

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125521Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Colleen Thomas, Ph.D.
ACTING BRANCH CHIEF: Patricia Hughes, Ph.D.

BLA: 125521
Applicant: Eli Lilly and Company
US License Number: 1891
Submission Reviewed: Original BLA
Product: ixekizumab (TALTZ™)
Indication: Plaque psoriasis
Dosage Form: Sterile, preservative-free solution for injection (80 mg/ml). Supplied in pre-filled syringes and pre-filled (b) (4)
DP Manufacturing Site: Eli Lilly and Company, Indianapolis, IN (FEI: 1819470)
FDA Receipt Date: 23 March 2015
Action Date: 23 March 2016

Conclusion and Approvability Recommendation

The application was reviewed for microbial control of the drug product manufacturing process and for drug product sterility assurance. Although no deficiencies have been found thus far that would preclude approval, additional information is needed in order to complete the review. Sections that require additional information are marked as “information request pending” in the review memo. Two post-marketing commitments have been identified thus far.

Product Quality Microbiology PMCs

1. Perform a repeat microbial retention study for the (b) (4) using a suitable surrogate solution. Alternatively, perform the study using a modified process, a modified formulation, or a reduced exposure time for the challenge organism. Provide the summary data, the associated report, and justification for any modifications to the study. If any (b) (4) parameters are changed as a result of the study, update the BLA file accordingly.
2. Provide data from two additional commercial drug product batches to support the maximum hold time for pooled drug substance. The hold time study should include the maximum hold time at (b) (4) followed by the maximum hold time under ambient conditions. Provide data from two additional commercial drug product batches to support the maximum hold time for drug product (b) (4). The supporting data should include bioburden and endotoxin testing results from samples taken (b) (4). Data from process simulations performed with media may be provided *in lieu* of data from drug product batches.

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	23 March 2015	Original BLA
0002	8 May 2015	Amendment - DMF LOAs
0010	8 July 2015	Amendment - question 10 (endotoxin testing)
0015	21 August 2015	Amendment - response to LCM package
0022	26 October 2015	Amendment - question 3 (endotoxin specification)
Not yet available	30 October 2015	Amendment - endotoxin specification

Module 3.2.P

P.1 Description and Composition of the DP

The drug product (DP) is a sterile, non-pyrogenic, preservative-free 80 mg/1 ml solution for subcutaneous injection. The DP composition is shown in the table below, which was provided in section P.1.

Table 3.2.P.1.1-1 Composition of Ixekizumab Injection, 80 mg/1 mL

Ingredient	Quantity(mg) per Syringe	Function	Reference to Standards
Active Ingredient			
Ixekizumab	80	Active Ingredient	Internal Standard: See Section S.4.1. Specifications
Other Ingredients			
Sodium Citrate Dihydrate	5.11	(b) (4)	USP, Ph.Eur., JP
Citric Acid Anhydrous	0.51	(b) (4)	USP, Ph.Eur., JP
Sodium Chloride	11.69	(b) (4)	USP, Ph.Eur., JP
Polysorbate 80	0.30	(b) (4)	USP, Ph.Eur., JP
Water for Injection	(b) (4)	(b) (4)	USP, Ph.Eur., JP

The DP primary container closure system consists of a 1 ml glass syringe barrel system (which includes a staked-in needle and rigid needle shield) closed with a plunger stopper. The components are described in more detail in section P.7. The DP in the primary container closure system is referred to as a (b) (4) syringe (b) (4) (b) (4) device used for patient administration.



Conclusion

1. The application was reviewed for microbial control of the drug product manufacturing process and for drug product sterility assurance. Although no deficiencies have been found thus far that would preclude approval, additional information is needed in order to complete the review. Sections that require additional information are marked as “information request pending” in the review memo. Two post-marketing commitments (listed at the beginning of this memo) have been identified thus far.
2. Product quality aspects other than microbiology should be reviewed by OBP and CDRH.
3. No inspection follow-up items were identified.

DP Quality Microbiology Information Requests Sent

8 May 2015: response in sequence 0002

1. Letters of Authorization (LOAs) for the Drug Master Files (DMFs) listed in Table 3.2.P.7.3-1 were not provided. The application indicates that this information is located in Module 1, Section 1.4.2, but Section 1.4.2 is missing from the BLA file. Please provide the missing information and ensure that the LOAs clearly indicate the location of the relevant information within the DMFs.
2. Table 3.2.P.5.3-2 references a report (LY2439821 Ixekizumab Rabbit Pyrogen and Bacterial Endotoxins Test Method Equivalency Data) that is missing from the BLA file. Please provide the missing information. In addition, compare the dosage used for the rabbit pyrogen tests listed in Table 3.2.P.5.3-1 to the dosage used in humans and provide the rabbit pyrogen test reports.

12 August 2015 - mid-cycle communication: response in sequence 0015

1. The microbial retention study did not consider the effect of the drug product on the challenge organism [REDACTED] (b) (4) [REDACTED] the product formulation or test process should be identified and the microbial retention study should be repeated accordingly. Possible re-test strategies include reduced exposure time, modification of a test parameter (e.g., temperature), or modification of the product formulation (further pH adjustment, placebo, etc.).
2. Low endotoxin recovery affects the drug substance, and endotoxin recovery results from three different batches of drug product were inconsistent. Endotoxin release testing strategies for the drug substance and drug product must be determined prior to approval.

19 October 2015: response in sequence 0022

1. The proposed drug product endotoxin specification does not include a safety margin over the specified limit for parenteral drugs (5.0 EU/kg). Please tighten the endotoxin specification for ixekizumab drug substance and drug product to include a 2-fold safety margin.

29 October 2015: response provided by e-mail 30 October 2015

1. The drug product endotoxin specification does not include a safety margin for the worst-case dose (160 mg). Due to the inherent variability of the endotoxin detection methods, please tighten the endotoxin specification for ixekizumab drug product to include a 2-fold

safety margin for the worst-case dose. Tighten the drug substance endotoxin specification accordingly.

Colleen
Thomas -S

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Food and Drug Administration
Center for Drug Evaluation and Research
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10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 10/30/2015
To: Administrative File, STN 125521/0
From: Bo Chi, Ph.D., CDER/OPQ/OPF/DMA
Endorsement: Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA
Subject: New Biologic License Applications (BLA)
Applicant: Eli Lilly and Company
US License: 1891
Facility: Eli Lilly S.A. – Irish Branch
Kinsale, County Cork, Ireland
FEI: 3002806888
Product: Ixekizumab
Dosage: 80mg/1 mL, solution for subcutaneous injection
Indication: Patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy
PDUFA date: March 23, 2016

Recommendation: The drug substance part of this BLA is recommended for approval from product quality microbiology perspective, pending the review of drug substance endotoxin spiking and hold study data. The pending data will be reviewed in an addendum to this review memo.

Review Summary

Eli Lilly has submitted this Biologics License Application (BLA) for ixekizumab to treat patients with moderate-to-severe plaque psoriasis. The drug substance (DS) is manufactured at the Eli Lilly S.A. facility at Kinsale, Ireland. The drug product (DP) is manufactured at Eli Lilly and Company in Indianapolis, IN. The application contains CMC information in an eCTD format.

This review contains the assessments of the manufacturing process of ixekizumab drug substance from microbiology perspective.

Assessment

Drug Substance (3.2.S)

General Information (3.2.S.1)

Ixekizumab is a humanized immunoglobulin G4 (IgG4) subtype monoclonal antibody against the pro-inflammatory cytokine interleukin-17A (IL-17A). [REDACTED] (b) (4)

Conclusion

- I. The drug substance part of this BLA is recommended for approval from product quality microbiology perspective, pending the review of drug substance endotoxin spiking and hold study data. The pending data will be reviewed in an addendum to this review memo.
- II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the OBP reviewer.
- III. See panorama for GMP status of the relevant facilities.

Cc: Chi
Hughes
Brown

Primary reviewer signature

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A

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Secondary reviewer signature

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