CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 125249/0

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

STN: BL 125249/0

BLA APPROVAL

FEB 27 2008

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Attention: Mierette R. Stocker
Associate Director, Regulatory Affairs

Dear Ms. Stocker:

Please refer to your biologics license application (BLA) dated May 25, 2007, received May 29, 2007, submitted under section 351 of the Public Health Service Act for Arcalyst (rilonacept).

We acknowledge receipt of your submissions dated June 26 (2), July 2, 24, and 26, August 20 and 24, September 24 and 27, October 3, 25, and 26, and December 19, 2007, and January 23 and 25, and February 13, 22, and 27, 2008.

We also acknowledge receipt of your submission dated October 26, 2007, which constituted a major amendment.

We are issuing Department of Health and Human Services U.S. License No. 1760 to Regeneron Pharmaceuticals, Tarrytown, New York, 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 Arcalyst (rilonacept). Arcalyst is indicated for treatment for cryopyrin-associated periodic syndromes (CAPS).

Under this license, you are approved to manufacture rilonacept drug substance at your Regeneron facility in Rensselaer, New York. The final lyophilized drug product will be manufactured at the [redacted] The final lyophilized drug product will be labeled and packaged at [redacted] You may label your product with the proprietary name Arcalyst and market it in 20-mL, single-use vials, each containing 220 mg of rilonacept.

The dating period for Arcalyst shall be 18 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 formulated drug product. The dating period for your formulated drug substance shall be 18 months when stored at ≤ -20°C. We have approved the stability protocols in your license

application for the purpose of extending the expiration dating period of your formulated drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of Arcalyst 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.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from 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 to the enclosed labeling text, submitted February 27, 2008, for the package insert and the patient package insert. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, **"SPL for approved STN BL 125249/0."**

Pursuant to 21 CFR 201.57(c)(18) and 201.80(f)(2), patient labeling must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling.

CARTON AND CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and container labels, submitted February 27, 2008, 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 125249/0."** 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.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

POSTMARKETING STUDY COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS OF 21 CFR 601.70

We acknowledge your written commitments as described in your letters dated February 27, 2008 as outlined below:

Nonclinical

1. To conduct a study in cynomolgus monkeys examining the effects of rilonacept exposure of the pregnant female during the third trimester of development. You will submit a detailed outline of the study and rationale for review.

   Protocol Submission: by April 2008
   Study Completion: by January 2010
   Final Report Submission: by October 2010

2. To conduct a juvenile animal study in cynomolgus monkeys to assess effects on sex hormones and bone development. You will submit a detailed outline of the study and rationale for review.

   Protocol Submission: by April 2008
   Study Start: by January 2010
   Final Report Submission: by October 2010

Clinical

3. To assess the safety of long-term use of rilonacept in the pediatric patient population by establishing a pediatric registry. The registry will collect information on growth and development as well as adverse events, particularly serious infections. The duration of the study will be at least five years.

   Study Completion: by July 2013
   Final Report Submission: by January 2014

4. To conduct a pharmacokinetics (PK) study in the pediatric population.

   Study Completion: by January 2010
   Final Report Submission: by July 2010

5. To assess whether either lower maintenance doses or a longer interval between doses could be equally effective as, but potentially safer than, the approved dose. The study could be designed to randomize patients on rilonacept to blindly continue on the approved dose or to switch to a lower dose or a longer interval between doses and to assess symptom scores over, for example, 9 weeks.

Submission of supporting data: by April 2008
Study Completion (if needed): by January 2010
Final Report Submission: by July 2010

POSTMARKETING STUDY COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS OF 21 CFR 601.70

1. Pharmacovigilance: In addition to standard pharmacovigilance practices, for the first five years of marketing, particular attention will focus on reports of serious infections, pregnancy outcomes, and off-label use.

   Study Completion: by January 2014
   Final Report Submission: Quarterly reporting for the first three years, then annually

2. To assess release and shelf-life specifications for rilonacept drug substance, formulated drug substance, and drug product, as appropriate. Data and specifications assessment will be provided two years from time of approval and reported in an annual report.

   Study Completion: by April 2010
   Final Report Submission: by Annual Report 2010

3. To perform validation studies on the modified assay that measures [redacted] in rilonacept drug substance, formulated drug substance, and drug product. Using those data, to establish [redacted] content specification for drug substance, formulated drug substance, and drug product release and stability, and drug substance, formulated drug substance, drug product reference standard qualification and stability. The protocol, final report, and proposed specifications will be submitted as a CBE-30 supplement.

   Study Completion: by January 2009 [redacted]
   Final Report Submission: by April 2009 (CBE-30)

4. To validate the [redacted] for measurement of [redacted] at the concentration of intended use with alternative [redacted] analytical methods. Methods such as [redacted] should also address [redacted]. The full validation package will be submitted as an annual report. In addition, a re-assessment of specifications based on the validated method will be included in the annual report.

   Study Completion: by April 2009
   Final Report Submission: by Annual Report 2009 [redacted]

5. To validate the DS, FDS, and DP rilonacept [redacted] assay for the new proposed acceptance criteria [redacted]

ranges). The validation protocol and report will be submitted to the Agency in the annual report.

Study Completion: by April 2009
Final Report Submission: by Annual Report 2009

6. To qualify the additional characterization assays used for [redacted]. Assay qualifications reports will be submitted in the annual report.

Study Completion: by April 2009
Final Report Submission: by Annual Report 2009

7. To perform an adequate [redacted] study [redacted]. The study will be performed [redacted] of rilonacept, and the study report will be submitted in the annual report.

Study Completion: by January 2009 [redacted]

Final Report Submission: by Annual Report 2009

8. To re-qualify [redacted] in the [redacted] test. The qualification procedures and summary data will be submitted in the annual report.

Study Completion: by April 2009
Final Report Submission: by Annual Report 2009

9. If Regeneron performs [redacted] testing in lieu of [redacted] testing and/or [redacted] testing, a direct or indirect correlation of the two tests will be performed. Correlation studies at a [redacted] that is comparable to the sensitivity of the [redacted] test will be performed. Results will be submitted in the first annual report after the testing is completed.

Study Completion: by April 2009
Final Report Submission: by Annual Report 2009

10. To perform stability testing on one lot of rilonacept formulated drug substance and one lot of drug product annually for each year in which rilonacept formulated drug substance or drug product is manufactured. The ongoing stability program will continue until testing of all remaining time points from the lots used to support the approved shelf life have been reached. These stability data will be submitted in the annual report.

Additionally, lots that are manufactured following significant changes to the approved manufacturing process or facility, and lots that are reprocessed outside of the approved manufacturing process will be placed on stability.

Study Completion: Annual reporting
Final Report Submission: Annual reporting

Submit clinical protocols to your IND, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this BLA. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments, as appropriate:

- Postmarketing Study Commitment Protocol
- Postmarketing Study Commitment - Final Study Report
- Postmarketing Study Correspondence
- Annual Status Report of Postmarketing Study Commitments

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 February 2006 Guidance for Industry: *Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997* (see http://www.fda.gov/cder/guidance/5569fnl.htm) for further information.

PROMOTIONAL MATERIALS

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the following address:

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

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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you 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 an electronic copy of the letter to both this BLA and to the following address:

MedWatch, HFD-001
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

REPORTING REQUIREMENTS

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 following address:

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.

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 following address:

Division of Compliance Risk Management and Surveillance
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20903

Biological product deviations sent by courier or overnight mail should also be sent to this address.

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 rilonacept or in the manufacturing facilities.

MEDWATCH-TO-MANUFACTURER PROGRAM

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.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Kathleen Davies, Regulatory Project Manager, at (301) 796-2205.

Sincerely,

MD, MPH

Curtis Rosebraugh, M.D., M.P.H.
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures (3):
Package Insert
Patient Package Insert
Carton and Immediate Container Labeling