for the assay

Summary of the response received 22 January 2014

- The test was conducted with (b) (4) and was based on the procedures for self-sealing capacity described in USP<381>. The USP test requires use of a 1.0 g/L (0.1%) methylene blue solution so the proposed dye concentration provides for improved detection compared to the compendial test.
- Cartridges were (b) (4). These criteria are more stringent than the USP<381> requirements.

- c. Detection is visual using a [REDACTED] (b) (4)
- d. The positive controls include [REDACTED] (b) (4)

**Table 3-** Results from antimicrobial effectiveness testing (Sponsor Table 3.2.P.2.2.1.4-1) (b) (4)

- **Justification for not having a microbial limit specification for a non-sterile drug product** – Not applicable.

**ADEQUATE**

**REVIEWER COMMENT – The microbiological attributes of the drug product have been described and are consistent with industry standards.**

**P.3 Manufacture**

**P.3.1 Manufacturers**

Lilly France (described In DMF 16307)  
2 rue du Colonel Lilly  
67640 Fegersheim France

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(b) (4)

The pen is assembled, packaged, and labeled at the following facility:  
Eli Lilly and Company  
Indianapolis, Indiana 46285 USA

**P.3.3 Description of the Manufacturing Process and Process Controls**

The proposed (b) (4) manufacturing process is justified because the drug product is heat sensitive and must be stored at 2-8°C to prevent degradation. The manufacturing process for the Fegersheim France site is described in DMF 16307 and was found acceptable in the 21 January 2014 review. Some product-specific information for the Lilly France site was provided in the NDA and will be included in this review as applicable.

(b) (4) MANUFACTURING PROCESS

(b) (4)

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**REVIEWER COMMENT – The stability data is acceptable and the stability program is consistent with industry standards.**



**REVIEWER COMMENT – The proposed manufacturing process does not utilize human or animal derived products.**

**R REGIONAL INFORMATION**

**R.1 Executed Batch Record**

Executed batch records were provided for the 6 lots described in Table 7 above.

**2. REVIEW OF COMMON TECHNICAL DOCUMENT-  
QUALITY (CTD-Q)  
MODULE 1**

**A. PACKAGE INSERT** –The package insert does not require product quality microbiology input.

**3. LIST OF MICROBIOLOGY DEFICIENCIES AND  
COMMENTS:**

None.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JESSICA COLE  
03/03/2014

BRYAN S RILEY  
03/03/2014  
I concur.