# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**125104**

## CHEMISTRY REVIEW(S)

# Review Cover Sheet

## BLA STN 125104/0

**TYSABRI™ (Natalizumab)**

**Biogen Idec, Inc**

**Elena Gubina, Ph.D. HFD-123**
**Joseph Kutza, Ph.D. HFD-123**
**Lei Zhang, M.D., Ph.D. HFD-123**
**Division of Monoclonal Antibodies**

# CMC Review Data Sheet

1. **BLA#** STN 125104/0

2. **REVIEW #:** 1

3. **REVIEW DATE:** 18-NOV-2004

4. **REVIEWERS:** Elena Gubina, Ph.D.
Joseph Kutza, Ph.D.
Lei Zhang, M.D., Ph.D.

5. **COMMUNICATIONS AND PREVIOUS DOCUMENTS[1]:**

| Previous Documents | Document Date[2] |
|---|---|
| Pre-BLA Meeting | 17-FEB-2004 |
| T-com | 7-JUL-2004 (1) |
| T-com | 7-JUL-2004 (2) |
| T-com | 16-JUL-2004 |
| Filing Review (74 days)/Deficiency Com. | 6-AUG-2004 |
| T-com | 11-AUG-2004 |
| T-com | 19-AUG-2004 |
| T-com | 24-AUG-2004 |
| T-com | 7-SEPT-2004 |
| T-com | 21-SEPT-2004 |
| T-com | 24-SEPT-2004 |
| T-com | 19-OCT-2004 |
| T-com | 26-OCT-2004 |
| T-com | 2-NOV-2004 |
| T-com | 4-NOV-2004 |
| E-com | 12-NOV-2004 |

[1] Chronology of previous CMC communications between CDER and the firm and/or reviews
[2] Applicant's letter date or date of review and/or communication with applicant

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

| Submission(s) Reviewed | | Document Date |
|---|---|---|
| STN 125104/0 | Original Submission | 24-MAY-2004 |
| STN 125104/0.001 | Immunogenicity Assay | 22-JUN-2004 |
| STN 125104/0.005 | Response to Day 74 letter | 16-AUG-2004 |
| STN 125104/0.006 | Immunogenicity Assay | 23-AUG-2004 |
| STN 125104/0.008 | Response to Day 74 letter | 10-SEPT-2004 |
| STN 125104/0.010 | Response to CMC IR | 15-SEPT-2004 |
| STN 125104/0.013 | Response to CMC IR | 23-SEPT-2004 |
| STN 125104/0.015 | Response to Day 74 letter | 13-OCT-2004 |
| STN 125104/0.017 | Response to CMC IR | 14-OCT-2004 |
| STN 125104/0.018 | Response to CMC IR | 14-OCT-2004 |
| STN 125104/0.019 | Response to CMC IR | 14-OCT-2004 |

| | | |
|---|---|---|
| STN 125104/0.021 | Response to CMC IR | 27-OCT-2004 |
| STN 125104/0.022 | Response to CMC IR | 28-OCT-2004 |
| STN 125104/0.023 | Response to Day 74 letter | 02-NOV-2004 |
| STN 125104/0.024 | Response to CMC IR | 03-NOV-2004 |
| STN 125104/0.026 | Response to CMC IR | 05-NOV-2004 |
| STN 125104/0.029 | Response to CMC IR | 09-NOV-2004 |
| STN 125104/0.035 | Response to CMC IR | 15-NOV-2004 |

7. **NAME & ADDRESS OF APPLICANT:**

| | |
|---|---|
| **Name:** | Biogen Idec, Inc. |
| **Address:** | 14 Cambridge Center<br>Cambridge, MA |
| **Representative:** | Nadine Cohen, Ph.D. |
| **Telephone:** | 617-679-3783 |

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: Tysabri™
b) Non-Proprietary Name: natalizumab
c) Code name: BG00002
d) Common name: anti-α4 integrin monoclonal antibody
e) Drug Review Status: Fast Track
f) Chemical Type: recombinant humanized monoclonal antibody

9. **PHARMACOL. CATEGORY:** Therapeutic monoclonal antibody to α4 integrin subunit.

10. **DOSAGE FORM:** Sterile parenteral solution.

11. **STRENGTH/POTENCY:**

(i) The concentration of Tysabri™ (natalizumab) Drug Substance and Drug Product is ——

(ii) ——

(iii) Dating period for vialed product is ——, when stored at 2°C -8°C. Following dilution into saline, the diluted drug product is stable for 8 hours post-dilution when stored at 2-8°C.

12. **ROUTE OF ADMINISTRATION:** Intravenous infusion when added to 100 ml of 0.9% Sodium Chloride for Injection, USP

2 Page(s) Withheld of
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§ 552(b)(4)

15. **RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | | | | 7 | N/A | | Meets USP requirements |
| | | | | 4 | N/A | | Meets USP/Ph. Eur.standards |

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| | | |
| BB IND | 6895 | Initial natalizumab development at Elan Pharmaceuticals, Inc. |

16. **STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

**OBP:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Establishment Status | Approval | 1-NOV-04 | Calvin Koerner |
| Labeling Nomenclature Committee | N/A | N/A | N/A |
| OPDRA[#] 040278 | Tradename under review | 28-OCT-04 | Charles Hopper |
| Environmental Assessment | Approval | 1-NOV-04 | Calvin Koerner |
| DMPQ | Approval | 1-NOV-04 | Calvin Koerner |

[#] Review trade name for medical error avoidance

17. **CMC Inspectional Activities**

1. Biogen Idec in Research Triangle Park, NC (08/23/04 to 08/27/04): This facility is referred to as RTP and is the site of drug substance manufacture. Product reviewers Joseph Kutza and Lei Zhang along with TFRB Inspectors Calvin Koerner and Gilbert Salud and Atlanta District Investigator DeVaughn Edwards participated in this inspection. A three-item FDA Form 483 was issued to the firm. None of the three items were derived from the product reviewers. Adequate responses to the 483 were received by the agency. The facility was found to be in compliance with cGMPs and capable of manufacturing natalizumab drug substance in a consistent manner.

2. Biogen Idec in Oceanside, CA (9/17/04 and 9/20/04): The majority of drug substance and drug product release testing, as well as stability testing is completed at this site. Product reviewers Joseph Kutza and Lei Zhang along with TFRB Inspectors Calvin Koerner and Gilbert Salud participated in this inspection. An FDA form 483 was not issued to the firm. The facility was found to be in compliance with cGMPs and capable of adequately testing natalizumab drug substance and drug product for release and stability.

3. [redacted]

# The Chemistry Executive Summary

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of natalizumab is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets or exceeds the parameters recommended by FDA. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs. It is recommended that this product be approved for human use (under conditions specified in the package insert).

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

We propose the following post-marketing commitments:

1. To re-evaluate drug substance and drug product lot release and in-process specifications after the first 30 lots of each are produced to ensure that these parameters adequately reflect the capability of the manufacturing process. Results should be submitted in an annual report.

2. To perform a study measuring the effect of freeze/thaw on natalizumab drug product quality. Testing should be comprehensive and include all critical quality attributes included in drug product lot release. Labeling will need to be changed if results indicate that product quality is significantly impacted by freeze/thaw conditions that could occur during natalizumab distribution.

3. To develop an assay that detects and quantifies [redacted] that could be present in [redacted] natalizumab drug product [redacted]

4. [redacted]

5. To develop an assay that quantifies the level of bispecific antibodies[2] that could form based on the *in vivo* exchange of natalizumab half antibody with half antibody from other IgG4 antibodies.

6. To develop an appropriately validated assay for the detection of neutralizing antibodies to natalizumab.

7. [redacted]

[2] R. C. Aalberse and J. Schuurman, "IgG4 breaking the rules," *Immunology* Volume 105, Issue 1, pp. 9-19.

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

- Tysabri™ is supplied as a sterile, single-use vial [redacted] Each 15 mL dose contains 300 mg natalizumab; 123 mg sodium chloride, USP; 17.0 mg sodium phosphate, monobasic, monohydrate, USP; 7.24 mg sodium phosphate, dibasic, heptahydrate, USP; 3.0 mg polysorbate 80, USP/NF, in water for injection, USP at pH 6.1. [redacted]

- The drug substance, natalizumab, is a recombinant humanized anti-α4 integrin monoclonal antibody (IgG4/κ). The drug substance is a colorless, clear to slightly opalescent solution. The key physicochemical properties of the natalizumab monoclonal antibody are as follows. The molecular weight of natalizumab is approximately 149 kDa. [redacted]

- [redacted]

- [redacted]

- [redacted]

- [redacted]

CH-2

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§ 552(b)(4)

[redacted]

- [redacted]

- [redacted]

- [redacted]

**B. Description of How the Drug Product is Intended to be Used**

- Tysabri™ is indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. The recommended dose of Tysabri™ is 300 mg IV infusion every four weeks.

- Tysabri™ is supplied as 300 mg natalizumab in a sterile, single-use vial [redacted]

- Tysabri™ is diluted by adding 15 mL of drug product to 100 ml of 0.9% Sodium Chloride for Injection, USP, for intravenous infusion. Diluted Tysabri™ solutions for infusion may be stored at 2°C-8°C for up to 8 hours.

- Tysabri™ vials should be refrigerated at 2°C-8°C and protected from light. Tysabri™ vials should not be shaken or frozen. The recommended expiration dating period for Tysabri™ Drug Product is ——— under these storage conditions. The sponsor plans to submit the additional data when it becomes available to increase the expiry dating.

**C. Basis for Approvability or Not-Approval Recommendation**

- Tysabri™ is manufactured ——— Tysabri™ is manufactured consistently, resulting in a safe and effective product, and should be approved for the proposed indication.

- Post-marketing commitments described in the recommendations section above will provide additional information to assure the continued safety of the product.

## III. Administrative

A. Reviewers' Signature

Product Reviewer: Elena Gubina , Ph.D.

Product Reviewer: Joseph Kutza, Ph.D.

Product Reviewer: Lei Zhang, M.D., Ph.D.

B. Endorsement Block

Product Team Leader: Patrick Swann, Ph.D.

Product Acting Division Director: Steven Kozlowski, M.D.

C. CC Block

Acting Office Director: Keith Webber, Ph.D.
Division of Monoclonal Antibodies File/BLA STN 125085/0

CH-3

130 Page(s) Withheld of
Deliberative Process
§ 552(b)(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

**Date:** 29 October 2004

**To:** Administrative File, **STN 124104/0**

**From:** Calvin Koerner, Committee Member, CDER/OC/DMPQ TFRB, HFD-328

**Through:** Michael D. Smedley, Branch Chief, CDER/OC/DMPQ/TRFB, HFD-328

**Subject:** **Review Memo: Biological License Application (BLA):** New BLA

**US License** #1697
**Applicant** Biogen Idec, Inc.
**Product** natalizumab
**Indication** Treatment of Multiple Sclerosis

**Due date:** 11/24/04

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**Recommendation:** Facility and equipment information related to this application and corresponding amendments has been reviewed and the application, as amended, is recommended for approval. Nine review items were noted during the review process and were subsequently resolved.

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## Review Summary

Biogen Idec, Inc. submitted this BLA to license natalizumab and the associated Drug Substance and Drug Product manufacturing processes. Drug Substance manufacturing is conducted by Biogen Idec, Inc. at their Research Triangle Park (RTP), NC facility. Drug Product manufacturing is conducted by [redacted]. Drug Substance and Product testing is primarily conducted by Biogen Idec, Inc at their Oceanside, CA laboratories. In addition, the firm is licensing two additional laboratories as back-up product release testing sites at their [redacted] RTP, NC facilities.

The BLA was submitted in an electronic Common Technical Document (CTD) format. Three application amendments were submitted at the request of the Therapeutics Facilities Review

Branch (TFRB). The following is a list of the requested amendments and their corresponding contents:

Amendment 0008 – Responses to 74 Day Letter
Amendment 0015 – Response to request for drug substance manufacturing process time limits
Amendment 0018 – Revision of drug product transport temperatures from ——— to 2-8°C

The scope of this review was limited to a TFRB functionality review for the Drug Substance's Manufacturer, Controls, Container/Closure, Facility/Equipment, and Adventitious Agents sections and the Drug Product's Pharmaceutical Development, Manufacturer, Controls, Container/Closure, Facility/Equipment, and Adventitious Agents sections and the Environmental Assessment.

An evaluation of the application for completeness and adequacy was completed on 20 July 2004. Nine review items and five inspection items were noted during this evaluation.

The firm was notified of Review Items #1-3 and #5-9 in a 74 Day Letter. The firm was notified of Review Item #4 during a teleconference on 2 September 2004 (See Teleconference Memo dated 2 September 2004). The nine review items were adequately addressed and resolved in three supplement amendments received by the Agency on 14 Sept 04, 13 Oct 04, and 14 Oct 04. See the Review Narrative Section for the review items and their subsequent resolution.

Inspections of the facilities were conducted from 23-27 August 2004 (Biogen Idec, RTP, NC) and 17-23 September 2004 (Biogen Idec, Oceanside, CA and ——————— ) by Calvin Koerner, Gilbert Salud, Lei Zhang, and Joseph Kutza. FDA Form 483s were issued for the Biogen Idec RTP and —— inspections, but an FDA Form 483 was not issued for the Oceanside inspection. A three-observation FDA Form 483 was issued to the Biogen Idec RTP facility on 27 August 2004 and a two-observation FDA Form 483 was issued to the ——————— facility on 23 September 2004. Response letters to the 483 observation were received and reviewed by myself and forwarded to CDER/OC/DMPQ/IPCB. IPCB evaluated the EIR, FDA Form 483s, and the firm's responses to the 483 items as part of their compliance check. The five inspection items were addressed during the inspection. See the Conclusion section of this memo for the individual inspectional items. The inspection item resolutions are in their respective EIR.

**Products Affected**

natalizumab

**Review Narrative**

***Drug Substance***

*Manufacturer, 3.2.S.2*
Section on Manufacturers Names, Description of Manufacturing Process and Process Controls, Control of Materials, and Controls of Critical Steps and Intermediates were provided.

*Manufacturers Names, 3.2.S.2.1* – This section included name, address, and responsibility of each manufacturer and their respective production facility involved in the manufacturing and testing of the product.

Review Comment – Information on two of the three testing labs did not delineate what specific QA/QC testing will be performed. One review item was noted and resolved as detailed below.

Review Item #1 – The application listed three testing labs, but did not specify what specific testing would be conducted at each specific testing site.

Resolution #1 – The firm was contacted and requested to amend the application with information depicting what tests they would like to have licensed at what testing lab. The firm agreed to submit the requested information and an amendment (0008) was received by the Agency on 14 September 2004. An evaluation of the amendment was completed on 5 October 2004 and the information adequately provided the specific testing for each testing site. The manufacturing sites and the specific testing for each testing site are listed in the following tables (Table 1.0 and 1.1). No further action is required.

Table 1.0, Manufacturers, Responsibility, and GMP Status

| **Name and Address** | **FEI Number and GMP Status** | **Responsibility** |
|---|---|---|
| [redacted] | | |
| Biogen Idec, Inc.<br>5000 Davis Drive<br>Research Triangle Park, NC 27709 | FEI: [redacted]<br><br>Inspected:<br>23-27 August 2004<br><br>FACTS No: [redacted]<br><br>TFRB DB No: [redacted] | Drug product QA/QC testing and release |

| Name and Address | FEI Number and GMP Status | Responsibility |
|---|---|---|
| Biogen Idec, Inc.<br>14 Cambridge Center<br>Cambridge, MA 02142 | FEI: [redacted]<br><br>Inspected:<br>Inspection Waiver Approved on 10 September 04<br><br>FACTS No:<br>N/A<br><br>TFRB DB No:<br>N/A | Drug product QA/QC testing and release |
| Biogen Idec, Inc.<br>One Antibody Way<br>Oceanside, CA 92056 | FEI: [redacted]<br><br>Inspected:<br>17-22 September 2004<br><br>FACTS No:<br>[redacted]<br><br>TFRB DB No:<br>[redacted] | Drug product QA/QC testing and release |
| [redacted] | [redacted] | [redacted] |

Table 1.1, Specific Test and Specific Testing Sites

| Test Name | Primary Testing Site | Alternative Testing Sites |
|---|---|---|
| [redacted] | Biogen Idec Oceanside | Biogen Idec Cambridge |
| [redacted] | Biogen Idec Oceanside | Biogen Idec Cambridge |
| [redacted] | Biogen Idec Oceanside | Biogen Idec Cambridge |

| Test Name | Primary Testing Site | Alternative Testing Sites |
|---|---|---|
| [redacted] | Biogen Idec Oceanside | Biogen Idec Cambridge |
| [redacted] | Biogen Idec Oceanside | Biogen Idec Cambridge |
| [redacted] | Biogen Idec Oceanside | Biogen Idec Cambridge |
| [redacted] | Biogen Idec Oceanside | Biogen Idec Cambridge |
| [redacted] | Biogen Idec Oceanside | Biogen Idec Cambridge |
| [redacted] | Biogen Idec Oceanside | Biogen Idec Cambridge |
| [redacted] | Biogen Idec Oceanside | Biogen Idec Cambridge |
| [redacted] | Biogen Idec Oceanside | Biogen Idec Cambridge/Biogen Idec RTP |
| [redacted] | Biogen Idec RTP | Biogen Idec Cambridge/Biogen Idec Oceanside |
| [redacted] | Biogen Idec Oceanside | Biogen Idec Cambridge |
| [redacted] | Biogen Idec RTP | |
| [redacted] | | Biogen Idec Cambridge/Biogen Idec Oceanside |
| [redacted] | | |

CH-4

9 Page(s) Withheld of
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§ 552(b)(4)

**Environmental Assessment**

A claim for a categorical exclusion from preparing an Environmental Assessment under 21 CFR 25.31(c) was provided by the firm on the grounds the substances associated with this submission occurs naturally in the environment and the actions associated with this submission do not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

Review Comment - The firm's claim for a categorical exclusion under 21 CFR 25.31(c) is appropriate. No review items were noted.

**cGMP Status**

Three of the five manufacturing sites were inspected over the course of reviewing this application as depicted in Table 1.0 on Pages 3 and 4. Two of the sites' (Biogen Idec, Cambridge Testing Lab [redacted] Based on the Inspections' EIR, FDA Form 483s, the firm's responses to the 483 items, and lack of pending regulatory issues, CDER/OC/DMPQ/IPCB completed a Compliance Check for this application and found no outstanding compliance issues.

**Conclusion**

I. The application was reviewed against existing regulations and guidelines for conformance and was found acceptable. Three amendments were requested to address nine review items. The application, as amended, is recommended for approval.

II. The Drug Substance's Control of Source and Starting Materials of Biological Origin, [redacted] Characterization, Batch Analyses, Justification of Specifications, Reference Standards, and Stability sections and/or subsections were wholly deferred to the product office.

In addition, the Drug Product's Composition, Batch Formula, Controls of Excipients, Reference Standards, and Stability sections and/or subsections were wholly deferred to the product office.

III. Five inspection items were identified and are listed below. These items were evaluated and adequately addressed during the Pre-License inspections as depicted in the appropriate EIR. None of the five inspection items were noted on the FDA Form 483.

Drug Substance Manufacturing – Biogen Idec, RTP, NC

[redacted]

Drug Product Manufacturing -

Cc: HFD-328, Smedley
HFM-328, Calvin Koerner
HFD-328, TFRB Blue Files (STN 125104)
HFD-108, W. Bryan, BLA Chair

Date prepared: Koerner, 28 October 2004
Comments by: Smedley, 3 November 2004
Revised by: Koerner, 4 November 2004