DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125104/0

NOV 23 2004

Biogen Idec Inc.
Attention: Nadine D. Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

We are issuing Department of Health and Human Services U.S. License No. 1697 to Biogen Idec Inc., Cambridge, Massachusetts, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Natalizumab. Natalizumab is indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.

Under this license, you are approved to manufacture Natalizumab drug substance at Biogen Idec, Research Triangle Park, North Carolina. The final formulated product will be manufactured and filled at (b)(4), and labeled and packaged at (b)(4). You may label your product with the proprietary name TYSABRI® and will market it in a 15 mL vial containing 300 mg (20 mg/mL).

The dating period for Natalizumab shall be 15 months from the date of manufacture when stored at 2°-8°C (36°-46°F). The date of manufacture shall be defined as the date of final (b)(4) of the formulated drug product. The dating period for your drug substance shall be 15 months when stored at 2°-8°C (36°-46°F). We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of Natalizumab to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your biologics license application (BLA) for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Natalizumab, or in the manufacturing facilities.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the full waiver granted on August 2, 2002, for the pediatric study requirement for this application, in accordance with 21 CFR.601.27(c)(2)(ii).

As requested in your letter of September 13, 2004, marketing approval of this product is granted under the accelerated approval of biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as basis for approvals of products intended for serious or life-threatening illnesses or conditions.

Approval under these regulations requires, among other things, that you conduct adequate and well-controlled studies to verify and describe the clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as increased survival or improvement in disease-related symptoms. You are required to conduct such studies with due diligence. If postmarketing studies fail to verify that clinical benefit is conferred by Natalizumab, or are not conducted with due diligence, the Agency may, following a hearing, withdraw or modify approval.

Granting of this approval is contingent upon completion of clinical studies to verify the clinical benefit of Natalizumab therapy, as outlined in your letters of November 19 and November 23, 2004. The postmarketing study is subject to the reporting requirements of 21 CRF 601.70:

1. To verify that the clinical benefit of reduction in exacerbations is sustained with continued Natalizumab administration by completing the ongoing Protocols C-1801 and C-1802, "A Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Natalizumab in Subjects with Relapsing-Remitting Multiple Sclerosis" and "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Natalizumab, When Added to Avonex® (Interferon beta-1a) in Subjects with Relapsing-Remitting Multiple Sclerosis" through the planned two years and to submit the results along with the appropriate label changes. The final protocols were submitted on September 16, 2003 (C-1801 and C-1802). Accrual was completed on July 31, 2002 (C-1801) and January 15, 2003 (C-1802). The studies will be completed by December 1, 2004, (C-1801) and March 31, 2005 (C-1802) and the final study reports and revised labeling will be submitted by September 30, 2005.

For administrative purposes, all submissions related to these postmarketing study commitments should be clearly designated "Subpart E Postmarketing Study Commitments."

In addition, we acknowledge your written commitments as described in your letters of November 19 and November 23, 2004, as outlined below:

Additional Postmarketing Studies subject to reporting requirements of 21 CFR 601.70 Studies

2. To further evaluate the safety of Natalizumab and the efficacy of Natalizumab on physical disability by completing the ongoing Protocols C-1801 and C-1802, "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Natalizumab in Subjects with Relapsing-Remitting Multiple Sclerosis" and "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Natalizumab, When Added to Avonex® (Interferon beta-1a) in Subjects with Relapsing-Remitting Multiple Sclerosis" through the planned two years and to submit the results along with the appropriate label changes. The final protocols were submitted on September 16, 2003 (C-1801 and C-1802). Accrual was completed on July 31, 2002 (C-1801) and January 15, 2003 (C-1802). The studies will be completed by December 1, 2004 (C-1801) and March 31, 2005 (C-1802) and the final study reports and revised labeling will be submitted by September 30, 2005.

3. To conduct intensive pharmacokinetic samplings of at least six months duration as part of Study C-1808, "An Open-label, Multicenter Extension Study to Evaluate the Safety and Tolerability of Natalizumab in Subjects with Multiple Sclerosis Who Have Completed Studies C-1801, C-1802, or C-1803," to determine the pharmacokinetics of chronically dosed Natalizumab in the presence of glatiramer acetate. The final protocol will be amended and submitted by March 31, 2005 accrual will be completed by December 31, 2005, study completion will occur by January 31, 2006 and the final study report will be submitted by October 31, 2006.

4. To conduct a Pregnancy Registry for Natalizumab to evaluate approximately 300 Natalizumab-exposed pregnancies for patterns or increases in birth defects in children of women with multiple sclerosis who are exposed to Natalizumab at the time of conception, or at any time during pregnancy. The protocol will include a concurrent control group, to assess birth defects in children of women with multiple sclerosis who are not exposed to Natalizumab prior to conception or during pregnancy. The final protocol will be submitted by June 30, 2005. Accrual will be completed by July 31, 2013. The study will be completed by July 31, 2014 and the final study report will be submitted by April 30, 2015.

5. To develop an immunogenicity screening assay that is less susceptible to interference by circulating drug. In the event that a suitable assay format that meets requirements is identified, the assay will be further developed and validated by June 30, 2006, for the detection of anti-Natalizumab specific antibodies. The final study report will be submitted by March 31, 2007.

6. To further optimize the existing assay or develop a new assay for the detection of neutralizing antibodies. Following optimization of assay parameters, the assay negative cut-point will be redefined and the assay revalidated. Assay validation will be completed by December 31, 2005. The final study report will be submitted by September 30, 2006.

7. To conduct a study to measure the effects of Natalizumab on percentages of lymphocytes including CD3+, CD4+, and CD8+ as well as B and NK cells and the associated α4 integrin expression and binding site saturation. The final protocol will be submitted by June 30, 2005. Accrual will be completed by December 15, 2006. The study will be completed by June 15, 2007 and the final study report will be submitted by March 15, 2008.

8. To conduct a single-center, multiple dose study to measure the effects of Natalizumab on responses to neo-antigen and recall vaccination in subjects with relapsing multiple sclerosis in approximately 40 subjects who have a series of two booster immunizations. The final protocol will be submitted by June 30, 2005. Accrual will be completed by December 15, 2006. The study will be completed by June 15, 2007, and the final study report will be submitted by March 15, 2008.

9. To develop an assay to quantify bispecific Natalizumab IgG4 antibodies in human serum samples. Reagent development feasibility studies will be completed by March 31, 2006, and if successful, an assay for detecting bispecific Natalizumab IgG4 antibodies will be developed and validated by June 30, 2006. The final study report will be submitted by March 31, 2007.

10. To test the samples obtained from the pharmacokinetic sampling cohort in Studies C-1803 and C-1808 for bispecific Natalizumab IgG4 antibodies, should a sensitive assay for Natalizumab IgG4 antibodies be developed. The final protocol for Study C-1803 was submitted on November 26, 2003. The final protocol for Study C-1808 will be amended and submitted by March 31, 2005. Accrual was completed for Study C-1803 on October 7, 2003 and will be completed for Study C-1808 by March 31, 2005. The study will be completed by June 30, 2007 and the final report will be submitted by March 31, 2008.

11. To use the current screening assay to assess the immunogenicity of Natalizumab by conducting a study of patients who are at least three months post-treatment. This commitment will be addressed as part of Study C-1808, "An Open-label, Multicenter Extension Study to Evaluate the Safety and Tolerability of Natalizumab in Subjects with Multiple Sclerosis Who Have Completed Studies C-1801, C-1802, or C-1803." The final protocol will be amended and submitted by March 31, 2005. Accrual will be completed by March 31, 2005. The study will completed by March 29, 2007. The final study report will be submitted by October 31, 2007.

12. To retest all available samples from completed studies C-1801 and C-1802 once new screening and neutralizing immunogenicity assays have been successfully developed (see commitments 5 and 6). The final protocols were submitted on September 16, 2003 (C-1801 and C-1802). Accrual was completed on July 31, 2002 (C-1801) and January 15, 2003 (C-1802). The study will be completed by December 31, 2006. The final study report will be submitted by June 30, 2007.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

13. To conduct a study measuring the effects of freeze/thaw on Natalizumab drug product. All drug product release tests will be performed. The final study report will be submitted by June 30, 2005.

14. To conduct a study to detect and quantify (b)(4) that could be present in (b)(4) of Natalizumab drug product. The study can use a placebo formulation if this facilitates the detection of (b)(4) . The study will identify and assess worst-case stability/shipping conditions in which (b)(4) could be found in Natalizumab drug product. The final study report will be submitted by June 30, 2005.

15. To re-evaluate drug substance and drug product release and in-process specifications after the first 30 lots of each are produced. Specifications and limits will be adjusted, if necessary. The data and analysis for the first 30 lots will be provided in the 2006 Annual Report to be submitted by January 31, 2007.

16. To submit the final study report for Study #309-33-01 for the prenatal and postnatal development study of Natalizumab in cynomolgus monkeys by March 31, 2005.

We request that you submit clinical protocols to your IND, BB-IND 6895, with a cross-reference letter to this BLA, STN BL 125104. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL125104. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**
- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,

- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

As required by 21 CFR 601.45, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement with a cover letter requesting advisory comment. Send two copies of the promotional materials to the Division of Drug Marketing, Advertising and Communications, HFD-42, Food and Drug Administration, 5600 Fishers Lane, Rockville MD 20852. Please submit final promotional materials with FDA Form 2253 to the above address at the time of initial dissemination of the labeling or at the time of initial publication of the advertisement.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation

involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Division of Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective Oct. 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Sincerely,

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Karen D. Weiss, M.D.
Director
Office of Drug Evaluation VI
Center for Drug Evaluation and Research