CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125196

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125196/0

Schering Corporation
Attention: Rachael Steiner
Associate Director and Liaison
Global Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

June 13, 2008

Dear Ms. Steiner:

We have approved your biologics license application for PegIntron™/REBETOL® Combo Pack (Peginterferon alfa-2b, REDIPEN® Single-dose Delivery System and REBETOL® Ribavirin, USP) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, PegIntron™/REBETOL® Combo Pack under your existing Department of Health and Human Services U.S. License No. 0994. PegIntron™/REBETOL® Combo Pack is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.

Under this authorization, you are approved to co-package Peginterferon alfa-2b and Ribavirin, USP at your facility in Kenilworth, New Jersey. You may label your product with the proprietary name PegIntron™/REBETOL® Combo Pack and it will be marketed in 50 mcg/0.5 mL REDIPEN® co-packaged with (56) 200 mg REBETOL® capsules, 80 mcg/0.5mL REDIPEN® co-packaged with (56) 200 mg capsules, 120 mcg/0.5 mL REDIPEN® co-packaged with (70) 200 mg capsules and 150 mcg/0.5 mL REDIPEN® co-packaged with (84 and 96) 200 mg capsules.

The expiration date for the combination package shall be dependent on the shortest expiration date of any component.

You currently are not required to submit samples of future lots of Peginterferon alfa-2b 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 Peginterferon alfa-2b, 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.

We are waiving the pediatric study requirement for ages 0 to 3 years for this application because necessary studies are impossible or highly impracticable. There are too few children in this age group with chronic hepatitis C who present with sufficiently advanced liver disease to justify clinical trials of a potentially toxic treatment.

We are deferring submission of your pediatric study requirement for ages 3 to 17 until June 30, 2008 because the individual components are approved for use in adults and the pediatric studies are complete but have not yet been submitted. We note that, as stated in our September 16, 2004, letter regarding STN BL [redacted] we required that you conduct a pediatric study to assess the safety, efficacy, tolerability and pharmacokinetics of Peginterferon alfa-2b when used in combination with ribavirin in approximately 100 pediatric patients 3 to 17 years of age with chronic hepatitis C infection. When submitted, this study will also meet the pediatric study requirement for STN BL 125196.

Your deferred pediatric study required under section 505(B)(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.70 and section 505B (a)(3)(B) of the FDCA. This required study is listed below.

> Deferred pediatric study under PREA to assess the safety, efficacy, tolerability and pharmacokinetics of Peginterferon alfa-2b when used in combination with ribavirin in approximately 100 pediatric patients 3 to 17 years of age with chronic hepatitis C infection.
>
> Final Report Submission: June 30, 2008

Submit a cross reference letter to STN BL 125196 when you submit the final study report to STN BL 103949/0. Use the following designator to prominently label all submissions:

> **Required Pediatric Assessment(s)**

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENT

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary

determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Under 21 CFR Part 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed PegIntron™/REBETOL® Combo Pack. Pursuant to 21 CFR Part 208, FDA has determined that PegIntron™/REBETOL® Combo Pack poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of PegIntron™/REBETOL® Combo Pack. FDA has determined that PegIntron™/REBETOL® Combo Pack is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use PegIntron™/REBETOL® Combo Pack. PegIntron™/REBETOL® Combo Pack is associated with numerous safety risks, including an increased risk of cerebrovascular complications due to stroke in patients with few or no expected risk factors for stroke.

Your proposed REMS, received May 6, 2008, is approved. The REMS consists of the Medication Guide approved with this letter and the timetable for submission of assessments of the REMS included in your May 6, 2008, submission. The timetable you submitted is as follows:

1st FDAAA assessment:	November 2009 (18 months from approval)
2nd FDAAA assessment:	May 2011 (3 years from approval)
3rd FDAAA assessment:	May 2015 (7 years from approval)

Information needed for assessment of the REMS should include but may not be limited to:

a. A survey of patients' understanding of the serious risks of PegIntron™ and REBETOL®
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

Use the following designator to prominently label all submissions, including supplements, relating to this REMS:

Risk Evaluation and Mitigation Strategy (REMS)

Please note that:

- This Medication Guide must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling [21 CFR 201.57(c)(18)] or 21 CFR 201.80(f)(2)];

- You are responsible for ensuring that this Medication Guide is available for distribution to every patient who is dispensed a prescription for this product [21 CFR 208.24];

- The final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including a minimum of 10 point text; and

- You are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided [21 CFR 208.24(d)].

ADVERSE EVENT REPORTING

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. 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, HFD-330, Montrose Metro 2, 11919 Rockville Pike, Rockville, MD 20852.

CONTENT OF LABELING

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. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "Product Correspondence – Final SPL for approved STN BL 125196/0" 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.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed draft labels 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 (October 2005).* 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 STN BL 125196/0.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

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.

If you have any questions, contact Victoria Tyson Medlock, Regulatory Project Manager, at 301-796-0827.

Sincerely,

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research