DEPARTMENT OF HEALTH AND HUMAN SERVICES

Our Reference Nos. 95-0979 & 95-0975

MAY 17 1996

Burt A. Adelman, M.D..
Vice President Development Operations
Biogen, Inc.
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Adelman:

Enclosed is Department of Health and Human Services Establishment License No. 1204 issued to Biogen, Inc., Cambridge, Massachusetts, in accordance with the provisions of Title III Part F of the Public Health Service Act of July 1, 1944 (58 Stat. 702) controlling the manufacture and sale of biological products. This license authorizes you to manufacture and ship for sale, barter or exchange those products for which your establishment holds unsuspended and unrevoked product licenses issued by the Department of Health and Human Services.

Also enclosed is a product license authorizing your establishment to manufacture and ship for sale, barter, or exchange in interstate and foreign commerce, Interferon beta-1a, under the trade name Avonex. Interferon beta-1a is approved for the treatment of relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. The bulk product will be manufactured at your Cambridge, Massachusetts facility. Formulation of the bulk and filling into a 30 mcg fill size will take place at
The product will be labeled and packaged at
. and distributed from

While you will not be required to submit samples of future lots of the product for release, you are requested to submit semi-annual trend analyses of results from tests performed for lot release.

The dating period for the dosage formulation of this product shall be 15 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the bulk. Results of ongoing stability studies should be submitted throughout the dating period as they become available including the results of stability studies from the first three production lots.

We acknowledge your letter of April 26, 1996 in which you commit to conduct the following:

1. A staged clinical research program in secondary chronic progressive multiple sclerosis that includes a randomized, controlled study using disability as the primary endpoint.

2. Randomized, controlled studies that will evaluate the dose efficacy relationship of Interferon beta-1a for the treatment of multiple sclerosis across the dose range of 30 to 90 mcg.

3. A randomized, controlled study to assess the usefulness of continued treatment with Interferon beta-1a beyond two years.

4. MRI assessments and examination of the strengths and weaknesses of MRI as a surrogate for clinical outcomes; evaluations to determine the extent of depression or aggravation of pre-existing psychiatric disease with Interferon beta-1a treatment; and evaluations of antibody formation against Interferon beta-1a, and assessment of possible clinical correlations with effectiveness when antibodies are developed. With regard to MRI assessments, you will prospectively define in study protocols the analytic plan to evaluate the correlation between MRI and clinical outcomes.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). These requirements became effective on December 27, 1994. All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit three copies of all final printed labeling at the time of use and include part II of the label transmittal form with completed implementation information. In addition, please submit three copies of introductory advertising and promotional labeling. You may wish to submit the proposed material in draft with FDA Form 2567 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Bethesda, MD 20852-1448. All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Please acknowledge receipt of the enclosed product license to the Director, Division of Application Review and Policy (HFM-585), and the enclosed establishment license to the Director, Division of Establishment Licensing (HFM-205), Center for Biologics Evaluation and Research.

Sincerely yours,

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Jerome A. Donlon, M.D., Ph.D.
Director
Office of Establishment Licensing
and Product Surveillance
Center for Biologics
Evaluation and Research

Enclosures