CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125476Orig1s000

CHEMISTRY REVIEW(S)

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

APPLICATION INFORMATION

PDUFA Action Date: May 20, 2014

Applicant Name: Takeda Pharmaceuticals U.S.A.
STN: STN 125476 (New BLA)
Product: Vedolizumab for Injection
(Experimental designation during clinical trials: MLN0002)

Short summary of application: New BLA proposing manufacture of Vedolizumab drug substance at [redacted] (b) (4) and Vedolizumab drug product manufacture at [redacted] (b) (4). The submission proposes other facilities for testing and master cell bank manufacture and storage as listed below.

This is the second TB-EER request that is due one month before the PDUFA date. One new facility, [redacted] (b) (4) (item 14), has been added to the list of testing laboratories. The additional lab will perform the rabbit pyrogen assay as a DP release test.

FACILITY INFORMATION

DRUG SUBSTANCE MANUFACTURING AND TESTING FACILITIES

(1) Firm Name: [redacted] (b) (4)
Address:

FEI: [redacted] (b) (4)
Short summary of manufacturing activities:

- Drug substance manufacture.
- Drug substance release testing except for microbiology (endotoxin, bioburden) testing and binding assay.
- Drug substance stability testing except for microbiology (endotoxin, bioburden) testing and binding assay.
- Manufacture and storage of working cell bank.

This site was inspected by CDER-OMPQ from [redacted] (b) (4) and classified VAI. This was a Pre-Liscensing inspection for vedolizumab routine and a CGMP surveillance inspection covering biotech drug substance manufacturing operations. The CBI profile was updated and is acceptable.

(2) Firm Name: [redacted] (b) (4)

Address: (b) (4)

FEI: (b) (4)

Short summary of manufacturing activities:

- Drug substance microbiology (endotoxin, bioburden) release testing.
- Drug substance microbiology (endotoxin, bioburden) stability testing.

This site was inspected by (b) (4)-DO from (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering biotech drug substance manufacturing operations as well as microbiological testing at the (b) (4) (b) (4) The CBI profile was updated and is acceptable.

(3) Firm Name: (b) (4)
Address:

FEI: (b) (4)

Short summary of manufacturing activities:

- Drug substance binding assay release testing.
- Drug substance binding assay stability testing.

This site was inspected by IOG from (b) (4) and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug substance & drug product testing operations. The CTL profile was updated and is acceptable.

(4) Firm Name: (b) (4)
Address:

FEI: (b) (4)

Short summary of manufacturing activities:

- In-process (b) (4).

This site was inspected by (b) (4) from (b) (4) and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug substance testing operations. The CTL profile was updated and is acceptable.

(5) Firm Name: (b) (4)
Address:

FEI: (b) (4)

Short summary of manufacturing activities:

- In-process testing for (b) (4).

- In-process testing for (b) (4).

This site was inspected by (b) (4) from (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering cell banking operations and biotech drug substance testing operations. The CTL profile was updated and is acceptable.

(6) Firm Name: (b) (4)
Address:

FEI: (b) (4)
Short summary of manufacturing activities:
- (b) (4).

This additional testing is of low significance from a GMP perspective. Therefore, an evaluation of this site is not required.

(7) Firm Name: (b) (4)
Address:

FEI: (b) (4)
Short summary of manufacturing activities:
- Storage of master cell bank.

MCB and WCB storage facilities are not routinely inspected for the sole purpose of covering these operations. An evaluation of this site is not required.

(8) Firm Name: (b) (4)
Address:

FEI:
Short summary of manufacturing activities:
- Storage of master cell bank.

MCB and WCB storage facilities are not routinely inspected for the sole purpose of covering these operations. An evaluation of this site is not required.

(9) Firm Name: (b) (4)
Address:

FEI: (b) (4)
Short summary of manufacturing activities:
- Manufacture of master cell bank.

- Manufacture of working cell bank.

This site was inspected by (b) (4) from (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering cell banking operations and biotech drug substance testing operations. The CTX profile was updated and is acceptable.

(10) Firm Name: (b) (4)
Address:

FEI: (b) (4)
Short summary of manufacturing activities:

- Drug product manufacture.
- Primary packaging.
- Drug product release testing (including particulates, endotoxin, and sterility).
- Drug product in-process testing.

In a 11/26/2013 memo, BMAB waived the PLI for this facility. This site was inspected by (b) (4) from (b) (4) and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug product manufacturing operations. The SVL profile was updated and is acceptable.

(11) Firm Name: (b) (4)

Address:

FEI: (b) (4)
Short summary of manufacturing activities:

- Labeling.
- Secondary packaging.

This site was inspected by (b) (4) from (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering drug product packaging operations. The SVL profile was updated and is acceptable.

(12) Firm Name: (b) (4)
Address:

FEI: (b) (4)
Short summary of manufacturing activities:

- Drug product release testing except for particulates, endotoxin, sterility and binding assay.
- Drug product stability testing except for binding assay.

This site was inspected by (b) (4) from (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering biotech drug substance manufacturing operations. (b) (4) has confirmed that the CTL profile was updated and is acceptable.

(13) Firm Name: (b) (4)
Address:

FEI: (b) (4)
Short summary of manufacturing activities:

- Drug product release binding assay.
- Drug product stability binding assay.

This site was inspected by IOG from (b) (4) and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug substance & drug product testing operations. The CTL profile was updated and is acceptable.

(14) Firm Name: (b) (4)
Address:

FEI: (b) (4)

- DP endotoxin release testing by the rabbit pyrogen method.

This site was inspected by (b) (4) from (b) (4) and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug substance testing operations. The CTL profile was updated and is acceptable.

OVERALL RECOMMENDATION

There are no pending or ongoing compliance actions that prevent approval of this application.

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/s/

CHRISTINA A CAPACCI-DANIEL
05/02/2014

BLA STN 125476
Addendum

Vedolizumab

Manufacturer: Takeda Pharmaceuticals, Inc.

Primary Reviewer: Qing Zhou, Ph.D.

Team Leader: Rashmi Rawat, Ph.D.

Division of Monoclonal Antibodies

Product Quality Review Data Sheet

(Includes only information updated since the initial review was finalized on Nov 20, 2013)

1. **BLA#** STN 125476-0

2. **REVIEW #:** 2 (Addendum 1)

3. **REVIEW DATE:** February 20, 2014

4. **REVIEWER(s):** Qing Zhou, Ph.D.
Rashmi Rawat, Ph.D., Team Leader

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS SINCE THE FINALIZATION OF THE INITIAL REVIEW:**

Communication/Documents	Date
Information Request-6	11-21-2013
Teleconference	11-25-2013

6. **SUBMISSION(S) REVIEWED UNDER THIS ADDENDUM:**

Submission(s) Reviewed	Document Date
STN 125476/47	11-29-2013
STN 125476/48	12-2-2013
STN 125476/51	12-9-2013
STN 125476/59	1-20-2014
STN 125476/65	2-10-2014

10. **STRENGTH/POTENCY:**

- The Entyvio (vedolizumab) Drug Product is supplied at 300 mg/vial in a 20 ml vial.
- Potency is defined as the percent activity relative to the reference standard, using a cell based binding assay that uses flow cytometry to measure the ability of vedolizumab to bind to α4β7-expressing HuT 78 cells, and a cell based adhesion assay that uses fluorescence absorbance to measure the ability of vedolizumab to block the adherence of α4β7-expressing RPMI8866 cells to the surface of mucosal addressin cell adhesion molecule-1 coated plates.
- Potency specification is (b) (4) relative to the reference standard as measured by the binding and adhesion assays.
- Dating period for vialed drug product is 36 months when stored at 5 ± 3°C and protected from light.

17. **ADMINISTRATIVE**

A. Signature Block

Qing Zhou, Ph.D., Product Quality Reviewer, Division of Monoclonal Antibodies

Rashmi Rawat, Ph.D., Team Leader, Division of Monoclonal Antibodies

Sarah Kennett, Ph.D., Review Chief, Division of Monoclonal Antibodies

B. CC Block
Clinical Division (DGIEP) BLA RPM: Kevin Bugin

Division of Monoclonal Antibodies File: BLA STN 125476

SUMMARY OF QUALITY UNIT ASSESSMENT

The following minor CMC issues were not resolved by the due date for the finalization of the primary review (Nov 20, 2013).

1. Revision of the proposed acceptance criteria for the potency in vedolizumab drug substance and drug product lot release and stability specifications to (b) (4) (or (b) (4)) relative to reference standard"
2. Revision of the proposed acceptance criteria for potency assays for the January 2014 reference standard requalification to reflect a requirement that the results be similar to the values obtained at the time of the initial qualification
3. Reinstate the commercial host cell protein ELISA method for use in vedolizumab drug substance lot release testing until a robust assay is developed and validated.
4. Revision of the post-approval stability protocols for vedolizumab drug substance and drug product to include the adhesion assay as a test method for the potency

The sponsor's responses to these minor CMC issues were reviewed and found to be acceptable. A review of the sponsor's responses is provided in this addendum.

I. Primary Reviewer Summary Recommendation

The data submitted in this Biologics License Application support the conclusion that the manufacture of Entyvio (vedolizumab) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. It is recommended that Entyvio (vedolizumab) be approved for human use.

I recommend an approval of the proposed release specifications for vedolizumab drug product and drug substance. Takeda will reassess release specifications after ≥ 30 lots of vedolizumab drug substance and drug product have been manufactured using the commercial process.

I recommend an expiry period of 36 months for vedolizumab drug product when stored at 2-8°C.

I recommend an expiry period of (b) (4) for vedolizumab drug substance when stored at (b) (4)

The stability protocols are acceptable and the updated stability data will be reported to the BLA in the Annual Report.

II. List of Deficiencies to Be Communicated

There are no CMC-related deficiencies precluding approval of this BLA.

III. List of Post-Marketing Commitments

1. To perform additional testing to confirm the monoclonality of the MCB. The study results will be provided by December 31, 2014.

2. To add osmolality testing to the vedolizumab drug product lot release specification. The analytical procedure, qualification report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be provided by September 30, 2014.

3. To add polysorbate 80 testing to the vedolizumab drug product lot release specification. The analytical procedure, qualification report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be provided by December 31, 2014.

4. To develop a non-reducing SDS-based assay that is capable of providing quantitative data for evaluation of size-related impurities and to implement this assay in the release and stability programs for vedolizumab DS and DP after sufficient data have been acquired to set appropriate acceptance criteria. The analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be provided by February 29, 2016

5. To develop a validated, sensitive, and accurate assay for the detection of binding antibodies to vedolizumab, including procedures for accurate detection of binding antibodies to vedolizumab in the presence of vedolizumab levels that are expected to be present in the serum or plasma at the time of patient sampling. The analytical procedure and validation report will be provided by December 31, 2014

6. To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to vedolizumab, including procedures for accurate detection of neutralizing antibodies to vedolizumab in the presence of vedolizumab levels that are expected to be present in the serum or plasma at the time of patient sampling. The analytical procedure and validation report will be provided by 31 December, 2014.

7. To develop and validate a product-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential host cell proteins compared to the current assay and to implement this assay in the vedolizumab drug substance release program. The analytical procedure, validation report, analysis of the approximate percent of HCP coverage, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be provided by 31 December, 2017.

8. To re-evaluate vedolizumab drug substance lot release and stability specifications after 30 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by December 31, 2016.

9. To re-evaluate vedolizumab drug product lot release and stability specifications after 30 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by December 31, 2018.

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/s/

QING ZHOU
02/20/2014

RASHMI RAWAT
02/20/2014

SARAH B KENNETT
02/20/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies

The Quality Team Leader's Executive Summary

From:	**Rashmi Rawat, Ph.D.** **Division of Monoclonal Antibodies (DMA)**
Through:	**Sarah Kennett, Ph.D., Review Chief** **Kathleen A. Clouse, Ph.D., Director** **DMA/OBP/OPS/CDER**
BLA Number:	**125476/125507**
Product:	**Vedolizumab (Entyvio)**
Sponsor:	**Takeda Pharmaceuticals, U.S.A., Inc.**
Date of Review:	**November 25, 2013**
Date of CDTL Memo:	**January 21, 2013**

Reference ID: 3414618

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, recommends approval of STN 125476/125507 for vedolizumab (Entyvio) manufactured by Takeda Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of vedolizumab (Entyvio) is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert.

II. APPROVAL LETTER INFORMATION

Under this license, you are approved to manufacture the vedolizumab drug substance at [redacted] (b) (4) Vedolizumab (Entyvio) drug product will be manufactured at [redacted] (b) (4).

The dating period for vedolizumab drug product shall be 36 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of [redacted] (b) (4)

The dating period for vedolizumab drug substance shall be [redacted] (b) (4) from the date of manufacture when stored at [redacted] (b) (4)

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

1. To perform additional testing to confirm the monoclonality of the MCB. The study results will be provided by December 31, 2014.

2. To add osmolality testing to the vedolizumab drug product lot release specifications. The analytical procedure, qualification report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30 by September 30, 2014.

3. To add polysorbate 80 testing to the vedolizumab drug product lot release specifications. The analytical procedure, qualification report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30 by December 31, 2014.

4. To develop a non-reducing SDS-based assay that is capable of providing quantitative data for evaluation of size-related impurities and to implement this assay in the release and stability programs for vedolizumab DS and DP after sufficient data have been acquired to set appropriate acceptance criteria. Takeda will provide a date by which this commitment can be completed.

5. To develop a validated, sensitive, and accurate assay for the detection of binding

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antibodies to vedolizumab, including procedures for accurate detection of binding antibodies to vedolizumab in the presence of vedolizumab levels that are expected to be present in the serum or plasma at the time of patient sampling. Takeda will provide a date by which this commitment can be completed.

6. To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to vedolizumab, including procedures for accurate detection of neutralizing antibodies to vedolizumab in the presence of vedolizumab levels that are expected to be present in the serum or plasma at the time of patient sampling. Takeda will provide a date by which this commitment can be completed.

7. To develop and validate a product-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential host cell proteins compared to the current assay and to implement this assay in the vedolizumab drug substance release program. Takeda will provide a date by which this commitment can be completed.

8. To re-evaluate vedolizumab drug substance lot release and stability specifications after 30 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by December 31, 2016.

9. To re-evaluate vedolizumab drug product lot release and stability specifications after 30 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by December 31, 2018.

IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

None

V. EXECUTIVE SUMMARY

A. Description of vedolizumab (Entyvio) drug substance and drug product

Vedolizumab is a recombinant, humanized, immunoglobulin IgG1, κ monoclonal antibody. It is directed to $\alpha_4\beta_7$ integrin, which is expressed on T and B cells.

Vedolizumab drug product (DP) is supplied as a sterile, lyophilized formulation for injection in a 20 mL single use vial. Each vial contains 300 mg (b) (4) of vedolizumab formulated in (b) (4) histidine (b) (4) L-histidine monohydrochloride), (b) (4) L-arginine hydrochloride, (b) (4) sucrose and (b) (4) polysorbate 80. Vedolizumab drug product is reconstituted with 4.8 mL of sterile water for injection (USP) to yield a solution with an approximate pH of 6.3. The reconstitution time for lyophilized DP is ≤ 30 minutes. The lyophilized DP is a white to

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off white color cake, whereas the reconstituted DP solution is clear to opalascent, colorless to slightly yellow, and free of visible particulates.

The recommended storage condition for vedolizumab drug product is 2-8°C, protected from light.

The primary packaging components for vedolizumab drug product consist of a USP/Ph. Eur. Type 1, 20 ml clear [redacted] (b) (4) glass vial that is sealed with a 20 mm, gray [redacted] (b) (4) rubber stopper with a [redacted] (b) (4). Vials are sealed with a 20 mm aluminum seal with a plastic cap.

Drug product does not contain preservatives. Drug product vials are single-dose and should be discarded after use.

The reconstituted vedolizumab DP is diluted into 250 mL of sterile 0.9% saline infusion bags prior to administration.

The vedolizumab drug product vial does not contain any overages.

A claim for a categorical exclusion from the Environmental Assessment (EA) requirement has been submitted under 21CFR section 25.31(c), which states that any application for marketing approval of a biologic product for substances that occur naturally in the environment, or supplement to such an application, is categorically excluded and ordinarily does not require an EA or an Environmental Impact Statement when there is not a significant alteration of the concentration or distribution of the substance, its metabolites or degradation product in the environment. The company states that, to their knowledge, no extraordinary circumstances exist, as described in 21 CFR 25.21, that would result in significant impact to the environment from the discharge of this substance. There is no indication that additional environmental information is warranted. The claim of categorical exclusion is deemed acceptable.

B. Clinical Trial Information

Vedolizumab is intended to be used for the treatment of patients with moderate to severe ulcerative colitis (UC) who have had an inadequate response to, lost response to, or are intolerant to either immunomodulators or anti-TNF-α therapy and treatment of patients with moderate to severe Crohn's Disease (CD) who have had an inadequate response to, lost response to, or are intolerant to either immunomodulators or anti-TNF-α therapy.

The route of administration of vedolizumab is IV infusion. The recommended dosing is 300 mg at 0, 2, and 6 weeks and then every 8 weeks thereafter.

The clinical efficacy and safety data supporting the UC indication came from study C13006, a phase 3 multinational, randomized, double-blind, placebo-controlled trial. This study evaluated the induction and maintenance of remission in subjects with moderate to severe UC. The total duration of therapy in Study C13006 was 52 weeks, which included

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a 6-week induction period followed by a 46-week maintenance period. The efficacy of vedolizumab for induction therapy in C13006 was supported by phase 2 study M200-022. The clinical efficacy and safety data supporting the CD indication came from studies C13007 and C13011, phase 3 studies that evaluated the induction, maintenance, and remission or induction and remission, respectively, of subjects with moderate to severe CD. Additional safety and efficacy data have been obtained from study C13008, which is an ongoing roll-over study for subjects in the previously described trials.

C. Stability

The BLA submission contained adequate stability data to support establishment of a drug substance (DS) shelf life and a drug product shelf life. Stability studies have been conducted in accordance with ICH Q1A(R2) and Q5C. Drug substance and drug product stability protocols, including specifications, conditions and testing intervals, were provided and found to be acceptable.

- The data support a shelf life of [redacted] (b) (4) for the vedolizumab drug substance when stored at [redacted] (b) (4). Although data are provided only through 30 months for the three registration batches at [redacted] (b) (4), there are data for three additional representative drug substance batches demonstrating stability out to [redacted] (b) (4) when stored at [redacted] (b) (4).
- Stability tests for drug substance lots stored at [redacted] (b) (4) include protein concentration, appearance , pH, potency by binding assay and adhesion assay, CEX-HPLC (main, acidic and basic peaks), SE-HPLC (monomer and aggregates), reducing and non-reducing SDS-PAGE, bacterial endotoxin, bioburden and tryptic peptide mapping. All tests except endotoxin, bioburden and tryptic peptide mapping are performed at 0, 1, 3, 6, 9, 12, 18, 24, 36, 48, and 60 month time points. Endotoxin, bioburden and tryptic peptide mapping are performed annually.
- The most sensitive stability-indicating assays for DS were shown to be CEX-HPLC (charge isoforms) and SE-HPLC (% aggregate).
- Photostability studies indicated that vedolizumab DS is light sensitive and should be stored protected from light.
- The DS was found to be stable through three freeze-thaw cycles in temperature cycling studies.
- The post-approval DS annual stability protocol testing includes pH, appearance, protein concentration, CEX-HPLC (charge profile), potency by binding assay and adhesion assay, SE-HPLC (% monomer and % aggregates), and reducing and non-reducing SDS-PAGE. Testing will be performed at 0, 6, 12, 24, 36 and 48 months.
- The data support a shelf life of 36 months from the date of manufacture for vedolizumab (Entyvio) drug product when stored at 2-8°C. The date of manufacture shall be defined as the date [redacted] (b) (4)

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- Stability tests for drug product lots stored at 2-8°C include color and clarity of the solution, protein concentration, appearance, pH, potency by binding assay and adhesion assay, CEX-HPLC (main, acidic and basic peaks), SE-HPLC (monomer and aggregates), reducing and non-reducing SDS-PAGE, endotoxin, moisture, subvisible particles, reconstitution time, sterility and container closure integrity (CCI). All tests are performed at 0, 1, 3, 6, 9, 12, 18, 24, 36, 48, and 60 months, except for CCI, which is performed on an annual basis, and sterility, which is performed at the end of the stability study on month 60.
- The most sensitive stability-indicating assays for drug product were shown to be CEX-HPLC (charge profile).
- The photostability studies indicate that the DP shows minimal changes when exposed to direct light; however, storage in cardboard boxes reduces the extent of the changes. The DP appears to be sufficiently stable to light exposure; however, the sponsor has recommended 'Protect from light' be included on the DP carton and container. The reconstituted DP is photosensitive.
- The DP was found to be stable through three freeze-thaw cycles in temperature cycling studies.
- The post-approval annual drug product stability protocol will store samples at 2-8°C and testing will include color and clarity, appearance (cake), SE-HPLC, CEX-HPLC, reducing and non-reducing SDS-PAGE, potency by binding assay and adhesion assay, moisture content, reconstitution time, pH, subvisible particles, endotoxin, sterility and CCI. Testing will be performed at 0, 6, 12, 24, and 36 and 48 months, with the exception of CC1 and sterility testing. The CCI test will be performed at 12 and 24 months, and the sterility test will be performed at 0, 36, and 48 months.

D. Complexity

- Vedolizumab is a recombinant IgG1 monoclonal antibody containing kappa light chains and is directed against human $\alpha_4\beta_7$ integrin. The Fc binding region of the vedolizumab contains (b) (4)

- The protein concentration of the vedolizumab DP is measured using UV-spectrophotometry (b) (4) using the theoretical extinction coefficient, (b) (4) (b) (4) The experimental extinction coefficient of vedolizumab is (b) (4) The sponsor will retain use of the theoretical extinction coefficient, given that it is close to the experimental value and will provide protein concentrations consistent with those used in clinical studies.

- The molecular mass of the main isoform of vedolizumab is 146.837 kDa, and the isoelectric point range is (b) (4). Vedolizumab contains (b) (4)

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H. Comparability

The vedolizumab manufacturing process has been changed twice during development. The original process (Process A) used a [redacted] (b) (4). Process B, which was used to produce the material used in phase 1 and 2 clinical trials, used a [redacted] (b) (4). Materials generated using the two processes were found to be analytically comparable. The third process (Process C) was developed to implement use of a [redacted] (b) (4) [redacted] (b) (4) Process C material, also produced from the [redacted] (b) (4), was used in phase 2 and 3 clinical trials, including the pivotal trials being evaluated under this BLA. Analytical comparability of Process B and Process C materials was established. Process C material was initially produced at a [redacted] (b) (4) scale, and the scale [redacted] (b) (4). The [redacted] (b) (4) Process C materials were shown to be analytically comparable. Process C at [redacted] (b) (4) is the commercial manufacturing process.

I. Immunogenicity

For detection and confirmation of anti-drug antibody (ADA) developed against vedolizumab, a bridging ELISA-based immunogenicity assay using a rabbit anti-human positive control antibody was developed and validated. A flow cytometry-based neutralization assay was also developed to further characterize the ADA response to vedolizumab. The validation reports provided indicate that the detection/confirmatory assay can detect 500 ng/mL ADA (considered to be a "clinically meaningful" response) in the presence of up to 0.5 µg/mL vedolizumab and the neutralization assay can detect 500 ng/mL ADA in the presence of up to 30 ng/mL of vedolizumab. The trough concentrations of vedolizumab in patient samples were up to 11 µg/mL and 35 µg/mL in the 300 mg Q8W group and 300mg Q4W group, respectively. Therefore, we conclude that the current assays are not sufficiently sensitive or drug tolerant to detect ADA in patients' samples. The sponsor was requested to provide a commitment to develop and validate sensitive detection and neutralization assays that can detect ADA in the presence of vedolizumab at levels that are expected to be present in the serum or plasma at the time of sampling.

VI. SIGNATURE BLOCK

Kathleen A. Clouse, Ph.D.
Director
Division of Monoclonal Antibodies

Sarah Kennett, Ph.D.
Review Chief
Division of Monoclonal Antibodies

Rashmi Rawat, Ph.D.
Acting Team Leader,
Division of Monoclonal Antibodies

Reference ID: 3414618

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/s/

RASHMI RAWAT
11/27/2013

SARAH B KENNETT
11/27/2013

KATHLEEN A CLOUSE STREBEL
11/27/2013

BLA STN 125476

Vedolizumab

Manufacturer: Takeda Pharmaceuticals, Inc.

Primary Reviewer: Qing Zhou, Ph.D.

Team Leader: Rashmi Rawat, Ph.D.

Division of Monoclonal Antibodies

OBP CMC Review Data Sheet

1. **BLA#:** STN 125476

2. **REVIEW DATE:** November 20, 2013

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Laurie Muldowney, Klaus Gottlieb, Anil Rajpal
Pharm/Tox: Tamal Chakraborti, Sushanta Chakder
Product Quality Team: Qing Zhou; Rashmi Rawat
BMT or Facilities: Reyes Candau-Chacon; Steven Fong
Clinical Pharmacology: Lanyan (Lucy) Fang, Yow-Ming Wang
Statistics: Milton Fan Mike Welch
OBP Labeling: Rashmi Rawat
RPM: Kevin Bugin

4. **MAJOR GRMP DEADLINES**
Filing Meeting: July 22, 2013
Mid-Cycle Meeting: September 26, 2013
Wrap-Up Meeting: January 21, 2014
Primary Review Due: November 20, 2013
Secondary Review Due: November 27, 2013
CDTL Memo Due: January 21, 2014
PDUFA Action Date: February 18, 2014

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
CMC pre-BLA Meeting	11-13-2012
Information Request-1 (IR-1)	6-12-2013
Teleconference-1	6-18-2013
Information Request-2	7-23-2013
Filing Review Memo	8-9-2013
Information Request-3	10-16-2013
Information Request-4	10-30-2013
Information Request-5	11-8-2013
Teleconference-2	11-12-2013
Teleconference-3	11-14-2013

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN **125476/0** (BLA Original Submission)	6-20-2013	Yes
STN **125476/3** (Sponsor's response to IR-1)	7-3-2013	Yes
STN **125476/10** (Sponsor's response to IR-2)	8-23-2013	Yes

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STN **125476/12** (Sponsor's response to IR-2)	8-28-2013	Yes
STN **125476/33** (Sponsor's response to IR-3)	11-4-2013	Yes
STN **125476/35** (Sponsor's response to IR-4)	11-11-2013	Yes
STN **125476/37** (Sponsor's response to IR-5)	11-14-2013	Yes
STN **125476/40** (Sponsor's response to comments during Tcon on 11/14/13)	11-18-2013	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Entyvio
   b. Trade Name: Entyvio
   c. Non-Proprietary/USAN: Vedolizumab
   d. CAS name: 943609-66-3; Immunoglobulin G1, anti-(human integrin LPAM-1 (lymphocyte Peyer's patch adhesion molecule 1)) (b) (4)
   e. Common name: MLN0002
   f. INN Name: Vedolizumab
   g. Compendial Name: N/A
   h. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P13612 (ITA4_HUMAN) & P26010 (ITB7_HUMAN) [MLN0002]
   i. Other Names: MLN0002, MLN02, LDP-02

8. **PHARMACOLOGICAL CATEGORY:** humanized IgG1 monoclonal antibody against α4β7 integrin
9. **DOSAGE FORM:** Injectable Solution Concentrate
10. **STRENGTH/POTENCY:**
    - The Entyvio (vedolizumab) Drug Product is supplied at 300 mg/vial in a 20 ml vial.
    - Potency is defined as the percent activity relative to the reference standard, using a cell based binding assay that uses flow cytometry to measure the ability of vedolizumab to bind to α4β7-expressing HuT 78 cells, and a cell based adhesion assay that uses fluorescence absorbance to measure the ability of vedolizumab to block the adherence of α4β7-expressing RPMI8866 cells to the surface of mucosal addressin cell adhesion molecule-1 coated plates.
    - Dating period for vialed drug product is 36 months when stored at 5 ± 3°C and protected from light.

11. **ROUTE OF ADMINISTRATION:** Intravenous
12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)		USP Type I (b) (4)	Provided in the BLA	Type III. Review in DARRTS 4/28/11 found this acceptable for NDA (b) (4) b(2). No further review required as all

Reference ID: 3410530

				the relevant information related to compatibility with the product was in the BLA.
(b) (4)		(b) (4)	Provided in the BLA	Type V. Review in DARRTS 8/16/2013 found the information provided is adequate. No further review required as sufficient information was provided in the BLA.
			Provided in the BLA	Type III. Review in DARRTS 9/25/12 found it acceptable to support NDA (b) (4). No further review required as sufficient information was provided in the BLA.

13. **INSPECTIONAL ACTIVITIES**

A pre-licensure inspection (PLI) of the biologics drug substance manufacturing facility was conducted following a request by the Biotech Manufacturing Team, Office of Compliance, CDER, under FEI No. (b) (4). The inspection covered the manufacturing operations for BLA STN 125476/0 for the vedolizumab drug substance at (b) (4). The inspection was conducted on (b) (4) by BMAB reviewer, Maria Candauchacon and product reviewers Jun Park and Qing Zhou in accordance with applicable sections of CP 7356.002M, Inspections of Licensed Therapeutic Drug Products and ICH Q7A. This inspection was limited to the manufacturing and testing of vedolizumab. This PLI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls.

One 483 item from Quality Micro (BMAB inspector) was identified during the PLI: Microbiology methods are not conducted adequately. Specifically, neither a qualified inoculum nor a previously approved batch of media is used to set acceptance criteria for growth promotion of the media. No 483 item was identified by the product quality team.

The following product quality item was identified and communicated verbally to the firm during the closeout meeting: A gap was identified between the record in the Refrigerator Freezer Unit Activity sheets and the SAP for drug substance tracking and storage. The firm is recommended to improve the transparency and clarity of drug substance tracking method.

14. **CONSULTS REQUESTED BY OBP:** NONE

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15. QUALITY BY DESIGN ELEMENTS:

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
X	Design of Experiments
	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

Design of Experiments studies were performed as part of process development.
Risk assessments were performed; the formal risk assessments were not provided.

16. PRECEDENTS: NONE

17. ADMINISTRATIVE

A. Signature Block
Qing Zhou, Ph.D., Product Quality Reviewer, Division of Monoclonal Antibodies

Rashmi Rawat, Ph.D., Team Leader, Division of Monoclonal Antibodies

Sarah Kennett, Ph.D., Branch Chief, Division of Monoclonal Antibodies

B. CC Block
Clinical Division (DGIEP) BLA RPM: Kevin Bugin

Division of Monoclonal Antibodies File: BLA STN 125476

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

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/s/

QING ZHOU
11/20/2013

RASHMI RAWAT
11/20/2013

SARAH B KENNETT
11/20/2013

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number:	Applicant:	Stamp Date:
STN 125476/0	Millennium Pharmaceuticals, Inc	6/20/2013
Established/Proper Name:	**BLA/NDA Type:**	
Vedolizumab	Fast Track, Priority, Original BLA	

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed ❑ including list of all establishment sites and their registration numbers	Y Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y Y Y Y Y N Y N Y N N Y N	 Defer to clinical reviewer Defer to clinical reviewer Not applicable Not applicable Not found

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
❑ legible	Y	
❑ English (or translated into English)	Y	
❑ compatible file formats	Y	
❑ navigable hyper-links	Y	
❑ interpretable data tabulations (line listings) & graphical displays	Y	
❑ summary reports reference the location of individual data and records	Y	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing arrangement	Y N	Defer to BMAB

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PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	N	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y	
❑ Novel Excipients	Y	
❑ Executed Batch Records	Y	provided in 3.2.R
❑ Method Validation Package	Y	provided in 3.2.R
❑ Comparability Protocols	N	Not applicable

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	N	
Drug Substance [3.2.S]		
❑ general info ○ nomenclature ○ structure (e.g. sequence, glycosylation sites) ○ properties	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control ○ batch numbering and pooling scheme ○ cell culture and harvest ○ purification ○ filling, storage and shipping	Y	
❑ control of materials ○ raw materials and reagents ○ biological source and starting materials ○ cell substrate: source, history, and generation ○ cell banking system, characterization, and testing	Y	
❑ control of critical steps and intermediates ○ justification of specifications ○ stability	Y	

Reference ID: 3355241

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	
❑ characterization of drug substance		
❑ control of drug substance	Y	
○ specifications	Y	
○ Justification of specs.		
○ analytical procedures		
○ analytical method validation		
○ batch analyses		
❑ reference standards		
❑ container closure system	Y	
❑ stability	Y	
❑ summary	Y	
❑ post-approval protocol and commitment		
❑ pre-approval		
○ protocol		
○ results		
○ method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
○ preservative effectiveness	Y N	Not applicable
○ container-closure integrity	Y Y	Container-closure integrity is provided in Section 3.2.P.5.2 Additional Analytical Procedures
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y	
❑ controls of critical steps and intermediates	Y	
❑ process validation including aseptic processing & sterility assurance:	Y	
○ Filter validation		
○ Component, container, closure depyrogenation		

Reference ID: 3355241

CTD Module 3 Contents	Present?	If not, justification, action & status
and sterilization validation ○ Validation of aseptic processing (media simulations) ○ Environmental Monitoring Program ○ Lyophilizer validation ○ Other needed validation data (hold times)		Environmental Monitoring Program is provided in Section 3.2.A.1
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
❑ reference standards or materials	Y	
❑ container closure system [3.2.P.7] ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ○ administration device(s)	Y	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	Y	
Diluent (vials or filled syringes) [3.2P′]		Vedolizumab is intended to be reconstituted in sterile water and diluted in standard saline solution. The sponsor does not have a diluent that is co-packaged. This section is not applicable to the BLA.
❑ description and composition of diluent	Y N	
❑ pharmaceutical development	Y N	
○ preservative effectiveness	Y N	
○ container-closure integrity	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through	Y N	

Reference ID: 3355241

CTD Module 3 Contents	Present?	If not, justification, action & status
finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)		
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance:	Y N	
o Filter validation		
o Component, container, closure depyrogenation and sterilization validation	Y N	
o Validation of aseptic processing (media simulations)		
o Environmental Monitoring Program	Y N Y N	
o Lyophilizer sterilization validation		
o Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system	Y N	
o specifications (vial, elastomer, drawings)		
o availability of DMF & LOAs		
❑ stability	Y N	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
Other components to be marketed (full description and supporting data, as listed above):	Y N	This section is not applicable
❑ other devices	Y N	
❑ other marketed chemicals (e.g. part	Y N	

Reference ID: 3355241

CTD Module 3 Contents	Present?	If not, justification, action & status
of kit)		
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination	Y N	Defer to BMAB
❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production	Y	Cell line qualification is provided in Section 3.2.S.2.3
❑ novel excipients	Y N	There are no novel excipients therefore it is not applicable
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	Y Y Y N	Not applicable
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y	

Reference ID: 3355241

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y	
Certification that all facilities are ready for inspection	Y N	Defer to BMAB
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	Y Y N Y Y N	LAL and sterility tests defer to BMAB
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	Not applicable
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	Defer to BMAB
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	Defer to BMAB

Reference ID: 3355241

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? **Yes** ~~No~~

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No issue to be sent at this time.

Reference ID: 3355241

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

/s/

QING ZHOU
08/09/2013

RASHMI RAWAT
08/09/2013

KATHLEEN A CLOUSE STREBEL
08/09/2013

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number: STN 125476/0
Applicant: Takeda Pharmaceuticals USA Inc.
Stamp Date: 3/27/2013
Established/Proper Name: **Not yet decided (vedolizumab)**
BLA/NDA Type: **Priority review**

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed ❑ including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y	
❑ PI –non-annotated	Y N	
❑ PI –annotated	Y N	
❑ PI (electronic)	Y N	
❑ Medication Guide	Y N	
❑ Patient Insert	Y N	
❑ package and container	Y N	
❑ diluent	Y N	
❑ other components	Y N	
❑ established name (e.g. USAN)	Y N	
❑ proprietary name (for review)	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
❑ legible	Y	
❑ English (or translated into English)	Y	
❑ compatible file formats	Y	
❑ navigable hyper-links	Y	
❑ interpretable data tabulations (line listings) & graphical displays	Y	
❑ summary reports reference the location of individual data and records	Y	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing arrangement	Y	

Reference ID: 3338062

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	N	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y N	Defer to OBP
❑ Novel Excipients	Y N	Defer to OBP
❑ Executed Batch Records	Y N	Defer to OBP
❑ Method Validation Package	N	Validation package included in 3.2.R
❑ Comparability Protocols	Y N	Comparability protocols: not applicable

CTD Module 3 Contents	Present ?	If not, justification, action & status
Module Table of Contents [3.1]	N	
Drug Substance [3.2.S]		
❑ general info	Y	
o nomenclature		
o structure (e.g. sequence, glycosylation sites)		
o properties		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	Manufacturers and FEI numbers included in section 1.1.2
❑ description of manufacturing process and process control	Y	
o batch numbering and pooling scheme		
o cell culture and harvest		
o purification		
o filling, storage and shipping		Shipping information is missing. It will be asked during the review process
❑ control of materials	Y N	Defer to OBP
o raw materials and reagents		
o biological source and starting materials		
o cell substrate: source, history, and generation		
o cell banking system, characterization, and testing		
❑ control of critical steps and intermediates	Y	
o justification of specifications		
o stability		

Reference ID: 3338062

CTD Module 3 Contents	Present ?	If not, justification, action & status
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	
❑ characterization of drug substance	Y N	Defer to OBP
❑ control of drug substance		
o specifications	Y	
o justification of specs.	Y	
o analytical procedures	Y	
o analytical method validation	Y	
o batch analyses	Y	Method suitability for endotoxin and bioburden is not included. They will be asked for during the review process
❑ reference standards	Y	
❑ container closure system	Y N	Defer to OBP
❑ stability	Y	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
o method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
o preservative effectiveness	N	Not applicable (no preservative)
o container-closure integrity	Y	Provided in Module 3.2.P.2.5.2.
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y	Labeling & packaging not described in sufficient detail. Will request information.
❑ controls of critical steps and intermediates	Y	
❑ process validation including aseptic processing & sterility assurance:	Y	
o Filter validation	Y	
o Component, container, closure depyrogenation and sterilization validation	Y	

Reference ID: 3338062

CTD Module 3 Contents	Present ?	If not, justification, action & status
○ Validation of aseptic processing (media simulations)	Y	
○ Environmental Monitoring Program	Y	EM program described in Facilities & equipment appendix, 3.2.A.1.
○ Lyophilizer validation	Y	
○ Other needed validation data (hold times)	Y	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	TBD by OBP.
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
❑ reference standards or materials	Y N	TBD by OBP.
❑ container closure system [3.2.P.7]	Y	
○ specifications (vial, elastomer, drawings)	Y	
❑ availability of DMF & LOAs	Y	Product quality review for this BLA will
○ administration device(s)	N	require review of DMF (b) (4) describing (b) (4).
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	Y	Not Applicable. No special administration devices. Stability information provided regarding sterility, endotoxin and container closure integrity. Other stability information TBD by OBP.
Diluent (vials or filled syringes) [3.2P′]	Y N	Not Applicable. Vedolizumab drug product is to be reconstituted with sterile WFI diluent prior to administration. The diluent is to be provided by the health services administrator and is not included with the drug product.
❑ description and composition of diluent	Y N	
❑ pharmaceutical development	Y N	
○ preservative effectiveness	Y N	
○ container-closure integrity		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	

Reference ID: 3338062

CTD Module 3 Contents	Present ?	If not, justification, action & status
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance:	Y N	
o Filter validation	Y N	
o Component, container, closure depyrogenation and sterilization validation	Y N	
o Validation of aseptic processing (media simulations)	Y N	
o Environmental Monitoring Program	Y N	
o Lyophilizer sterilization validation	Y N	
o Other needed validation data (hold times)	Y N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system	Y N	
o specifications (vial, elastomer, drawings)	Y N	
o availability of DMF & LOAs	Y N	
❑ stability	Y N	
❑ summary	Y N	
❑ post-approval protocol and commitment	Y N	
❑ pre-approval		
o protocol		
o results		
Other components to be marketed (full description and supporting data, as listed above):		This section is not applicable.
❑ other devices	Y N	
❑ other marketed chemicals (e.g. part of kit)	Y N	
Appendices for Biotech Products [3.2.A]		
❑ facilities and equipment	Y	

Reference ID: 3338062

CTD Module 3 Contents	Present ?	If not, justification, action & status
○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination		Other products made at the DP site not listed (will request)
❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production	Y N	TBD by OBP
❑ novel excipients	Y N	TBD by OBP
USA Regional Information [3.2.R]		
❑ executed batch records	Y N	TBD by OBP
❑ method validation package	Y	Micro reviewed tests provided in 3.2.S and 3.2.P. Other tests to be reviewed by OBP
❑ comparability protocols	Y N	Not applicable
Literature references and copies [3.3]	Y N	TBD by OBP

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y N	TBD by OBP
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	TBD by OBP
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	TBD by OBP
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities	Y N	TBD by OBP

Reference ID: 3338062

Examples of Filing Issues	Yes?	If not, justification, action & status
have occurred)		
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	TBD by OBP
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	 Y Y N Y N	 TBD by OBP Not applicable—sterility test performed
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	Not applicable.
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	General information provided, but other products made in the same area of the DP site are not identified (will request)

Reference ID: 3338062

PRODUCT QUALITY (Biotechnology)

FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? **Yes** ~~**No**~~

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.
No filing issues from a microbiology quality perspective.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None.

Reyes Candau-Chacon, Ph.D. 7/9/2013
Drug Substance Microbiology Reviewer
OC/OMPQ/DGMPA/BMAB

Steven Fong, Ph.D. 7/9/2013
Drug Product Microbiology Reviewer
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Peter Qiu, Ph.D. 7/9/2013
Branch Chief
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Reference ID: 3338062

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/s/

STEVEN FONG
07/09/2013
Recommended for filing from a microbiology quality standpoint.

REYES CANDAU-CHACON
07/09/2013

ZHIHAO PETER QIU
07/09/2013