DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125290/0

BLA APPROVAL
August 14, 2009

Novartis Pharmaceuticals Corporation
Attention: Xin Du, Ph.D.
Sr. Associate Director, VP, Global Regulatory CMC
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Du:

We have approved your biologics license application for interferon beta-1b effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, interferon beta-1b under your existing Department of Health and Human Services U.S. License No. 1244. Interferon beta-1b is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.

Under this authorization, you are approved to manufacture interferon beta-1b at your facility in Emeryville, California. You may label your product with the proprietary name Extavia and will market it as lyophilized 0.3mg IFN-b-1-b, in 3 mL total capacity vials.

The dating period for interferon beta-1b shall be 24 months from the date of manufacture when stored at 25°C. The date of manufacture shall be defined as the date of the (prior to the fill) of the formulated drug product. The dating period for your drug substance (b) (4)) shall be (b) (4) when stored at 5°C or for when stored at -20°C.

You currently are not required to submit samples of future lots of interferon beta-1b 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 for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of interferon beta-1b, or in the manufacturing facilities.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

There is no pediatric study requirement for this application because the application does not involve a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIRMENTS OF SECTION 506B

We remind you of your postmarketing study commitments agreed to in your submission dated July 22, 2009.

1. Novartis has committed to monitor endotoxin for the (b) (4) pool. Endotoxin data will be collected for the next 10 batches or for three years, whichever is shorter. Please provide endotoxin data and the proposed endotoxin limits for the (b) (4) pool at the end of the study.

Final Protocol submission:	January 31, 2010
Study completion:	January 31, 2013
Final report submission:	March 31, 2013

2. Novartis has committed to collect bioburden data for (b) (4) pools maintained at 2-8 degree C for thirty days. Once this data is collected and analyzed, the alert and action bioburden limits for the (b) (4) pool will be assessed and based on this assessment, the adjustment of the limits will be evaluated. Please provide the collected data and the proposed new bioburden limits for the (4) pool at the end of the study.

Final Protocol submission:	November 30, 2009
Study completion:	December 31, 2010
Final report submission:	February 28, 2011

3. Novartis has committed to use 100 mL sample volume instead of 10 mL for the pre-filtration bioburden test. Data will be collected for the next 10 batches or for 3 years and the bulk pre-filtration bioburden limit will be set based on the 100 mL sample volume. Please provide the collected data and the proposed new bulk pre-filtration bioburden limit at the end of the study.

Final Protocol submission:	December 31, 2009
Study completed:	December 31, 2012
Final report submission:	February 28, 2013

4. Novartis has committed to develop an analytical test method for use in release and stability testing of the Extavia drug product to provide appropriate control of the size of the IFN /HSA complexes to ensure product quality.

Final Protocol submission:	June 30, 2010
Study completed:	January 15, 2011
Final report submission:	February 15, 2011
New Specification submission:	March 15, 2011

Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA 125,290. In addition, under 21 CFR 601.70, you should include a status summary of each commitment in your annual report to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**", "**Postmarketing Commitment Final Report**", or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Your proposed REMS, submitted on June 12, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. An evaluation of patients' understanding of the serious risks of Extavia
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125290 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125290
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125290
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

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 Food and Drug Administration, Center for Drug Evaluation and Research, Division of Compliance Risk Management and Surveillance, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Biological product deviations sent by courier or overnight mail should be addressed to Food and Drug Administration, CDER, Office of Compliance, Division of Compliance Risk Management

and Surveillance, 10903 New Hampshire Ave. Bldg. 51, Rm 4203, Silver Spring, MD 20993-0002.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. For administrative purposes, please designate this submission "Product Correspondence – Final SPL for approved STN BL 125290/0." In addition, within 21 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug. Based on the agreement between the company and the Agency on June 11, 2009, the approved labeling will be used for the second and sequential commercial batches of Extavia.

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

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.

Sincerely,

/Russell Katz/
Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research