DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103949/5153

SUPPLEMENT BLA APPROVAL
March 29, 2011

Schering Corporation
Attention: Brenda Marques, PharmD
Associate Director and Liaison, Global Regulatory Affairs
2000 Galloping Hill Road
Location: K-6-1, Mailstop: 1350
Kenilworth, NJ 07033

Dear Dr. Marques:

Please refer to your Supplemental Biologics License Application (sBLA), dated September 27, 2007, and received September 27, 2007, submitted under section 351 of the Public Health Service Act for peginterferon alfa-2b.

We acknowledge receipt of all amendments submitted through March 21, 2011. The September 24, 2010, submission constituted a complete response to our October 29, 2009, action letter.

This "Prior Approval" efficacy supplement to your biologics license application provides for the new indication of adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy. For this indication, peginterferon alfa-2b will be marketed under the new proprietary name, Sylatron.

PRODUCT LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed package insert, Medication Guide, and Patient Instructions for Use. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U

CM072392.pdf. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 103949/5153**."

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted via electronic mail on March 26, 2011, as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA STN 103949/5153**." Approval of this submission by FDA is not required before the labeling is used.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since peginterferon alfa-2b was approved on January 19, 2001, we have become aware of the following:

- Serious debilitating fatigue, depression which may result in suicidal ideation and completed suicides, and anorexia that limits activities of daily living, from the clinical trial EORTC 18991 that was used to demonstrate safety and efficacy for the treatment of advanced melanoma.
- There has not been an evaluation on the effect of the four-fold increase in the dose of peginterferon alfa-2b for the treatment of advanced melanoma on the QT/QTc interval.

- There has not been an evaluation of the immunogenicity of peginterferon alfa-2b in patients with melanoma. Patients with chronic hepatitis C have an incidence of 8% to 15% for binding antibodies and 2% for neutralizing antibodies. The lack of an adequate immunogenicity characterization (anti-drug antibody responses) of peginterferon alfa-2b could expose patients with melanoma to the toxicities of the drug without providing benefit.
- There has not been an evaluation for possible drug-drug interaction at the four-fold increase in the dose of peginterferon alfa-2b in patients with melanoma. Drug-drug interaction data from a healthy volunteer trial and a chronic hepatitis C trial have shown opposite effects on CYP2D6 activity, demonstrating data from the underlying patient population being treated are necessary for adequate assessment of potential drug-drug interactions.
- There has not been a safety and pharmacokinetics (PK) evaluation of the four-fold increase in the dose of peginterferon alfa-2b in accordance with the "FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function" in patients with melanoma.

We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of anti-drug antibody response.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR #1: To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to peginterferon alfa-2b, including procedures for accurate detection of neutralizing antibodies to peginterferon alfa-2b in the presence of peginterferon alfa-2b levels that are expected to be present in the serum or plasma at the time of patient sampling. In the event such an assay cannot be developed, evidence of due diligence in attempting to develop the assay will be provided.

The timetable you submitted on March 18, 2011, states that you will develop this assay according to the following schedule:

Final Report Submission (Assay and Methodology): December 30, 2011

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to address the following:

- Assess a known serious risk of whether the toxicity spectrum observed with peginterferon alfa-2b as administered in Trial EORTC 18991 is reduced with an alternative regimen that is also effective. There is a specific need for characterization of the incidence and severity of toxicities which result in drug discontinuation, which include debilitating fatigue, depression which may result in suicidal ideation and completed suicides, and anorexia that limits activities of daily living, with an alternate regimen. Risks to patients will be mitigated if this alternate dose and schedule of peginterferon alfa-2b is effective and is less toxic than that studied in EORTC 18991.
- Identify the unexpected serious risk of peginterferon alfa-2b prolongation of the QT/QTc interval
- Assess the known risk of anti-drug antibody responses
- Identify an unexpected serious risk of drug-drug interactions
- Identify an unexpected serious risk of increased peginterferon alfa-2b toxicity secondary to impaired renal clearance.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify or assess these unexpected serious risks, signals of a serious risk, or known serious risks of peginterferon alfa-2b.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR #2: To conduct a randomized, multicenter, observation-controlled trial of peginterferon alfa-2b as adjuvant therapy in 1200 patients with ulcerated primary cutaneous melanoma with negative sentinel lymph node biopsy (T1b-T4bN0M0) randomized 1:1 to peginterferon alfa-2b 3.0 mcg/kg SC administered weekly for 24 months or observation alone for 24 months. The trial will characterize toxicity of treatment, specifically debilitating fatigue, depression, and anorexia, and evaluate relapse-free survival (RFS). Secondary endpoints will include overall survival. The trial will be powered to detect an increase in RFS rate by 6.8% at 2 years, by 9.4% at 5 years, and by 10% at 10 years. The trial will be powered to detect a hazard ratio of 0.7 for overall survival. The trial design and statistical analysis plan must adequately address the comments provided to you in our December 10, 2010, letter to IND 7194 regarding proposed trial 18081.

The timetable you submitted on March 18, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: September 15, 2011
Trial Completion Date: January 15, 2020
Final Report Submission: July 15, 2020

PMR #3. To conduct a clinical trial that will assess the effect of peginterferon alfa-2b on the QT/QTc interval. This QT assessment must be performed in an adequate

number of subjects receiving the highest clinical dose approved and at the steady state maximum therapeutic exposure that is anticipated in patients with melanoma to ensure that changes of 20 ms in QTc interval can be excluded. ECG with time-matched PK samples will be collected at the anticipated steady state concentration and across the entire dosing interval at steady state. ECGs will be collected in replicates and centrally read. Statistical analyses will include central tendency analysis, concentration-QT analysis and categorical analysis.

The timetable you submitted on March 18, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: October 31, 2011
Trial Completion Date: July 31, 2013
Final Report Submission: May 31, 2014

PMR #4: To conduct an assessment of anti-drug antibody (ADA) and neutralizing ADA responses to peginterferon alfa-2b with validated assays capable of sensitively detecting ADA responses in the presence of peginterferon alfa-2b levels that are expected to be present at the time of patient sampling. ADA responses will be evaluated in all available samples from Trial EORTC 18991. Samples tested positive for binding ADA will be evaluated for neutralizing ADA responses. The final report will include information on the level of peginterferon alfa-2b in each patient's test sample at each sampling time point.

The timetable you submitted on March 18, 2011, states that you will conduct this assessment according to the following schedule:

Final Report Submission: April 30, 2012

PMR #5: To conduct a drug interaction trial in 24 healthy subjects receiving subcutaneous peginterferon alfa-2b 6 mcg/kg once weekly for four weeks with probe substrates for multiple cytochrome P450 enzymes administered before the first dose and after the last dose of peginterferon alfa-2b. Pharmacokinetic blood and urine samples will be collected after the administration of the probe substrates and peginterferon alfa-2b (up to 168 hours) to measure enzyme activities and peginterferon alfa-2b systemic exposure.

The timetable you submitted on March 18, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: October 31, 2011
Trial Completion Date: July 31, 2013
Final Report Submission: May 31, 2014

PMR #6: To conduct a dedicated clinical trial assessing the safety and pharmacokinetics (PK) of peginterferon alfa-2b in accordance with the

"FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis and Impact on Dosing and Labeling." The renal function subgroups should have similar demographic characteristics with respect to age, gender and weight. The number of patients enrolled in the trial should be sufficient to detect clinically important PK differences that would warrant dosage adjustment recommendation. The frequency and duration of blood sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan should be included in the final protocol submitted to FDA.

The timetable you submitted on March 18, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: July 31, 2011
Trial Completion Date: October 31, 2012
Final Report Submission: August 31, 2013

Submit clinical protocols to your IND 7194, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this BLA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, please call Ms. Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

/Patricia Keegan/
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURES:
- Content of Labeling
- Carton and Container Labeling
- Medication Guide
- Patient Instructions for Use