CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205747Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 18 March 2015

TO: NDA 205-747

FROM: Denise Miller
CDER/OPQ/OPF/DMA/Branch II, Microbiologist

THROUGH: Neal J. Sweeney Ph.D.
CDER/OPQ/OPF/DMA/Branch II, Senior Microbiologist

SUBJECT: NDA 205-747 Class II resubmission
Product: Humalog (lispro insulin) injection
Sponsor: Eli Lilly and Co

The subject submission is a resubmission of the NDA providing responses to a Complete Response letter (dated 10 March 2014). The CR letter identified clinical pharmacology, device biocompatibility, and device human factors concerns.

A quality microbiology review was completed on 01 January 2014 recommending approval of the NDA. The subject resubmission contains no new product quality microbiology information for review.

Reviewer's Comment: NDA 215-747 is recommended for approval from a quality microbiology perspective.

Reviewer's Signature Denise Miller -A Digitally signed by Denise Miller -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Denise Miller -A, 0.9.2342.19200300.100.1.1=2000286872 Date: 2015.03.20 06:31:29 -04'00'

Denise A. Miller
Microbiologist, OPF/DMA/Branch II

Endorsement Block Neal J. Sweeney -A Digitally signed by Neal J. Sweeney -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1649105587, cn=Neal J. Sweeney -A Date: 2015.03.20 09:44:17 -04'00'

Neal J. Sweeney, Ph.D.
Senior Microbiologist, OPF/DMA/Branch II

Product Quality Microbiology Review

06 January 2014

NDA: **205-747/N000**

Drug Product
Proprietary: Humalog [redacted] KwikPen
Non-proprietary: Insulin Lispro Injection (rDNA Origin)

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
10 May 2013	10 May 2013	14 May 2013	16 May 2013
6 September 2013	9 September 2013	--	--

Submission History (for 2nd Reviews or higher) - NA

Applicant/Sponsor
Name: Eli Lilly and Company
Address: Lilly Corporate Center
Indianapolis IN 46285
Representative: Joerg Pfeifer, Ph.D.
Advisor, U.S. Regulatory Affairs
Telephone: (317) 276-2146

Name of Reviewer: Denise A. Miller

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: New drug application

2. SUBMISSION PROVIDES FOR: The manufacture of a 200 unit/mL formulation.

3. MANUFACTURING SITE:
Lilly France
2, rue du Colonel Lilly
67640 Fegersheim France

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Dosage Form: Sterile solution for injection (b) (4)
- Route of Administration: Subcutaneous injection
- Strength/Potency: 200 Units/mL

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Treatment of hyperglycemia

B. SUPPORTING/RELATED DOCUMENTS:
NDA 20-563 Humalog 100 units/mL LOA dated 30 April 2013
NDA 21-018 Humalog mix 50/50
NDA 21-017 Humalog mix 75/25
DMF 16307 " (b) (4)
Fegersheim, France" Complete update 05 September 2013. Reviewed by NDMS on 1 October 2013 and was adequate in support of subject NDA.

C. REMARKS:
1) Application was in e-CTD format.
2) This is a new formulation of an existing FDA approved product. The manufacturing/filling of this product is identical to the existing product.
3) Quality microbial questions were included in the 74-day letter to which the sponsor responded on 9 September 2013.

filename: N205747N000R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for approval from a quality microbiology perspective.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - NA

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is (b) (4) The cartridges fit into an injector pen.

B. Brief Description of Microbiology Deficiencies – None identified in the information provided.

C. Assessment of Risk Due to Microbiology Deficiencies – NA

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**
(If yes, provide a brief description and a reference to the page where the precedent is discussed in depth)

III. Administrative

A. Reviewer's Signature _____
Denise A. Miller
Microbiologist, OPS/NDMS

B. Endorsement Block_____
Bryan S. Riley, Ph.D.
Senior Microbiologist, OPS/NDMS

C. CC Block
N/A

Product Quality Microbiology Assessment

This drug is an FDA approved product manufactured under NDA 20-563 at 100 units/mL. This is the same product but at a higher concentration (200 units/mL). The new concentration (b) (4) referenced NDA 20-563 in addition to DMF 016307. DMF 016307 was reviewed and was adequate in support of NDA 205-747/000.

This review is limited to the method suitability testing for sterility and endotoxin, (b) (4) and container closure integrity.

Reviewer note: The KwikPen dosing dial was modified (b) (4) This modification has no impact to the sterility assurance of the product and is being reviewed by CDRH.

(b) (4)

(b) (4)

-ACCEPTABLE-

Reviewer comment: (b) (4)

Container Closure Integrity:

The container closure integrity (CCI) was evaluated with a fluorescein dye ingress method. The sponsor submitted data (b) (4)

-ACCEPTABLE-

Reviewer comment: The CCI testing supports the integrity of the container closure.

(b) (4) **validation**:

Both NDAs 21-018 and 21-017 were referenced (b) (4) under those NDAs (b) (4)

[redacted] The [redacted] validation could not be found in the electronic information in these two NDAs and was requested to be submitted to the subject NDA in the 74 day letter.

Method suitability for Sterility test:
Method suitability for the sterility test could not be located in the submission. The test was requested in the 74 day letter.

Method suitability for the Endotoxin test:
The method suitability for the endotoxin test could not be located in the submission. The test was requested in the 74 day letter.

Information request in the 74 day letter:

1) *The method suitability study for the endotoxin testing could not be located in application section 3.2.P.5.2. Provide either the location in the submission, the report, or a justification of why the study was not performed.*
2) *The method suitability for the sterility testing could not be located in application section 3.2.P.5.2. Provide either the location in the submission, the report, or a justification of why the study was not performed.*
3) *It is acknowledged that NDA 21-017 and 21-018 includes the [redacted] lispro solution at 200 units/mL but the [redacted] validation studies could not be located in the electronic information of these NDAs. Submit the [redacted] validation report to this NDA.*

Review of Responses:
Item 1: The method suitability for the endotoxin test was provided for the kinetic chromogenic method and follows USP <85>. The sponsor pools three units for testing [redacted] The product is tested [redacted]

-ACCEPTABLE-

Reviewer comment: The endotoxin method is suitable for this new formulation.

Item 2: The method suitability for the sterility test was provided [redacted] and follows USP <71>.

-ACCEPTABLE-

Reviewer comment: The sterility test method is suitable for this new formulation

Item 3: The sponsor provided the (b) (4) validation for Insulin Lispro U-200 (Humalog U200), Manufactured and Filled (b) (4)

-ACCEPTABLE-

Reviewer comment: The (b) (4) validation provided was supportive (b) (4)

P.8 Stability

P.8.1 Stability Summary and Conclusion

MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS

Long term: 2-8°C for 36 months
Accelerated: 30°C for 3 months
Simulated in-use patient conditions: (b) (4) at 30°C

Shelf life of 2-8°C 36 months and for patient use 28 days at 30°C.

P.8.2 (b) (4)

P.8.3 Stability Data

Three (b) (4) L commercial scale batches A835149, A835151, and A835153 were manufactured (b) (4) at the Fegersheim Lilly France site and placed on stability. These have completed up to the 18 months time point. These batches used a (b) (4) cartridge plunger (b) (4)

Three Primary stability lots A915537, A915538, and A915540 were manufactured (b) (4) at commercial (b) (4) L scale at the commercial site using the proposed container closure. These lots have completed 12 months of stability testing.

Sterility, endotoxin and [redacted] (b) (4) testing time points are at 0, 24, and 36 months. All quality microbiology tests to date meet the acceptance criteria.

-ADEQUATE-

REVIEWER COMMENT – The stability program is adequate from a quality microbiology perspective.

A APPENDICES - NA

R REGIONAL INFORMATION

R.1 Executed Batch Record

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

A. PACKAGE INSERT – multiuse [redacted] (b) (4) solution. The drug product is to be administered using a pen injector; not to be diluted.

-ADEQUATE-

Reviewer's Comment – There are no quality microbiology concerns for the labeling.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: None

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/s/

DENISE A MILLER
01/21/2014

BRYAN S RILEY
01/21/2014
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 205-747 **Applicant:** Eli Lilly **Letter Date:** 10 May 2013

Drug Name: Humalog (lispro insulin) injection 200 units/mL **NDA Type:** 505(b)(1) **Stamp Date:** 10 May 2013

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	√		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	√		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	√		(b) (4) validation not included – see comments DMF 16307 is referenced for the other controls
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		√	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	√		(b) (4) CCI studies were submitted.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	√		
7	Has the applicant submitted the results of analytical method verification studies?		√	No B/F or E/I studies
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	NA		
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?	NA		Product will not be diluted
10	Is this NDA fileable? If not, then describe why.	√		

Additional Comments:

1) DMF 16307 is referenced for CMC information that is not product specific. Product specific information was to be included in the NDA submission.
2) NDA 20-563 is cross referenced.
3) Letter of authorizations to Drug Master Files for the syringes and stoppers was included in the application.
4) (b) (4) validation was not performed for this application. The sponsor stated that (b) (4) is validated for the 200 units/mL concentration in NDA 21-017 and NDA 21-018. The validation report was not located in the electronic file of these NDAs.

Information request:

1) The method suitability study for the endotoxin testing could not be located in application section 3.2.P.5.2. Provide either the location in the submission, the report, or a justification of why the study was not performed.
2) The method suitability for the sterility testing could not be located in application section 3.2.P.5.2. Provide either the location in the submission, the report, or a justification of why the study was not performed.
3) It is acknowledged that NDA 21-017 and 21-018 includes the (b) (4) lispro solution at 200 units/mL but the (b) (4) validation studies could not be located in the electronic information of these NDAs. Submit the (b) (4) validation report to this NDA.

Denise A. Miller — Date
Microbiologist, OPS/NDMS

Bryan S. Riley, Ph.D. — Date
Senior Microbiologist, OPS/NDMS

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

/s/

DENISE A MILLER
06/12/2013

BRYAN S RILEY
06/13/2013
I concur.