CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 125249/0

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies, NIH Bldg 29B, HFD-123
29B Lincoln Drive, Bethesda, MD 20892

The Quality Team Leader's Executive Summary

From: **Chana Fuchs, Ph.D., Division of Monoclonal Antibodies (DMA)** 2/26/08

Through: **Patrick Swann, Ph.D., Deputy Director, DMA** Patrick Swann 2/26/08
Kathleen Clouse, Ph.D., Director, DMA Kathleen Clouse 2/26/08

BLA Number: **125249/0**
Product: **Arcalyst™ (Rilonacept or IL-1 Trap)**
Sponsor : **Regeneron Pharmaceuticals, Inc.**

Date of Review : **January 23, 2008**

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of Arcalyst (rilonacept) is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use (under conditions specified in the package insert).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The sponsor has agreed to the following CMC post-marketing commitments:

1. 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 in 2 years from time of approval and reported in an annual report.
2. To perform stability testing of one rilonacept formulated drug substance lot and one drug product lot annually for each year in which rilonacept formulated drug substance or drug product is manufactured. As part of the post approval commitment, 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.
3. To perform validation studies on the modified assay that measures ——— in rilonacept drug substance, formulated drug substance, and drug product. Accordingly, Regeneron will establish ——— ontent specification for DS, FDS, and DP release and stability, and DS, FDS, DP reference standard qualification and stability. The protocol, final report, and the proposed specification should be submitted as a CBE-30.
4. To validate accuracy of the ——— method for measurement of ——— t the concentration of intended use with alternative——— analytical methods. Methods such as ——— should also address ———
5. To validate DS, FDS, and DP rilonacept ——— ssay for the new proposed acceptance criteria (——— Validation protocol and report should be submitted to the Agency in the next annual report.

6. To qualify the additional [redacted] assays used for [redacted]. Assay qualifications reports will be submitted in the next annual report.
7. To perform an adequat[redacted] study [redacted]. The study should be performed [redacted] of rilonacept, and the study report will be submitted in the next annual report.
8. To re-qualify [redacted] in the [redacted] test. [redacted] The qualification procedures and summary data will be submitted in the next annual report.
9. As committed in Regeneron's response to FDA questions communicated in the filing letter, "in the event that Regeneron plans to perform [redacted] esting in lieu of [redacted], a direct or indirect correlation of the two tests will be performed". Correlation studies [redacted] that is comparable to the sensitivity of the [redacted] test will be performed. Results will be submitted in the next annual report.

II. Summary of Quality Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- Arcalyst (rilonacept) is supplied as a sterile, single use, 20 mL glass vial containing lyophilized powder for reconstitution with 2.3mL sterile water for injection (sWFI). Prior to lyophilization, formulated drug substance contains – mg/mL rilonacept [redacted] histidine [redacted] glycine, [redacted] arginine [redacted] sucrose, [redacted] polyethylene glycol 3350 (PEG 3350), pH 6.5. After reconstitution, the resulting solution is clear and colorless to pale yellow and the final volume in the vial is 2.7 mL of an 80 mg/mL rilonacept solution.

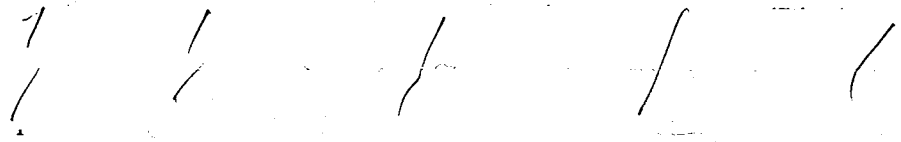
- Each carton of Arcalyst contains four 20-mL glass vials of lyophilized rilonacept. The diluent sterile Water for Injection, and the needles, syringes, and alcohol swabs are not supplied with the Arcalyst package. Based on discussions with Regeneron, [redacted] Sterile Water for Injection, USP is available on the market both as single use, which contains no bacteriostatic or antimicrobial agents, and as multidose vials, bacteriostatic, for injection. Data from the BLA shows that Arcalyst is not stable in water containing preservatives, so only preservative free sterile water for injection (sWFI) should be used to resuspend the product. As the size of vials most commonly available are 10 mL and larger, the package insert and/or instructions to the patient [redacted]

- The lyophilized rilonacept DP is reconstituted with 2.3 mL of sterile water for Injection. This results in a vial containing 2.7 mL of an 80 mg/mL rilonacept solution. For adults, maintenance dosing consists of 160 mg administered as a single, 2 mL, subcutaneous injection. This may result in as much as 0.7 mL of reconstituted rilonacept remaining in the vial. Regeneron claimed that this extra volume is necessary to enable accurate withdrawal of the 2.0 mL of reconstituted solution. The viscosity of rilonacept DP is — centipoise (cP) (water is ~ 1 cP). Based on clinical experience, lower reconstitution volumes resulted in difficulty in withdrawing accurate volume of reconstituted solution. Less volume can also be an issue because the large size of the 20 mL glass vial provides a large surface area. Discussions with the clinical reviewer identified that subcutaneous administrations of 320 mg of rilonacept and intravenous infusion of up to 2000 mg of rilonacept have been administered in various clinical trials under IND, without an apparent increase in safety signals as compared to the dosage used in the supporting pivotal trial. Additionally, USP/NF 30 <1151> Pharmaceutical Dosage Form, Injections recommends that for a 20 mL vial, an excess volume for up to 0.90 mL for viscous liquids is acceptable for reconstituted product. Based on these facts, we have no reason to deny the current presentation. However, in discussions with Regeneron it was agreed (amendment 16) that to mitigate accidental overfill of the syringe, Regeneron would assure that standard syringes with 0.1 mL graduations will be supplied to the patients at the time of drug dispensing by the — pharmacy.

- Stability of the Rilonacept drug product has been established for up to 18 months at 2° to 8° C. The lyophilized IL-1 Trap product is to be stored refrigerated at 2 to 8 °C (36° to 46°F) inside the original carton to protect from light. Photostability studies have identified that rilonacept degrades when exposed to light under the tested conditions.

- After reconstitution, IL-1 Trap may be kept at room temperature, but should be used within three hours of reconstitution. IL-1 Trap does not contain preservatives; therefore, unused portions should be discarded.

- Rilonacept is a dimeric, in-line fusion glycoprotein that is made up of the extracellular domain sequences of the IL-1 Type I receptor (IL-1RI), and the IL-1 receptor accessory protein (IL-1RAcP), fused. — to the Fc portion of human IgG1. Rilonacept binds IL-1β, IL-1α, and IL-1ra and prevents IL-1 ligand binding to the IL-1 receptor. The equilibrium dissociation constants for rilonacept binding to IL-1β, IL-1α and IL-1ra were determined by SPR to be 0.5 pM, 1.4 pM and 6.1 pM, respectively. The molecular weight of rilonacept is approximately 251 kDa,



- Rilonacept's mechanism of action is mediated via direct binding and capture of the IL-1 receptor ligands. Although the molecule contains the Fc portion of a human IgG1, rilonacept does not appear to activate Fc and complement receptors. Studies evaluated

in [redacted] ave a potential to impact on the clearance and immunogenicity of rilonacept, Regeneron was asked to include a [redacted] assay that can measure [redacted] content in rilonacept DS, FDS, and DP as well as to update acceptance criteria for both the [redacted] assays.

- Rilonacept was observed to be more chemically stable when the pH is [redacted]. The formation of [redacted] was not observed when the pH was below this level, while the lowest [redacted] was observed at pH 6.5.

- Rilonacept drug substance is produced by a cell culture process at the [redacted] scale, using a [redacted] Chinese hamster ovary (CHO) [redacted] cell line [redacted] [redacted]. The manufacturing process includes steps validated to remove impurities [redacted] No animal-derived raw materials are used directly in the current manufacturing process of rilonacept, other than the CHO cells [redacted] Measures such as testing of cell banks and raw materials, lot traceability, and acceptance criteria have been implemented to prevent product contamination from potential viral and non-viral adventitious agents.

- The rilonacept drug substance and drug product manufacturing processes have been modified a number of times during clinical development. Biochemical comparability study results between successive processes were reviewed. Based on biochemical and biophysical data submitted, products appear comparable. Drug product used in the pivotal trial Study IL1T-AI-0505 was produced by the commercial process.

- The potency of rilonacept is defined as [redacted] e [redacted], using a proprietary [redacted] l assay [redacted] [redacted]. Potency specification is [redacted]

- Regeneron suggested relatively broad acceptance criteria for a number of release and stability indicating assays. The proposed specifications are being narrowed to better reflect the rilonacept manufacturing and clinical experience, and based on knowledge gained from assay validation and product characterization. Because manufacturing experience is so limited, appropriate statistical assessment of the data is difficult. Therefore, specifications will be re-assessed after additional manufacturing experience is gained as part of a post-marketing commitment [See PMCs].

B. Description of How the Drug Product is Intended to be Used

- Arcalyst (rilonacept) is indicted for treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

- Arcalyst (rilonacept) drug product is provided as a sterile, single-use, 20-mL glass vial configuration containing 220 mg of rilonacept as a lyophilized powder for reconstitution. No diluent (sWFI) is provided with Arcalyst.

- Arcalyst vials should be stored under refrigeration at 2° C to 8°C inside the original carton to protect it from light. The recommended expiration dating period for Arcalyst vials is 18 months from date of manufacture when stored under these conditions.

- The recommended dosage regimen for Arcalyst in adults is a loading dose of 320 mg delivered as two, 2 mL, subcutaneous injections of 160 mg each, followed by once-weekly injections of 160 mg administered as a single, 2 mL, subcutaneous injection.

- Rilonacept should be reconstituted with 2.3 mL sterile water for injection to a final concentration of 80 mg/mL, allowing sufficient volume for withdrawal of the 2mL dose.

- Reconstituted rilonacept solution may be kept at room temperature for up to 3 hours

- Arcalyst is packaged as a single use presentation. Formulation does not include preservatives so any unused portion remaining in the vial must be discarded.

C. Basis for Approvability or Not-Approval Recommendation

- Rilonacept is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. Rilonacept is manufactured consistently, leads to a safe and effective product, and approval is recommended for the proposed indication.

- Post-marketing commitments described in the recommendations section above will provide additional information to assure the continued safety of the product.

Quality unit Assessment

I. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

The review of module 3.2 is attached as a separate document that also includes review of the immunogenicity. A quality review of the PK analytical assays was performed as an independent consult to the review team and provided to Dr. Zhang as an independent document.

II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

Regeneron claims categorical exclusion from the requirements of environmental assessment (BLA section S1.12.14) based on:

- 21CFR25.31(b) - the estimated concentration of the substance at the point of entry into the aquatic environment be below 1 ppb
- 21CFR25.51(a) -expected introduction concentration (EIC) calculation
- Calculated EIC of — ppb based on: — batches/year, average yield of — batch, and estimated 1.22 x 10exp11 lt/day total flow of wastewater (POTW) from the 1996 clean water needs survey by US EPA.

Regeneron concludes that the calculated amount introduced is not expected to affect the quality of the human environment

III. LIST OF DEFICIENCIES TO BE COMMUNICATED

The deficiencies have been addressed in the communications with the sponsor. A number of issues have been resolved as post-marketing commitments (see above).

Review Cover Sheet

BLA STN 125249/0

ARCALYST (Rilonacept)

Regeneron, Inc.

Ruth Cordoba Rodriguez, Ph.D.
Gurpreet Gill-Sangha, Ph.D.
Jun Park, Ph.D.
Division of Monoclonal Antibodies; HFD-123

Product Quality Review Data Sheet

1. **BLA#** STN 125249/0

2. **REVIEW #:** 1

3. **REVIEW DATE:** 26-Feb-08

4. **REVIEWERS:** Ruth Cordoba, Ph.D
Gurpreet Gill-Sangha, Ph.D.
Jun Park, Ph.D.
Chana Fuchs, Ph.D. – Team Leader

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS:**

Communication/Document	Date
Clinical Pre-BLA Meeting	19-SEP-2006
CMC Pre-BLA Meeting	12-DEC-2006
Facilities meeting	08-AUG-2006
Information Request Letter	22-JUN-2007
inspection Waiver	14-JUN-2007
Telecon	18-JUL-2007
Filing Review memo (45 days).	26-JUL-2007
Regeneron 483	21-SEP-2007
Information Request Letter	8-AUG-2007
Filing Deficiency Letter	10-AUG-2007
Information Request Letter	11/SEP-2007
Information Request Letter	10-SEP-2007
Information Request Letter	16-OCT-2007
Telecon	17-OCT-2007
Information Request Letter	16-NOV-2007
Information Request Letter	27-NOV-2007
Meeting with Regeneron	28-NOV-2007
Telecon	10-JAN2008
Telecon	16-JAN-2008
Telecon	26-FEB-2008

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
STN 125249/0/1 Original Submission–CMC RU	13-FEB-2007
STN 125249/0/2	26-FEB-2007
STN 125249/0/3	25-MAY-2007
STN 125249/0/4	26-JUN-2007
STN125249/0/6	2-JUL-2007
STN 125249/0/7	24-JUL-2007
STN 125249/0/9 (tradename review)	20-AUG-2007
STN 125249/0/10	24-AUG-2007

STN 125249/0/11	24-SEPT-2007
Response to Regeneron 483	27-SEPT-2008
STN 125249/0/13	3-OCT-2007
STN 125249/0/15	25-OCT-2007
STN 125249/0/16 (major amendment)	26-OCT-2007
STN 125249/0/17	19-DEC-2007
STN 125249/0/18 (final specs)	25-JAN-2008

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Regeneron Pharmaceuticals, Inc.
Address:	777 Old Saw Mill River Road Tarrytown, New York 10591-6707 USA FDA registration number: 2436285
Representative:	Mierette Stocker
Telephone:	914-345-7590

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: Arcalyst
b) Non-Proprietary/USAN: Rilonacept
c) Code name: IL-1 Trap (CAS) registry number is 501081-76-1
d) Common name: IL-1 Trap
e) Drug Review Status: Accelerated
f) Chemical Type: recombinant Fc Fusion Protein

9. **PHARMACOL. CATEGORY:** Therapeutic Fc Fusion Protein to IL-1

10. **DOSAGE FORM:** Sterile parenteral solution

11. **STRENGTH/POTENCY:**

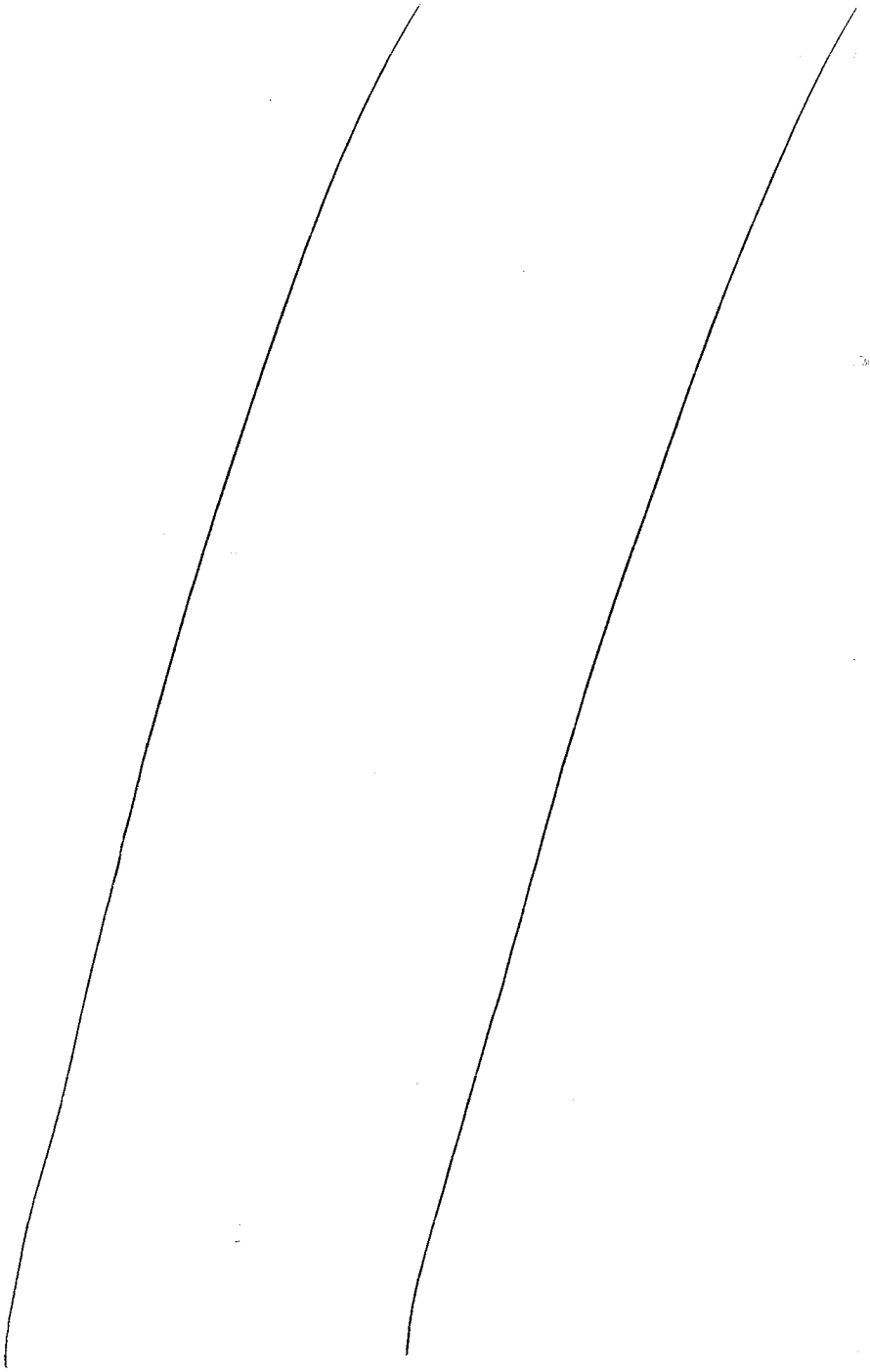
a) The concentration of Arcalyst (rilonacept) Drug Product is 80 mg/ml when reconstituted with 2.3 mL WFI
b) Potency is defined as [redacted] using a proprietary [redacted] assay [redacted]. Potency specification is [redacted]
c) Dating period for vialed drug product is 18 months when stored at 2°C -8°C and protected from light.
d) Rilonacept is filled into 20 mL glass vials containing 220 mg of rilonacept.

12. **ROUTE OF ADMINISTRATION:** Subcutaneous injection.

13. **ACID (Animal Component Information Database)**

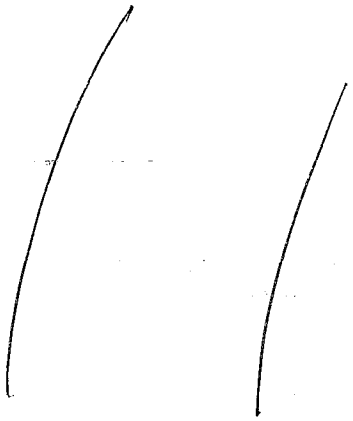
Section 3.2.A.2. lists starting materials of biological origin. No animal derived raw materials are directly used in the current rilonacept manufacturing process. The animal

derived raw materials listed below are used to manufacture components used in the rilonacept manufacturing process:



14. **PRIMARY STRUCTURE, PHARMACOLOGICAL CATEGORY,**

Rilonacept is a dimeric, in-line fusion glycoprotein, produced in CHO cells, and contains the extracellular domain sequences of the IL-1 Type I receptor (IL-1RI), and the IL-1 receptor accessory protein (IL-1RAcP), fused to the Fc portion of human IgG1.



The physicochemical and biochemical properties of rilonacept are summarized in the following table.

APPEARS THIS WAY
ON ORIGINAL

Characteristic	Data
Description	IL-1 Trap is a dimeric glycoprotein with a total molecular weight of ~251 kDa,
Ligand binding specificity	IL-1β, IL-1α, IL-1ra
IL-1 ligand binding affinity (dissociation constant). K_D determined by BiaCore SPR technology.	0.5 pM for IL-1β, 1.4 pM for IL-1α, and 6.1 pM for IL-1ra

In addition to the properties listed in the table above, the following characterization of rilonacept is supported from the contents of the quality section (section 3.2.S.3):

15. **RELATED/SUPPORTING DOCUMENTS:**

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
/	V	/	/	/	4- Sufficient information in application	N/A	Information for the manufacturing process is in the BLA. A PAI was waived.

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

16. **STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Status	Approve	1-JAN-2008	Gil Salud
Environmental Assessment	Approve	1-JAN-2008	Ruth Cordoba
DMPQ – memo for Drug Substance facilities review	Approve	23-OCT-2007	Michelle Clark-Stuart
DMPQ – memo for Drug Product facilities review	Approve	22-APRIL-2007	Bo Chi
DDMAC Carton and vial labeling	Approve	23-OCT-2007	Walter Fava
DMA Carton and vial labeling	Approve	21-FEB-2008	Sheila Rawls
DMETS/DDMAC – tradename review	Approve	24-AUG-2007	Walter Fava
EIR for Regeneron	VAI	1-JAN-2008 (1)	Clark-Stewart/Chi/ Park/Cordoba
Inspection Waiver for —	Waive PAI	12-SEP-2007	Chi/Cordoba/Gil-Sangha
Inspection Waiver for —	Waive PAI (2) compliance check completed	22-JAN-2008	Bo Chi

(1) DMPQ review date states VAI has not been changed since EIR

(2) — was inspected and granted NAI 11/2007.

17. **Inspectional Activities**

A pre-approval inspection (PAI) for rilonacept bulk drug substance and formulated drug substance production at the Regeneron-Rensselaer facility was conducted on September 13-21, 2007 by TFRB inspectors Michelle Clark-Stuart, and Bo Chi, and product reviewers Jun Park

and Ruth Cordoba-Rodriguez. Regeneron-Rensselaer is responsible for manufacturing of rilonacept drug substance, formulated drug substance, QC testing of drug substance, formulated drug substance, and drug product and final QA review and approval. Regeneron-Rensselaer has been inspected by the FDA previously with no regulatory actions, prior warnings or recalls. A four-observation form 483 was issued at the end of this inspection. Observations consisted of re-working of batches without written procedures, inadequate employee training records, failure to investigate and resolve deviations in a timely manner, and inadequate procedures for cleaning of product contact equipment. Five issues not considered observations were presented to the firm during the close-out of the inspection. These issues consisted of failure to provide appropriate pre-inspectional requests to inspectors, such as a comprehensive list of Out-Of-Specifications, late data entry on laboratory log books, deficient written procedures, release of formulated drug substance with limited testing identified as 'on status' release, and lack of documentation on a spill that occurred in the [redacted] These issues were either resolved during the inspection or did not result in a 483 citation, but were noted in the EIR report in section XIII. Five recommendations were made to the firm during inspection close-out. These recommendations consisted of the [redacted]

[redacted] These recommendations were included in the EIR report section XIV. The issues and recommendations described above should be followed-up in future inspections.

Inspection at [redacted] under contract to Regeneron, was waived. This waiver was based on the criteria as required per SOPP 8410 v.2, "Determining When Pre-licensing/pre-approval Inspections (PLI/PAI) are Necessary." The review committee recommended that the inspection be waived due to the type of activities performed at this site as well as to a compliance check confirming that there are no pending actions to prevent approval at this site. There are no substantive differences between the drug product manufacturing processes described in the BLA and those used for other licensed biotechnology parenteral products at the same [redacted] area of the facility. Activities at [redacted]

[redacted] is the contract [redacted] Inspection was not conducted in this facility due to the low risk of activities performed at this site as well as to a compliance check identifying that there are no pending actions to prevent approval at this site.

18. **Recommendations on Approvability**

The data submitted in this application support the conclusion that the manufacture of Arcalyst (rilonacept) is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use under conditions specified in the package insert.

Administrative

A. Reviewers' Signatures

Product Reviewer: Ruth Cordoba-Rodriguez, Ph.D. 2/26/08

Product Reviewer: Gurpreet Gill-Sangha , Ph.D. Gurpreet Gill-Sangha 2/26/08

Product Reviewer: Jun Park , Ph.D. 2/26/08

B. Endorsement Block

Product Division Team Leader: Chana Fuchs, Ph.D 2/25/08

Product Division Deputy Director: Patrick Swann, Ph.D. 2/26/08

Product Division Director: Kathleen A. Clouse, Ph.D. Kathleen A. Clouse 2/26/08

C. CC Block

OBP Office Director: Steven Kozlowski, M.D.
DAARP Deputy Division Director: Rigoberto Roca, M.D.
DAARP Division Director: Bob Rappaport, M.D.
Division of Monoclonal Antibodies File/BLA STN 125249/0

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_____ Draft Labeling

_____ Deliberative Process

DEPARTMENT OF HEALTH AND HUMAN SERVICES — Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: January 22, 2008

To: Administrative File, STN **125249/0**

From: Gilbert Salud, CSO, CDER/OC/DMPQ BMT, HFD-328 1/23/08

Through: Edwin Rivera, Branch Chief, CDER/OC/DMPQ/BMT, HFD-328 1/23/08

Subject: CMC Team Leader Review Summary: Original BLA for Rilonacept® (IL-1 Trap)

US License # 1760

Applicant Regeneron Pharmaceuticals Inc.

Product Rilonacept® (IL-1 Trap)

Indication Treatment of cryopyrin-associated periodic syndromes.

Due date: February 27, 2008

Recommendation: The Manufacturing Assessment and Pre approval Compliance Branch recommends approval of the BLA from an equipment, facility, and microbiology perspective (microbial/sterile quality).

Summary

Manufacturers:

The Drug Substance Manufacturing and formulation occur at:

Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike
Rensselaer, New York 12144-3423
USA
FEI: 1000514603

Drug Product Manufacturers:

The [redacted] *occur at:*

[redacted]

The Proposed Labeling and Packaging of the drug product occur at:

[redacted]

The Analytical Testing and Release Assays occur at:

Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike,
Rensselaer, New York 12144-3423
USA
FEI: 1000514603

[redacted]

On December 7, 2007, a compliance verification was conducted on the manufacturing sites listed above. There was no compliance issues found. A pre approval inspection was conducted on September 13-21, 2007 for the Regeneron Pharmacueitcals Inc site. This inspection was classified VAI. Currently, .there is no compliance issue that would prevent approval of these manufacturing sites.

General Product Quality

Drug Substance

The drug substance review was conducted by Ms. Michelle Clark-Stuart, MS. This review covered the following: Summary of the DS manufacturing process, Process Equipment Cleaning and preparation, Process Hold Times, Control of Critical Steps and Intermediates, Process Validation, Control of Drug Substance, Container Closure, and Stability. One review issue was identified.

The review is adequate. For additional information on her review please refer to CMC Review, Dated October 23, 2007.

Drug Product

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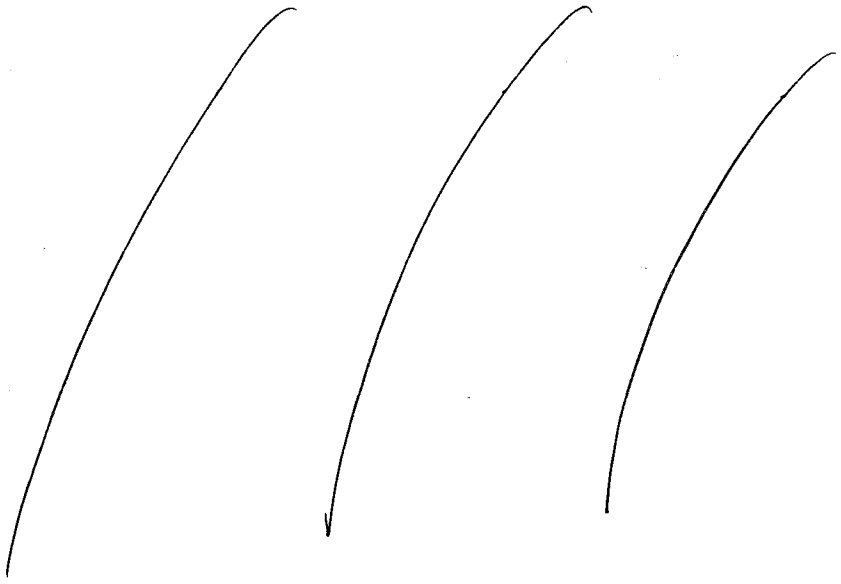
✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process



Dr. Chi's review is adequate. For additional information on her review please refer to CMC Review, Dated January 22, 2008.

Conclusion

I. The supplement was reviewed for conformance to the appropriate regulations and guidance and found acceptable. The supplement is recommended for approval.

II. Information and data in this submission not related to drug product sterility assurance, drug substance control (source /starting material), [redacted], characterization, batch analysis, product specifications, [redacted] and product stability were deferred to the OPS/OBP.

III. A post approval inspection follow up should be conducted on items identified in the 9/13/07 – 9/21/07 inspection.

Cc: HFD-328, Rivera
HFD-123, Fuchs
HFD-170, Davies
HFD-320, Friedman
HFD-328, BMT Blue Files (STN 125249)

Archived File: S:\archive\BLA\125249\125249.0.TL.memo.1/22/08.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES — Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: **1/22/2008**
To: Administrative File, **STN 125249/0**
From: Bo Chi, CDER/OC/DMPQ/TFRB, HFD-328
Endorsement: Patricia Hughes, CDER/OC/DMPQ/TFRB, HFD-328
Gilbert Salud, acting team leader, CDER/OC/DMPQ/TFRB, HFD-328
Edwin Rivera Martinez, branch chief, CDER/OC/DMPQ/MAPCB, HFD-322
Subject: New Biologic License Application (BLA)
Applicant: Regeneron Pharmaceuticals, Inc.
US License: 1760
Facility:

Product: Rilonacept (IL-1 Trap)
Dosage: Lyophilized powder, 160 mg/vial, subcutaneous injection
Indication: Treatment of cryopyrin-associated periodic syndromes
PDUFA date: February 27, 2007

Recommendation: The drug product part of this application is recommended for approval from sterility assurance and product quality microbiology perspective.

Review Summary

Regeneron Pharmaceuticals, Inc has submitted this BLA for rilonacept, a product indicated to treat cryopyrin-associated periodic syndromes. The drug substance is manufactured at Regeneron Pharmaceuticals, Inc. at 81 Columbia Turnpike, Rensselaer, NY 12144, USA. The drug product (DP) is manufactured at the contract Labeling and Packaging is performed at The application contains CMC information in an eCTD format.

Assessment

Drug Product

Description of the Composition of the Drug Product (3.2.P.1):

IL-1 Trap Drug product is supplied as lyophilized powder in 20 mL clear glass vials. The vials are stoppered with 20 mm stoppers. Upon reconstitution with 2.3 mL of sterile Water For Injection (WFI), the solution contains

80 mg/mL IL-1 Trap in aqueous buffered solution at pH 6.5 containing — histidine, — (w/v) polyethylene glycol 3350, — w/v) Glycine, — arginine, and — sucrose. Two mL can be withdrawn from the vial, which provides a dose of 160 mg IL-1 Trap. IL-1 Trap is administered as a 160 mg dose by subcutaneous injection once weekly.

Reviewer comment: The information provided is sufficient.

Satisfactory

Pharmaceutical Development (3.2.P.2):
IL-1 Trap is a recombinant fusion protein consisting of human IL-1 receptor extracellular domains and the Fc portion of human IgG1. The protein is manufactured in recombinant Chinese Hamster Ovary (CHO) cells. IL-1 Trap is a dimeric glycoprotein with a total molecular weight of around 251 kDa,

Microbiological Attributes (3.2.P.2.5):

Container-closure and package integrity (CCI):

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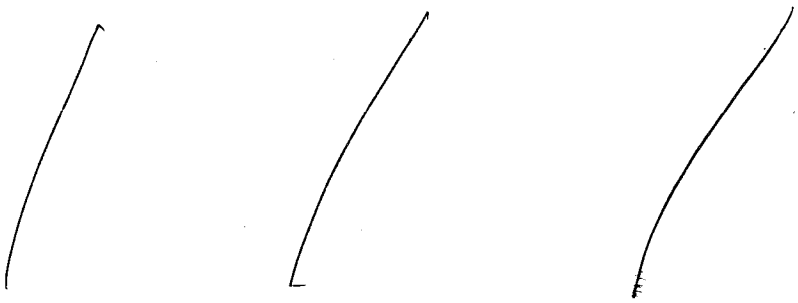

Reviewer comments: Facility and equipment information was adequately provided.

Satisfactory

Environmental Assessment:

A claim for a categorical exclusion from preparing an Environmental Assessment under 21 CFR 25.31(a) was provided by the firm on the grounds that small amount introduced is not expected to affect the quality of the human environment and no extraordinary circumstances exist that would otherwise require an environmental assessment.

cGMP Status:

In response to our request of December 7, 2007, the Investigations and Pre-approval Compliance Branch has completed the review and evaluation on December 10, 2007. "There are no pending or going compliance issues to prevent approval of STN 125240/0 at this time. [redacted] was last inspected on 9/24-27/2007 and classified NAI. There is no final district endorsement nor has the profiles been updated."

"The Manufacturing Assessment and Pre-approval Compliance Branch has completed its review and evaluation of the compliance check below. There are no ongoing or pending compliance actions that would prevent approval of STN 125249/0 at this time. [redacted] was last inspected on 11/19-11/21/2007 and found acceptable for [redacted] That inspection was classified NAI."

Conclusion

I. The BLA is recommended for approval from a product quality microbiology perspective.
II. Information and data in this submission not related to drug product sterility assurance was not evaluated and should be reviewed by an OBP reviewer.
III. No inspectional follow up items were identified.

Cc: HFD-328, Chi
HFD-170, Davies
HFD-123, Gill-Sangha
HFD-123, Cordoba-Rodriguez
HFD-123, Fuchs
HFD-123, Park
HFD-320, Rivera
HFD-328, TFRB Blue Files (STN 125249)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date:	**October 23, 2007**
To:	Administrative File, **STN 125249/0**
From:	Michelle Y. Clark-Stuart, MGA, MT (ASCP), CDER/OC/DMPQ/BMT, HFD-328
Through:	Gil Salud, Acting Team Leader, CDER/OC/DMPQ/BMT, HFD-328
Subject:	**Review Memo: Biological License Application (BLA):** New BLA
US License	#1760
Applicant	**Regeneron Pharmaceuticals, Inc.**
Product	**rilonacept (IL-1 Trap®)**
Indication	**Treatment of CAPS (Cryopryin-Associated Periodic Syndromes)**
Dosage:	**Lyophilized powder for reconstitution, 160 mg/vial, subcutaneous injection**
Due date:	February 27, 2008

Recommendation: The drug substance (DS) section of the application (3.2.S) application was reviewed from an equipment, facility, and microbiology quality perspective. The application is recommended for approval.

Review Summary

Regeneron Pharmaceuticals, Inc. submitted this BLA in support of the manufacturing of rilonacept, a recombinant fusion protein that blocks IL-1 signaling both *in vitro* and *in vivo*. IL-1 Trap consists of the human cytokine receptor extracellular domains of both IL-1RI and IL-1AcP fused to the Fc portion of human IgG1. IL-1 Trap is a dimeric glycoprotein with a [redacted] to give a total molecular weight of approximately 250 kDa. DS is manufactured at Regeneron Pharmaceuticals, Inc. in Rennselaer, NY.

The drug substance (DS) CMC sections of this electronic BLA were evaluated in this review for adequacy from an equipment, facility, and microbiology perspective. The sections evaluated included in part 2.3.S.2, 2.3.S.4, 2.3.S.6, and 2.3.S.7

An inspection of the facilities was conducted from September 13 – 21, 2007 by Michelle Y. Clark-Stuart, Bo, Chi, Ruth Cordoba-Rodriguez, and Jun Park. A Form FDA 483 was issued to the facility on September 21, 2007.

Review Narrative

Drug Substance

Manufacturer – 3.2.S.2

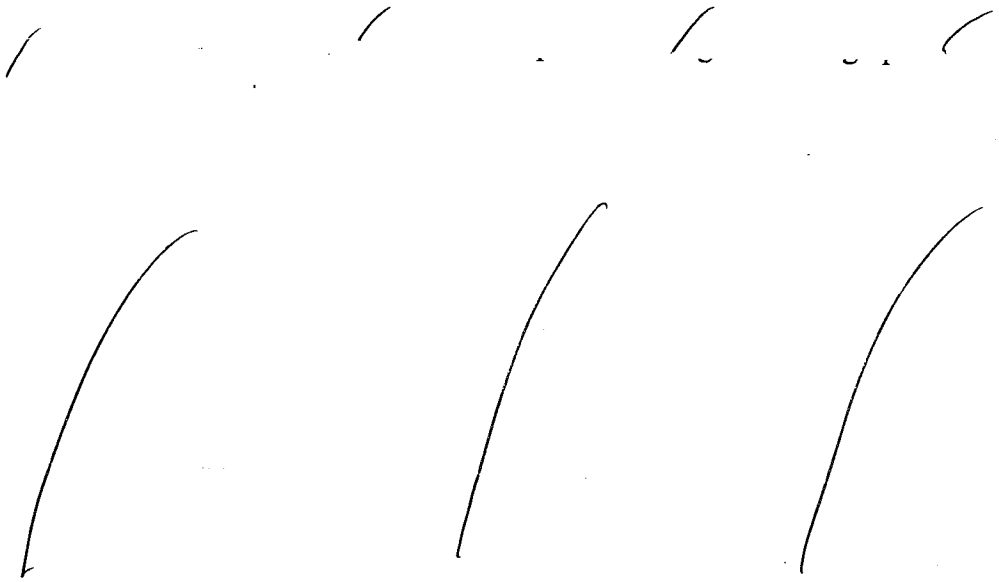
The manufacturer of the drug substance is:

Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike
Rennselear, NY 12144
FEI pending (this is the first license application for a product from Regeneron)
FDA registration number: 1320218

Quality control testing is also performed at this site.

Description of Manufacturing Process and Process Controls - 3.2.S.2.2 and 3.2.A.2

The manufacturing process changed during the course of clinical development and each process was evaluated for comparability to the previous process. The process intended for commercial manufacturing is the — process and was used in phase 2 and 3 clinical studies. The — manufacturing process involves



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Comment:
This section is satisfactory.

Environmental Assessment

The BLA states under section 1.12.14 in FDA regional information that "IL-1 Trap is subject to a categorical exclusion under the provisions of 21 CFR 25.15(d) and 21 CFR 25.31 (c) based on considerations of its effects when exposed to the environment."

Specifically, under 21 CFR 25.31(c), an action on a BLA is categorically excluded on the grounds the substances associated with this submission occurs naturally in the environment and the actions associated with this submission do not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

cGMP Status

The Investigations and Preapproval Compliance Branch has completed its review and evaluation of the compliance check below. There are no pending or ongoing compliance actions that would prevent approval of STN 125249/0. Regeneron Pharmaceuticals, Inc, Rensselaer, NY was last inspected on 10/21-10/27/05 and classified NAI for profile VBP.

Conclusion

I. The drug substance section of the application is acceptable from an equipment, facility, and microbiology product quality perspective. The application is recommended for approval.

II. The Drug Substance's Control of Source and Starting Materials of Biological Origin, [redacted], Characterization, Batch Analyses, Justification of Specifications [redacted], and Stability sections and/or subsections were not evaluated in this review.

In addition, the Drug Product's Composit ion, Batch Formula, Controls of Excipients, [redacted], and Stability sections and/or subsections were not evaluated in this

review.

III. Any items identified during the 9/13 – 21/07 inspection at Regeneron Rensselaer, NY manufacturing site are addressed in the corresponding Establishment Inspection Report (EIR).

Cc: HFD-322, Rivera Martinez
HFM-328, Clark-Stuart
HFD-328, Randazzo,
HFD-328, TFRB Blue Files (STN 125249)

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Inspection Waiver Memorandum

Date: June 12, 2007

From: Bo Chi, HFD-328, CDER/OC/DMPQ/TFRB

To: BLA File – STN 125249/0

Subject: Recommendation to waive a pre-approval inspection at contract drug product manufacturing facility

Sponsor: Regeneron Pharmaceuticals, Inc.
U.S. License # 1760

Contract: / / /

Product: Rilonacept (IL-1 Trap)

Dosage: Lyophilized powder, 160 mg/vial, subcutaneous injection

Indication: cryopyrin-associated periodic syndromes

Through: Patricia Hughes, HFD-328, CDER/OC/DMPQ /TFRB PFH 6/14/07
Michelle Clark-Stuart, Acting team leader, HFD-328, CDER/OC/DMPQ/TFRB MCS 6/19/07

Waiver Recommendation:
There are no substantive differences between the drug product manufacturing processes described in the BLA and those used for other licensed parenteral products at [redacted]. These processes have been inspected four times in the past three years with no significant regulatory findings. Concurrence is requested to waive pre-approval inspection.

Clearance Routing

CONCUR / DO NOT CONCUR DATE 6/14/07

Rick Friedman, Director, Division of Manufacturing and Product Quality, Office of Compliance, CDER, HFD-320

Kathleen Clouse CONCUR / DO NOT CONCUR DATE 9/12/2007

Kathleen Clouse, Director, Division of Monoclonal Antibodies, Office of Biotechnology Products, Office of Pharmaceutical Science, CDER, HFD-123

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