

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125476Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



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

Date: 04/16/2014
To: Administrative File, STN 125476
From: Steven Fong, Ph.D., Reviewer, CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D. Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Original BLA
US License: 1898
Applicant: Takeda Pharmaceuticals USA, Inc.
Facility: (b) (4)
Product: Vedolizumab
Dosage: 300 mg per dose administered by intravenous infusion
Indication: Treatment for moderate to severe active ulcerative colitis or Crohn's Disease
Due date: PDUFA goal date: 05/20/2014

Recommendation on Approvability – The BLA, as amended, was reviewed from a microbiology quality perspective and is recommended for approval. The current assessment provides an Addendum to an initial Review submitted to DARRTS 11/26/2013. The Addendum considers seven Amendments, 125476/0.43, 125476/0.53, 125476/0.58, 125476/0.61, 125476/0.68, and 125476/0.78, and 125476/0.80, that contained information regarding container closure integrity testing, stopper (b) (4) bulk hold period, (b) (4) (b) (4). Three PMCs are listed at the end of the Addendum.

The current assessment represents an Addendum to an initial Microbiology Quality Review for STN 125476 submitted to DARRTS 11/26/2013. The initial Review did not include a concluding recommendation regarding BLA approvability because the following were not provided by the Sponsor prior to the GRMP review deadline:

- (b) (4)
- (b) (4)
- Data for CCI validation studies performed with positive controls consistent with method sensitivity.
- Justification for the use of a (b) (4) configuration for validation of stopper (b) (4) that was different than the configuration used for production.
- Submission of a bulk drug product hold period, and data from commercial scale studies justifying the hold period.

27 Pages Have Been Withheld In Full As b4 (CCI/TS)
Immediately Following This Page

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

/s/

STEVEN FONG

04/16/2014

Recommended for approval from a microbiology quality standpoint.

PATRICIA F HUGHES TROOST

04/16/2014



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 08 April, 2014
To: Administrative File, STN 125476/0
From: Reyes Candau-Chacon, PhD. Reviewer, OC/OMPQ/DGMPA/BMAB
Through: Patricia Hughes, Ph.D., Team Leader, OC/ OMPQ/DGMPA/BMAB
Subject: Addendum to New Biologic License Application (BLA) to address potential Low Endotoxin Recovery in the formulated drug substance and to review risk assessment and validation protocol for microbial quality of maximum (b) (4) hold times

US License: 1898

Applicant: [Redacted] (b) (4)
Facilities: [Redacted]

Product: ENTYVIO (vedolizumab)

Dosage: Sterile lyophilized powder for reconstitution with SWFI to be delivered as injectable intravenous (IV) infusion in 20 mL glass vials containing 300 mg of vedolizumab

Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNF α) antagonist.

Due date: 20 May 2014

Recommendation for Approvability: The drug substance part of BLA 125476, as amended, is recommended for approval from a microbial control and microbiology product quality perspective with the following post-marketing commitments:

To conduct a maximum hold time study for the formulated drug substance using representative containers by July 2014. If low endotoxin recovery is found in the formulated drug substance during the maximum hold time study, either hold times will be reevaluated or an alternative method to measure endotoxin in formulated drug substance will be developed and validated by December 31, 2014.

To verify the endotoxin recovery results for the [Redacted] (b) (4) and establish action limits for this solution once the results are confirmed by a validated method. If low endotoxin recovery is found, maximum hold times [Redacted] (b) (4)

^{(b) (4)} The activities associated to this commitment will be completed and the final report will be submitted on or before 31 December 2014

(b) (4)



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

/s/

REYES CANDAU-CHACON
04/14/2014

PATRICIA F HUGHES TROOST
04/14/2014



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 12 December, 2013
To: Administrative File, STN 125476/0
From: Reyes Candau-Chacon, PhD. Reviewer, OC/OMPQ/DGMPA/BMAB
Through: Patricia Hughes, Ph.D., Team Leader, OC/ OMPQ/DGMPA/BMAB
Subject: New Biologic License Application (BLA)
US License: 1898
Applicant: Takeda Pharmaceuticals USA, Inc.
Facilities: [REDACTED] (b) (4)
Product: ENTYVIO (vedolizumab)
Dosage: Sterile lyophilized powder for reconstitution with SWFI to be delivered as injectable intravenous (IV) infusion in 20 mL glass vials containing 300 mg of vedolizumab
Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNF α) antagonist.
Due date: 18 February 2014

Recommendation for Approvability: The drug substance part of BLA 125476, as amended, is recommended for approval from a microbial control and microbiology product quality perspective with the following post-marketing commitment:

The sponsor commits to providing a risk assessment and validation protocol for microbial quality of maximum [REDACTED] (b) (4) hold times; the validation protocol will identify the [REDACTED] (b) (4) hold steps to be qualified, number of runs, and proposed action limits. The risk assessment and validation protocol will be submitted to the Agency as a Prior-Approval Supplement by March 30, 2014; the results from the validation study will be submitted to the Agency in the following Annual Report.

33 Pages Have Been Withheld As b4 (CCI/TS) Immediately Following This Page

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

/s/

REYES CANDAU-CHACON
12/12/2013

PATRICIA F HUGHES TROOST
12/12/2013



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

Date: 11/26/2013
To: Administrative File, STN 125476
From: Steven Fong, Ph.D., Reviewer, CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D. Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Original BLA
US License: 1898
Applicant: Takeda Pharmaceuticals USA, Inc.
Facility: (b) (4)
Product: Vedolizumab
Dosage: 300 mg per dose administered by intravenous infusion
Indication: Treatment for moderate to severe active ulcerative colitis or Crohn's Disease
Due date: PDUFA goal date: 02/18/2014

Recommendation on Approvability – The approvability of the drug product portion of this application is pending until the following have been resolved. The Review will be amended when the additional information is received.

- Endotoxin spiking and recovery data for undiluted drug product.
- Rabbit pyrogen test results for three drug product lots.
- Data for microbial and dye ingress container closure integrity validation studies (b) (4) and positive controls consistent with method sensitivity.
- Justification for the use of a (b) (4) for validation of stopper (b) (4) that was different than the configuration used for production.
- Submission of a bulk drug product hold period, and data from commercial scale studies justifying the hold period.
- Readjustment of the endotoxin acceptance criterion for drug product (b) (4)
- A more detailed description of shipping validation conducted under worst case conditions, and the conditions to be used for commercial shipment.
- Implementation of container closure integrity testing in lieu of (b) (4) for the post-marketing stability protocol annually and at expiry.

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

/s/

STEVEN FONG

11/26/2013

Responses to information requests regarding microbiology quality were not received prior to Review submission. Approvability of the drug product portion of the application is pending until the requested information has been received and assessed.

PATRICIA F HUGHES TROOST

11/26/2013