

Davies, Kathleen

From: Davies, Kathleen
Sent: Friday, December 14, 2007 2:43 PM
To: 'Mierette Stocker'
Subject: RE: BLA 125249 - CMC Request for advice regarding proposed acceptance criteria for

DEC 20 2007

KNO

Importance: High

Hi Mierette,

Please find the product team's responses to your two questions below. If you have further questions, please let me know.

Kathleen

1. Regarding the

v
m

2. Regarding the specifications for _____ you should provide your proposed acceptance criteria with the 12/19/07 responses and summary of supporting data, including the new data used in their revised acceptance criteria. We will evaluate this in conjunction with the other data we have. Agreements on final release specifications will follow review of the full data package.

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Wednesday, December 12, 2007 2:43 PM
To: Davies, Kathleen
Subject: BLA 125249 - CMC Request for advice regarding proposed acceptance criteria for _____

Dear Kathleen,

Regeneron would like the opportunity to revise the proposed acceptance criteria for _____ best methods. The revised acceptance criteria will be based upon the inclusion of data from the _____ batch lots manufactured this year and an evaluation of _____. We can provide the proposals for the revised acceptance criteria with complete, supportive data packages at the same time we submit our complete responses to the latest IRs targeted for Dec 19, 2007 or we can provide as a separate submission to the BLA. Please let me know as soon as possible how the Division would like for us to proceed.

Thanks and kind regards,

Mierette
 O: 914-345-7590
 M: 914-548-4390

12/19/2007

Davies, Kathleen

From: Clark-Stuart, Michelle
Sent: Thursday, December 06, 2007 12:58 PM
To: Davies, Kathleen; Randazzo, Giuseppe; Chi, Bo
Subject: FW: Facility check for the following BLA

DEC 10 2007
Kr. Davies

Please read the establishment evaluation request reply below.

Michelle Y. Clark-Stuart, MGA/MIS, MT (ASCP)

FDA/CDER/OC/DMPQ

HFD-328

MM II, Rm. 334

Phone - 301-827-8953

Fax - 301-827-0005

e-mail: Michelle.Clark-Stuart@fda.hhs.gov

Please note, Moved to MM II on 4/30/07.

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify me via e-mail or telephone.

From: Ferguson, Shirnette D
Sent: Thursday, December 06, 2007 12:55 PM
To: Clark-Stuart, Michelle; CDER-TB-EER
Subject: RE: Facility check for the following BLA

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.

Shirnette Ferguson

From: Clark-Stuart, Michelle
Sent: Wednesday, December 05, 2007 10:15 AM
To: CDER-TB-EER; Davies, Kathleen; Randazzo, Giuseppe
Cc: Clark-Stuart, Michelle
Subject: Facility check for the following BLA
Importance: High

Please provide a check for BLA, STN 125249/0 from Regeneron Pharmaceuticals, Inc.

This is their first application for a license to commercialize a product at the following manufacturing site:

81 Columbia Turnpike

Rensselaer, NY 121444-3423

FDA registration number = 1320218

Product - riloncept (IL-1 Trap) drug substance, an orphan drug for treatment of Cryopryin-Associated Periodic Syndromes (CAPS).

PDUFA date = 2/27/08

DEC 10 2007

Please note that I will be on leave after Friday, 12/7/07 until next year and they want all reviews by 12/20/07.

Thanks,

Michelle

Michelle Y. Clark-Stuart, MGA/MIS, MT (ASCP)

FDA/CDER/OC/DMPQ

HFD-328

MM II, Rm. 334

Phone - 301-827-8953

Fax - 301-827-0005

e-mail: Michelle.Clark-Stuart@fda.hhs.gov

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Davies, Kathleen

From: Clark-Stuart, Michelle
Sent: Monday, December 10, 2007 10:37 AM
To: Randazzo, Giuseppe; Davies, Kathleen; Chi, Bo
Cc: Clark-Stuart, Michelle
Subject: FW: Facility check for the following BLA.rtf
Importance: High

DEC 10 2007

I have received the additional one for _____ and it is below.

Michelle Y. Clark-Stuart, MGA/MIS, MT (ASCP)

FDA/CDER/OC/DMPQ

HFD-328

MM II, Rm. 334

Phone - 301-827-8953

Fax - 301-827-0005

e-mail: Michelle.Clark-Stuart@fda.hhs.gov

Please note, Moved to MM II on 4/30/07.

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From: Ferguson, Shirnette D
Sent: Monday, December 10, 2007 10:32 AM
To: Clark-Stuart, Michelle; CDER-TB-EER
Subject: RE: Facility check for the following BLA.rtf

The Investigations and Preapproval Compliance Branch has completed its evaluation and review of the compliance check below. There are no pending or going compliance issues to prevent approval of STN 125240/0 at this time. _____ was last inspected on 9/24-27/2007 and classified NAI. There is no final district endorsement nor has the profiles been updated.

Shirnette

From: Clark-Stuart, Michelle
Sent: Friday, December 07, 2007 12:16 PM
To: CDER-TB-EER
Cc: Clark-Stuart, Michelle
Subject: Facility check for the following BLA.rtf
Importance: High

From: Clark-Stuart, Michelle
Sent: Wednesday, December 05, 2007 10:15 AM
To: CDER-TB-EER; Davies, Kathleen; Randazzo, Giuseppe
Cc: Clark-Stuart, Michelle
Subject: Facility check for the following BLA

Importance: High

Please provide a check for BLA, STN 125249/0 from Regeneron Pharmaceuticals, Inc.

I am adding another site for an establishment evaluation request below, I only need the information for _____

This is their first application for a license to commercialize a product at the following manufacturing site:

81 Columbia Turnpike

Rensselaer, NY 121444-3423

FDA registration number = 1320218

Product - riloncept (IL-1 Trap) drug substance, an orphan drug for treatment of Cryopryin-Associated Periodic Syndromes (CAPS).

PDUFA date = 2/27/08

Please note that I will be on leave after Friday, 12/7/07 until next year and they want all reviews by 12/20/07.

Thanks,
Michelle

DEC 10 2007

**Michelle Y. Clark-Stuart, MGA/MIS, MT (ASCP)
FDA/CDER/OC/DMPQ**

HFD-328

MM II, Rm. 334

Phone - 301-827-8953

Fax - 301-827-0005

e-mail: Michelle.Clark-Stuart@fda.hhs.gov

Please note, Moved to MM II on 4/30/07.

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REGENERON

Patrice A. Gilooly
Director
Quality Assurance

Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike
Rensselaer, NY 12144

Phone 518 488 6054
Fax 518 488 6451
www.regeneron.com

December 12, 2007

Edwin Rivera Martinez, Branch Chief
FDA/CDER/DMPQ, Montrose Metro II
11919 Rockville Pike
Rockville, MD 20852
Tel (310) 827-9012
Fax (310) 827-8909

RE: Regeneron Pharmaceuticals, Inc. Revised Response Letter to FDA 483 Observations

On October 19, 2007, FDA CDER/DMPQ Inspectors Michelle Y. Clark-Stuart and Bo Chi, Biotech Manufacturing Team (BMT) Acting Team Leader Gil Salud and Project Manager Giuseppe Randazzo contacted Regeneron Pharmaceuticals, Inc. to discuss Regeneron's 483 response letter dated September 27, 2007 regarding the Pre-Approval Inspection conducted from September 13-21, 2007, for rilonacept bulk drug substance manufacturing. In attendance from Regeneron was Patrice Gilooly, Director of Quality Assurance and Gerry Underwood, Vice President of Technical Operations. The FDA team expressed dissatisfaction with Regeneron's response to 483 Observation #7 and requested that the response be revised and resubmitted.

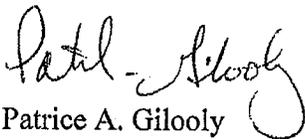
We have considered the FDA request and are pleased with the opportunity to confirm and expand on information and guidance indicated during the teleconference. Please accept the enclosed response to 483 Observation #7 as a substitute for the original response in its entirety.

We note that our response to the observation include certain confidential company information.

If I can be of further assistance or answer additional questions, please contact me at (518) 488-6054.

Thank you for your courtesy and consideration in this matter.

Sincerely,


Patrice A. Gilooly

Enclosure

2

10 Page(s) Withheld

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Draft Labeling

Deliberative Process

Davies, Kathleen

From: Davies, Kathleen
Sent: Tuesday, November 27, 2007 1:23 PM
To: 'Mierette Stocker'
Cc: Lenh Mong
Subject: RE: Nov 28 Meeting
Attachments: IR Request_11-26-2007.pdf

JAN 16 2008

WMD

Hi Mierette,

Please find the remaining items attached. We look forward to meeting with you tomorrow.

Kathleen

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Tuesday, November 27, 2007 12:30 PM
To: Davies, Kathleen
Cc: Lenh Mong
Subject: Nov 28 Meeting

Hello Kathleen,

If you are able to send the remaining items for discussion this afternoon, could you please copy Lenh on the communication?

I will be traveling this afternoon – if you need to reach me, please call my cell phone (number below).

Kind regards,

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com

0

3 Page(s) Withheld

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Draft Labeling

Deliberative Process

Davies, Kathleen

From: Davies, Kathleen
Sent: Wednesday, November 21, 2007 9:30 AM
To: 'Mierette Stocker'
Subject: BLA 125249 - Portion of IR
Importance: High
Attachments: IR Request_11-16-2007.pdf

JAN 16 2008

KMD

Hi Mierette,

Please refer to BLA 125249 and our upcoming meeting on November 28. Please see attached IR that contains 3 items. The remaining items will be provided prior to the meeting on November 28.

In addition, provide a list of attendees at least 24 hours prior to the meeting so that I can notify security. I do not have a finalized list of attendees from the Agency; it will be product reviewers and potentially the clinical team. Dr. Roca is not attending.

Regards,
Kathleen

1/16/2008

Ⓟ

2 Page(s) Withheld

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Draft Labeling

Deliberative Process

Davies, Kathleen

From: Davies, Kathleen
Sent: Monday, November 19, 2007 10:44 AM
To: 'Mierette Stocker'
Subject: BLA 125249 - Request for meeting
Importance: High

JAN 16 2008



Hi Mierette,

I am following up to a voicemail I left you this morning regarding BLA 125249/IL-1 Trap. The Division requests a meeting with Regeneron to discuss the major amendment received October 26, 2007. The Division prefers a face-to-face meeting but a teleconference is acceptable if it is not feasible to have a face-to-face meeting.

I would like to schedule the meeting for Wednesday, November 28, from 3:00 - 4:00 PM (EST). Please let me know if this time is acceptable to Regeneron. The Division requests pertinent product reviewers responsible for the data in the major amendment and other members of Regeneron you feel necessary to attend. Attendees from the Agency will include review members from the Office of Therapeutic Products, the clinical team leader, Dr. Rappaport, and Dr. Rosebraugh, the Acting Director of Office of Drug Evaluation II.

Regards,

Kathleen

Davies, Kathleen

From: Davies, Kathleen
Sent: Thursday, November 01, 2007 12:55 PM
To: 'Mierette Stocker'
Subject: BL 125249/IL 1 Trap - Major Amendment Notification
Importance: High
Attachments: BL125249_MA_1Nov07.pdf

NOV 2 2007
KM Davies

Hi Mierette,

Please refer to your BLA 125249 for Riloncept (IL-1 Trap). We also refer to your recent submission, dated October 26, 2007, a product amendment. We consider this submission a major amendment and are extending the review clock; your new PDUFA goal date is February 29, 2008.

Please see attached letter outlining this information. If you have questions, let me know.

Regards,

Kathleen



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125249/0

NOV 1 2007

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

Attention: Mierette R. Stocker
Director, Regulatory Affairs

Dear Ms. Stocker:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Rilonecept (IL-1 Trap).

We received your October 26, 2007 amendment to this application on October 26, 2007 and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to February 29, 2008, to provide time for a full review of the amendment.

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, please contact the Regulatory Project Manager, Kathleen Davies, at (301) 796-2205.

Sincerely,

Sara Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125249/0

NOV 1 2007

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

Attention: Mierette R. Stocker
Director, Regulatory Affairs

Dear Ms. Stocker:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Rilonacept (IL-1 Trap).

We received your October 26, 2007 amendment to this application on October 26, 2007 and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to February 29, 2008, to provide time for a full review of the amendment.

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, please contact the Regulatory Project Manager, Kathleen Davies, at (301) 796-2205.

Sincerely,

Sara Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

surface receptors and generate signals that can trigger disease activity in tissues. Once attached to the Trap, IL-1 cannot bind to the cell surface receptors and, together with the Trap, is flushed from the body. Clinical investigator inspections were conducted at four clinical sites (Drs. Throne, Boling/Sebai,* Noss, and Fogel) submitting data in support of BLA 125249. These sites were inspected due to high study drug response rates and enrollment of large numbers of study subjects. The goals of inspection included validation of submitted data and compliance of study activities with FDA regulations. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, documentation of adverse events, and protection of subjects' rights, safety, and welfare.

The inspections covered studies performed under protocol IL1T-AI-0505.06: "A Multicenter, Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Efficacy of IL-1 Trap in Subjects with *CIAS1* Associated Periodic Syndromes (CAPS) Using Both Parallel Group and Randomized Withdrawal Designs." The primary objective was to assess the effect of IL-1 Trap on the clinical signs and symptoms of CAPS when used for chronic therapy. The primary (efficacy) endpoint was the change from baseline to endpoint in the mean key symptom score of signs and symptoms (rash, feeling of fever/chills, joint pain, eye redness/pain, and fatigue).

The study design included two randomized, double-blind, placebo-controlled phases: a parallel group comparison during Weeks 1 – 6 (Part A) and a randomized withdrawal comparison during Weeks 15 – 24 (last portion of Part B). Upon completion of the randomized withdrawal phase, all subjects were eligible to enter a 24-week open label extension phase, and receive IL-1 Trap 160 mg once weekly. Following the 24-week open label extension phase, all subjects were eligible to enter a 64-week Long Term Open Label Extension phase and receive IL-1 Trap 60 mg once weekly.

II. RESULTS (by site):

Clinical Investigator/Site	Protocol(s)	Inspection Date	EIR Received Date	Final Classification
Dr. Martin Throne, Site #007 Radiant Research, Inc. 1100 Lake Hearn Drive NE, Suite 360 Atlanta, GA 30342-1524	IL1T-AI-0505	9/17/2007- 9/21/2007	10/5/2007	NAI
Dr. Eugene Boling/Dr. Mohamed Sebai,* Site #016 510 N. 13th Avenue, Suite 302 Upland, CA 91786	IL1T-AI-0505	9/10/2007- 9/17/2007	10/2/2007	NAI

* Please note that Dr. Boling was the initial clinical investigator for Site #016, but was succeeded by Dr. Sebai following Dr. Boling's death on November 22, 2006. Dr. Sebai received IRB approval as the succeeding clinical investigator in January 2007.

Page 3 of 6 - BLA 125249 Interleukin-1 (IL-1) Trap (Rilonacept®)
Summary Report of U.S. Inspections

Dr. Michael Noss, Site #001 Radiant Research 11500 N. Lake Drive, Suite 320 Cincinnati, OH 45249	IL1T-AI-0505	10/16/2007- presently ongoing	pending	pending (NAI)
Dr. Ronald Fogel, Site #029 Clinical Research Institute of Michigan, LLC 30795 23 Mile Road, Suite 207 Chesterfield, MI 48047	IL1T-AI-0505	9/5/2007- 9/6/2007	10/9/2007	VAI

Key to Classifications

NAI - No deviation from regulations. Data acceptable.

VAI - No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI - Response Requested = Deviation(s) from regulations.

OAI - Significant deviations from regulations. Data unreliable.

(1) **Dr. Martin Throne, Site #007**
Atlanta, GA

a. What was inspected?

Thirteen (13) subjects consented to participate in the study; six subjects were enrolled in the randomized portion and continued in the open-label extension phase, and seven subjects were enrolled directly into the open-label portion of the study. The FDA investigator performed a complete review of seven subjects' records. The review included subject eligibility, source documents, case report forms, and data listings of efficacy endpoints. An audit of all 13 informed consent forms was conducted.

b. Limitations of inspection: None.

c. General observations/commentary:

Data in sponsor-provided data listings, including efficacy and safety endpoints, were supported by data in source documents and case report forms. There were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted.

Recommendation: Data from this clinical site appear acceptable for use in support of this BLA.

**(2) Dr. Eugene Boling/Dr. Mohamed Sebai, Site #016
Upland, CA**

a. What was inspected?

Seven (7) subjects consented to participate in the study. Of these, five subjects participated in the initial blinded portions of the study, while two subjects were screened after the blinded portions of the study were completed and were enrolled directly into the open label phase. A complete review of records was performed for all seven enrolled subjects. The review included consent forms, source documents, case report forms, data listings of efficacy endpoints, drug accountability records, and correspondence with the IRB and sponsor.

b. Limitations of inspection: None.

c. General observations/commentary:

Data in sponsor-provided data listings, including efficacy and safety endpoints, were supported by data in source documents and case report forms. There were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted.

Recommendation: Data from this clinical site appear acceptable for use in support of this BLA.

**(3) Dr. Michael Noss, Site #001
Cincinnati, OH**

a. What was inspected?

Three (3) subjects consented to participate in the study, completed the blinded portions of the study, and continue in the open label extension phase of the study. A complete review of records was performed for all three enrolled subjects. The review included consent forms, source documents, case report forms, data listings of efficacy endpoints, drug accountability records, and correspondence with the IRB and sponsor.

b. Limitations of inspection: Unknown at this time, as the investigation is ongoing and the Establishment Inspection Report (EIR) is not available at this time.

c. General observations/commentary:

Data in sponsor-provided data listings, including efficacy and safety endpoints, were supported by data in source documents and case report forms. There were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted.

The observations noted above are based on verbal communications with the field investigator. If significant problems are noted and/or conclusions change upon receipt and review of the EIR, an inspection summary addendum will be generated.

Recommendation: Data from this clinical site appear acceptable for use in support of this BLA.

**(4) Dr. Ronald Fogel, Site #029
Chesterfield, MI**

b. What was inspected?

Eight (8) subjects consented to participate in the study. Of these, one subject failed screening criteria, one subject withdrew from the study, and the six remaining subjects continue in the open label extension phase of the study. A complete review of records was performed for all eight consented subjects. The review included consent forms, source documents, case report forms, data listings of efficacy endpoints, drug accountability records, and correspondence with the IRB and sponsor.

b. Limitations of inspection: None.

c. General observations/commentary:

The inspection revealed minor inconsistencies in adverse event reporting for one subject (pertaining to injection site redness and dizziness). Also, there were minor discrepancies in drug accountability logs for two subjects. However, data in sponsor-provided data listings, including efficacy and safety endpoints, were supported by data in source documents and case report forms. There were no significant inspectional findings that would adversely impact data acceptability.

Recommendation: Data from this clinical site appear acceptable for use in support of this BLA.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, for the four clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. Overall, data generated for Protocol IL1T-AI-0505 at these clinical sites appear acceptable for use in support of BLA 125249.

Observations noted above for Dr. Michael Noss are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.


Sheryl Gunther, Pharm.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:


Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

Preliminary Findings 10/22/07

Indication	Protocol #	Site (Name and Address)	Inspection Status and Preliminary Findings
CAPS	ILIT-AI-0505	Martin Throne, MD Radiant Research, Atlanta 1100 Lake Hearn Drive, Suite 360 Atlanta, GA 30342	Inspection completed. There were no significant inspectional findings that would adversely impact data acceptability. Expected classification = NAI.
CAPS	ILIT-AI-0505	Eugene Boling, MD Boling Clinical Trials 510 N. 13th Avenue, Suite 302 Upland, CA 91786	Inspection completed. There were no significant inspectional findings that would adversely impact data acceptability. Expected classification = NAI.
CAPS	ILIT-AI-0505	Michael Noss, MD Radiant Research 11500 N. Lake Drive, Suite 320 Cincinnati, OH 45249	Inspection ongoing. There were no significant inspectional findings that would adversely impact data acceptability. Expected classification = NAI.
CAPS	ILIT-AI-0505	Ronald Fogel, MD Clinical Research Institute of Michigan, LLC 30795 23 Mile Road, Suite 207 Chesterfield, MI 48047	Inspection completed. The inspection revealed a deficiency in adverse event reporting for one subject (pertaining to injection site redness and dizziness). Also, there were minor deviations in drug accountability logs for two subjects. Expected classification = VAI.

Davies, Kathleen

From: Gunther, Sheryl
Sent: Tuesday, August 07, 2007 12:05 PM
To: Davies, Kathleen
Subject: RE: DSI consult request for new BLA under priority review
Attachments: 0505 1572 016 Dr Sebai.pdf

SEP 19 2007

Hi Kathleen:

The consult request to DSI lists one of the four sites to be inspected as that of Dr. Eugene Boling of Boling Clinical Trials, located at 510 N 13 Ave, Suite 302, in Upland CA 91786. However, in response to a request for background materials, the sponsor provided the Form FDA 1572 (Statement of Investigator) for this site (Site #016), which identifies the investigator as Mohamed Bassam Sebai.

I have just learned from the sponsor that Dr. Boling died in an accident, and Dr. Sebai took over his responsibilities at Site #016. I will include a note to this effect in the inspection assignment DSI will issue to the field investigator.

I have attached the Form 1572 signed by Dr. Sebai.

Thanks,
Sheryl Gunther

Sheryl D. Gunther, R.Ph., Pharm.D.
LCDR, USPHS
Senior Regulatory Review Officer
FDA/CDER/OC/DSI/GCP1
7520 Standish Place, HFD-46
Metro Park North 1, Room 1442
Rockville, MD 20855
Phone: 240-276-8843
Fax: 240-276-8844
Email: sheryl.gunther@fda.hhs.gov

From: Davies, Kathleen
Sent: Monday, August 06, 2007 3:14 PM
To: Gunther, Sheryl
Subject: RE: DSI consult request for new BLA under priority review

Hi Sheryl,

This document is located in the CBER EDR. The link is:

\\Cbsap58\MleCTD_Submissions\STN125249\125249.enx

If you cannot access it you will have to contact ERIC to gain access. There are no paper copies of this application.

If you have further questions, please let me know.

Kathleen

From: Gunther, Sheryl
Sent: Monday, August 06, 2007 3:12 PM
To: Davies, Kathleen
Subject: FW: DSI consult request for new BLA under priority review
Importance: High

Hi Kathleen:

I do not have access to BLA applications. Could you please send me the link for this application? I will be the GCP reviewer for this application.

Thanks,
Sheryl Gunther

Sheryl D. Gunther, R.Ph., Pharm.D.
LCDR, USPHS
Senior Regulatory Review Officer
FDA/CDER/OC/DSI/GCP1
7520 Standish Place, HFD-46
Metro Park North 1, Room 1442
Rockville, MD 20855
Phone: 240-276-8843
Fax: 240-276-8844
Email: sheryl.gunther@fda.hhs.gov

From: Lewin, Constance
Sent: Wednesday, July 18, 2007 2:37 PM
To: Davies, Kathleen; Gunther, Sheryl; Walters, Dana L
Cc: Currier, Carolanne
Subject: FW: DSI consult request for new BLA under priority review
Importance: High

Hi, Kathleen - Please send your consult requests to my attention rather than Carolanne's, and I will let you know who the assigned GCP reviewer is. For this particular application, it will be Sheryl Gunther. Please work directly with Sheryl as needed on the application. Should you need my assistance at all, I'm available to you as well, so don't hesitate to get in touch.

Sheryl - Please follow through on this as the assigned GCP reviewer.

Dana - Please update the database accordingly.
Thanks,
Connie

From: Davies, Kathleen
Sent: Wednesday, July 18, 2007 1:56 PM
To: Currier, Carolanne
Cc: Lewin, Constance
Subject: DSI consult request for new BLA under priority review

9/19/2007

Hi Carolanne,

Please fine the DSI consult request for new BLA 125249 attached. This is a priority review application, with the PDUFA date of November 29, 2007. All requested sites are domestic.

Since this is a BLA, please retain this copy I've attached for your records, since you will not receive a DFS notification. Please let me know if you have any questions.

Thanks so much,

Kathleen Davies, MS
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: (301) 796-2205
Email: kathleen.davies@fda.hhs.gov

Davies, Kathleen

From: Davies, Kathleen
Sent: Monday, October 22, 2007 1:52 PM
To: 'Mierette Stocker'
Subject: RE: BL 125249 - Items for discussion - request for clarification on Item 21

Km Davies
OCT 22 2007

Hi Mierette,

I would be acceptable to submit an EXCEL document in the essence of time. Please understand that we need all this information as soon as possible, so if you have this information prior to Friday, that would be appreciated. If you have further questions, let me know.

Attendees of the teleconference were:

Rigoberto Roca, MD, Deputy Division Director, DAARP
Keith Burkhardt, MD, Clinical Reviewer, DAARP
Lei Zhang, MD, Clinical Pharmacology Reviewer, DAARP
Kathleen Davies, MS, Regulatory Health Project Manager, DAARP

Patrick Swann, PhD, Deputy Division Director, DMA
Chana Fuchs, PhD, Team Leader, DMA
Ruth Cordoba-Rodriguez, PhD, Reviewer, DMA
Gurpreet Gill-Sangha, PhD, Reviewer, DMA
Jun Park, PhD, Reviewer, DMA

Regards,
Kathleen

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Monday, October 22, 2007 11:17 AM
To: Davies, Kathleen
Subject: RE: BL 125249 - Items for discussion - request for clarification on Item 21

Hello Kathleen,

Regarding Item 21 and FDA request for individual raw data points used for the determination of the historical mean in our drug substance validation studies: These data are in an EXCEL workbook format, which we can provide instead of converting to a PDF document. We believe the EXCEL format will be more useful to the product reviewers.

Please confirm that this will be acceptable.

If acceptable, then I will send the EXCEL file separately by e-mail, and this will be noted in the complete response that we anticipate sending by Friday of this week.

Thanks.

Mierette

O: 914-345-7590

M: 914-548-4390

mierette.stocker@regeneron.com

10/22/2007

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Tuesday, October 16, 2007 4:51 PM
To: Mierette Stocker
Subject: BL 125249 - Items for discussion
Importance: High

Hi Mierette,

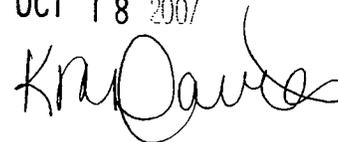
Please find the list of items from the product reviewers attached. We will discuss these at the teleconference tomorrow.

Kathleen

Davies, Kathleen

To: Mierette Stocker
Subject: BL 125249 - Items for discussion
Importance: High
Attachments: CMC IR- BLA 125249_16Oct07.doc

OCT 18 2007



Hi Mierette,

Please find the list of items from teh product reviewers attached. We will discuss these at the teleconference tomorrow.

Kathleen



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 Draft Labeling

 Deliberative Process

Davies, Kathleen

From: Davies, Kathleen
Sent: Tuesday, October 09, 2007 1:33 PM
To: 'Mierette Stocker'
Subject: BL125249 - Manufacturing IR follow-up
Importance: High
Attachments: STN 125249_Manufacturing IR.doc

OCT 9 2007
Km Davies

Hi Mierette,

Please refer to you BLA 125249 for Riloncept (IL-1 Trap). After reviewing the 74-day letter responses, the manufacturing reviewers have some additional follow-up questions. Please find the questions attached.

If you have any questions, please let me know.

Regards,

Kathleen

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 Draft Labeling

 Deliberative Process

Davies, Kathleen

From: Davies, Kathleen
Sent: Tuesday, September 11, 2007 9:27 AM
To: 'Mierette Stocker'
Subject: Product IR
Attachments: BLA 125249_Product IR_11Sep07.doc

SEP 11 2007



Hi Mierette,

Please refer to your BLA 125249 for IL-1 Trap (Riloncept). The product reviewers have drafted an IR (see attached). We request prompt feedback in order to continue our review under priority status.

If you have any questions, let me know.

Kathleen

5

2 Page(s) Withheld

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Draft Labeling

Deliberative Process

Davies, Kathleen

From: Davies, Kathleen
Sent: Friday, September 07, 2007 4:02 PM
To: 'Mierette Stocker'
Subject: BL 125249 - Pharm Tox IR
Attachments: Blank Bkgrd.gif

SEP - 7 2007



Hi Mierette,

Please refer to your BLA 125249 for Riloncept (IL-1 Trap). The pharmacology/toxicology reviewer has the following information request regarding this application:

Provide the **historical control data** from the monkey for the Segment II reproductive toxicity study which was conducted in the _____ Lab and for the Segment

I and Segment III study in the mice which were conducted in: _____

If possible, provide the monkey Segment II study historical control data from the Covance Lab.

Although you did not conduct your Segment II study in Covance, Covance has a big monkey facility where they conduct a lot of Seg II studies. This additional data would provide useful information for review of your application.

If you have any questions, please let me know.

Thanks,
Kathleen

Davies, Kathleen

From: Davies, Kathleen
Sent: Wednesday, August 15, 2007 9:25 AM
To: 'Mierette Stocker'
Subject: BL 125249 - CMC Information Request
Importance: High

AUG 15 2007
K. Davies

Good morning Mierette,

Please refer to your BLA 125249 for IL-1 Trap. The Product reviewers have the following information requests:

Provide justification for not having _____ assays as part of release assays for IL-1 Trap drug product.

Provide all data available on _____ for drug product using P4A and P4B processes.

We request that you provide this information no later than August 22, 2007 in order for the product reviewers to continue their review under priority status. If you have any questions, let me know.

Regards,

Kathleen

8/15/2007

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Friday, August 10, 2007 1:31 PM
To: Davies, Kathleen
Subject: RE: IL-1 Trap tradename
Attachments: emfinfo.txt

Hi Kathleen,

We will continue with ARCALYST.

I will communicate to the BLA as you had recommended, however, I am out of the office at a conference until next Wednesday. Please accept this e-mail as official notification until I am able to send to the eCTD.

Thanks and have a good weekend.

Mierette

Tel: 914-345-7590

Fax: 914-345-7688

Cell: 914-548-4390

mierette.stocker@regeneron.com

From: Mierette Stocker
Sent: Thursday, August 09, 2007 4:10 PM
To: Kathleen.Davies@fda.hhs.gov
Subject: RE: IL-1 Trap tradename

Dear Kathleen,

I should have a decision from management by tomorrow. I will let you know as soon as I am notified and I will also submit notification to the BLA.

Kind regards,

Mierette

Tel: 914-345-7590

Fax: 914-345-7688

Cell: 914-548-4390

mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Thursday, August 09, 2007 1:21 PM
To: Mierette Stocker
Subject: IL-1 Trap tradename

AUG 13 2007

Kathleen Davies

Hi Mierette,

Do you have a status update regarding the trade name of IL-1 Trap?

Thanks,

Kathleen



STN: BL 125249/0

FILING COMMUNICATION

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

AUG 10 2007

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 Riloncept (IL-1 Trap).

We also refer to your submissions dated July 2 and July 24, 2007.

We have completed an initial review of your application to determine its acceptability for filing. Under 21 CFR 601.2(a) this application was filed on July 27, 2007. The review classification for this application is **Priority**. Therefore, the user fee goal date is November 29, 2007. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

We request that you submit the following information:

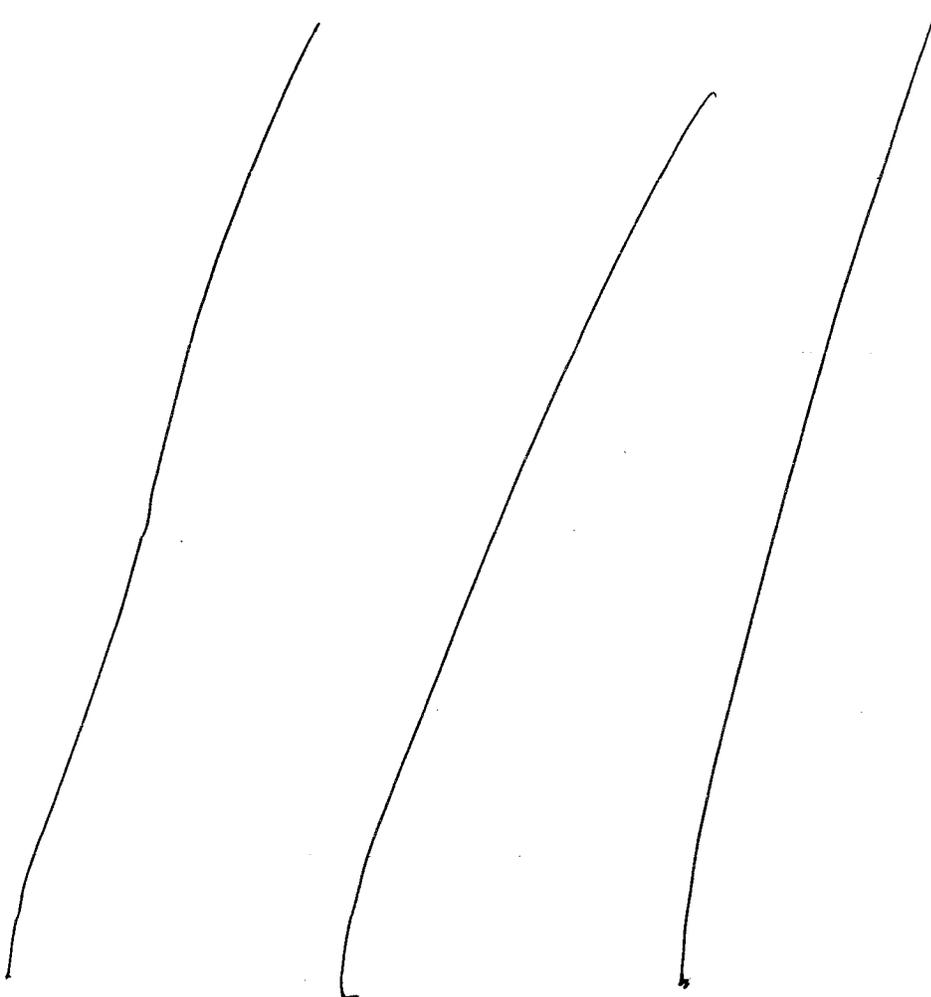
CLINICAL

1. On FDA form 3454 Certifications: Financial Interests and Arrangements of Clinical Investigators, you note that Eugene P. Boling, MD, and Fitzhugh Lee Hamilton, MD, were replaced. Submit a statement clarifying whether you had financial arrangements with these two investigators.
2. For the safety update, you propose to provide patient profiles for the pediatric subjects who enrolled in the open-label Study IL1T-AI-0505. Provide updated profiles for all the subjects for the open-label extension of IL1T-AI-0505 (Similar to those provided in Appendix 11.4.2 of the IL1T-AI-0505 clinical study report).
3. In the randomized withdrawal phase, 7 out of 22 subjects missed riloncept doses, while no subject assigned to placebo missed a dose. Provide details as to why riloncept subjects missed doses.

PRODUCT

1. Provide a summary and relevant data on the results of the evaluation of F_c function of IL-1 Trap proposed in _____ 145).
2. Identify the _____ (Section 3.2.S.2.2.5).
3. Attachment V in Section 3.2.S.2.5 does not appear to be included in the BLA (PEP-R-MA-ILIT-8.0). Provide the document and its appropriate link.
4. In Section 3.2.R.2.5.4, the assay validation information does not include appropriate validation data for the ability of the _____
_____ Provide the necessary data.

DRUG PRODUCT QUALITY MICROBIOLOGY



(T)

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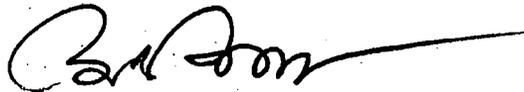
Deliberative Process

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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,

A handwritten signature in black ink, appearing to read "Bob Rappaport", with a long horizontal flourish extending to the right.

Bob Rappaport, M.D.

Director

Division of Anesthesia, Analgesia

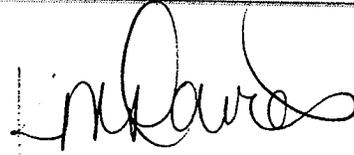
and Rheumatology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Davies, Kathleen

From: Davies, Kathleen
Sent: Friday, July 27, 2007 11:14 AM
To: 'Mierette Stocker'
Subject: BL 125249



AUG - 1 2007

Hi Mierette,

At this time, the Division does not require any additional information from Regeneron in order to make a filing decision. You will be receiving a filing letter in the next two weeks (prior to August 11, 2007), that will detail further requests for information and any potential review issues.

Thank-you for the update regarding the clinical pharmacology IR, if the reviewer has additional questions I will let you know.

Kathleen

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Friday, July 20, 2007 9:15 AM
To: Davies, Kathleen
Subject: RE: BLA 125249: revised proposal for comparative charge variant analysis
Attachments: emfinfo.txt

Thank you Kathleen for the very quick feedback. We will then proceed as described below.

Kind regards,

Mierette

Tel: 914-345-7590

Fax: 914-345-7688

Cell: 914-548-4390

mierette.stocker@regeneron.com

AUG - 3 2007

Km Davies

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Friday, July 20, 2007 8:09 AM
To: Mierette Stocker
Subject: RE: BLA 125249: revised proposal for comparative charge variant analysis
Importance: High

Good morning Mierette,

Your proposal to provide the — data is acceptable with the following understanding:

[Handwritten signature lines]

If you have any questions, let me know.
Kathleen

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Thursday, July 19, 2007 3:41 PM

8/3/2007

0

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Deliberative Process

Davies, Kathleen

From: Mierette Stocker [Mierette.Stocker@regeneron.com]
Sent: Tuesday, July 17, 2007 10:11 AM
To: Stradley, Sara
Cc: Davies, Kathleen
Subject: RE: BLA 125249/TC on WED
Attachments: emfinfo.txt

AUG - 3 2007

We will plan to provide the information requested below before the filing date.

Thank you for the confirmation below. However, Kathleen had suggested that there would be questions from the Product, Facility, and Clinical groups and that each group will have various questions relating to their initial review of the application. Can you please confirm that the clinical reviewers (or reviewers from other disciplines) will have no questions for which we need to prepare a response?

Please excuse this follow-up question and I hope that you will not consider it a nuisance. We just want to be certain that we are prepared to answer all of the Division's questions during the teleconference tomorrow.

Thank you and regards,

Mierette

Tel: 914-345-7590

Fax: 914-345-7688

Cell: 914-548-4390

mierette.stocker@regeneron.com

From: Stradley, Sara [mailto:sara.stradley@fda.hhs.gov]
Sent: Tuesday, July 17, 2007 6:25 AM
To: Mierette Stocker
Cc: Davies, Kathleen
Subject: RE: BLA 125249/TC on WED

There are no other items.

Sara

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Monday, July 16, 2007 9:53 PM
To: Stradley, Sara
Cc: Davies, Kathleen
Subject: RE: BLA 125249/TC on WED

Thank you.

Please confirm if this is the only item for discussion on Wednesday or if there will be remaining questions sent tomorrow morning.

Regards,

Mierette

Tel: 914-345-7590
Fax: 914-345-7688
Cell: 914-548-4390
mierette.stocker@regeneron.com

From: Stradley, Sara [mailto:sara.stradley@fda.hhs.gov]
Sent: Monday, July 16, 2007 9:32 PM
To: Mierette Stocker
Cc: Davies, Kathleen; Stradley, Sara
Subject: BLA 125249/TC on WED

Mierette:

The following information request will be discussed during the telecon on Wed. Kathleen will be back on the office on WED morning.

Provide the following stability data for comparison of drug product (DP) process P4A to P4B prior to the 60 day filing date for BLA 125249.

1. Comprehensive stability data for all P4A drug product batches on stability. Stability data should be provided for all storage conditions and time points available to date.
2. For all accelerated stability data available on DP lots manufactured by processes P4A and P4B, please provide individual data points, line plots for each assay and comparative rate of degradation for batches manufactured with each process.
3. Please identify whether you have data on ϵ _____, and reconstitution time for your DP stability time points and submit all such data for lots manufactured by processes P4A and P4B. Analysis of these and other critical parameters should be provided as described in item no 2 above.

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
email: Sara.Stradley@fda.hhs.gov



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Deliberative Process

Davies, Kathleen

From: Davies, Kathleen
Sent: Thursday, July 12, 2007 2:17 PM
To: Mierette Stocker
Subject: BL 125249 - IR request: Clinical Pharmacology
Importance: High

JUL 12 2007
Km Davies

Hi Mierette,

Please refer to your new BLA 125249 for Riloncept (IL-1 Trap). During the initial filing review of the application, the clinical pharmacology review has the following requests:

Provide the following datasets to support the review of your population PK analysis of Riloncept (BLA-125249):

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

A model development decision tree and/or table which gives an overview of modeling steps.

Please let me know if you have any questions and when we can expect to receive these responses from you.

Thanks so much,

Kathleen

Davies, Kathleen

From: Davies, Kathleen
Sent: Tuesday, June 26, 2007 3:27 PM
To: 'Mierette Stocker'
Subject: RE: BL 125249 - Information Request

JUL 12 2007



Hi Mierette,

To clarify, you may not have small scale validations, however, as we are asking for data to assess the impact of the _____ for the 2 processes, if some parameters of this was supported by studies done at small scale rather than at full scale of production, you would want to include this data too.

I hope that helps,
Kathleen

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Tuesday, June 26, 2007 12:00 PM
To: Davies, Kathleen
Subject: RE: BL 125249 - Information Request

Thank you Kathleen, I believe I understand now. Can you please let me know when we will have clarification on the phrase "small scale validation parameters" in the context of Question #4?

Thanks,

Mierette

Tel: 914-345-7590

Fax: 914-345-7688

Cell: 914-548-4390

mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Tuesday, June 26, 2007 11:07 AM
To: Mierette Stocker
Cc: _____
Subject: RE: BL 125249 - Information Request

Hi Mierette,

To clarify further, I just spoke with our PLR team, and the PLR must be in a WORD document that looks exactly like the XML rendering. There is a template in WORD at the following:

<http://www.fda.gov/cder/regulatory/physLABEL/default.htm>

Scroll down the page to the bullet that says "Sample Tool Illustrating the Format for Highlights and Contents"

Having the WORD version in the proper PLR format is critical to our ability to review and negotiate the label. This may be a matter of sort of "type setting" a WORD document separate from the version that is used to render into xml, if that makes any sense.

I hope that helps clarify further what we are looking for.

Kathleen

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Tuesday, June 26, 2007 10:52 AM
To: Davies, Kathleen
Cc: _____
Subject: RE: BL 125249 - Information Request

Dear Kathleen,

Regarding the request to provide a Word document of the PLR-formatted label, we believe that it is present in the current BLA and can be located in Module 1.14.1.3.

I have asked Dr. _____, my colleague at _____ to contact you for further clarification. She should be calling you this morning.

Kind regards,

Mierette

Tel: 914-345-7590

Fax: 914-345-7688

Cell: 914-548-4390

mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Saturday, June 23, 2007 9:04 AM
To: Mierette Stocker
Subject: BL 125249 - Information Request
Importance: High

Good morning Mierette,

Please refer to BLA 125249, received May 29, 2007, for Arcalyst (IL-1 Trap). In our initial review to assess the filability of this BLA, we could not find the following items (see attached document). Provide the requested information in full, as soon as possible, but no later than July 9, 2007. If any of these items

are currently in the BLA, please identify the location in the BLA where we can find this information.

I will follow up with you Monday to determine the availability of this information.

In addition, provide a Word document of the PLR-formatted label, in addition to the draft labeling already provided in the BLA.

If you have any questions, we can discuss them further on Monday.

Regards,
Kathleen

Davies, Kathleen

From: Davies, Kathleen
Sent: Tuesday, June 26, 2007 11:07 AM
To: 'Mierette Stocker'
Cc: _____
Subject: RE: BL 125249 - Information Request

JUL 12 2007
Km Davies

Hi Mierette,

To clarify further, I just spoke with our PLR team, and the PLR must be in a WORD document that looks exactly like the XML rendering. There is a template in WORD at the following:

<http://www.fda.gov/cder/regulatory/physLABEL/default.htm>

Scroll down the page to the bullet that says "Sample Tool Illustrating the Format for Highlights and Contents"

Having the WORD version in the proper PLR format is critical to our ability to review and negotiate the label. This may be a matter of sort of "type setting" a WORD document separate from the version that is used to render into xml, if that makes any sense.

I hope that helps clarify further what we are looking for.

Kathleen

From: Mierette Stocker [mailto:Mierette.Stocker@regeneron.com]
Sent: Tuesday, June 26, 2007 10:52 AM
To: Davies, Kathleen
Cc: _____
Subject: RE: BL 125249 - Information Request

Dear Kathleen,

Regarding the request to provide a Word document of the PLR-formatted label, we believe that it is present in the current BLA and can be located in Module 1.14.1.3.

I have asked Dr. _____, my colleague at _____ to contact you for further clarification. She should be calling you this morning.

Kind regards,

Mierette

Tel: 914-345-7590

7/12/2007

Fax: 914-345-7688
Cell: 914-548-4390
mierette.stocker@regeneron.com

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Saturday, June 23, 2007 9:04 AM
To: Mierette Stocker
Subject: BL 125249 - Information Request
Importance: High

Good morning Mierette,

Please refer to BLA 125249, received May 29, 2007, for Arcalyst (IL-1 Trap). In our initial review to assess the filability of this BLA, we could not find the following items (see attached document). Provide the requested information in full, as soon as possible, but no later than July 9, 2007. If any of these items are currently in the BLA, please identify the location in the BLA where we can find this information.

I will follow up with you Monday to determine the availability of this information.

In addition, provide a Word document of the PLR-formatted label, in addition to the draft labeling already provided in the BLA.

If you have any questions, we can discuss them further on Monday.

Regards,
Kathleen

Davies, Kathleen

From: Davies, Kathleen
Sent: Saturday, June 23, 2007 9:04 AM
To: 'Mierette Stocker'
Subject: BL 125249 - Information Request
Importance: High
Attachments: Product IR 22Jun07.doc

JUL 12 2007



Good morning Mierette,

Please refer to BLA 125249, received May 29, 2007, for Arcalyst (IL-1 Trap). In our initial review to assess the filability of this BLA, we could not find the following items (see attached document). Provide the requested information in full, as soon as possible, but no later than July 9, 2007. If any of these items are currently in the BLA, please identify the location in the BLA where we can find this information.

I will follow up with you Monday to determine the availability of this information.

In addition, provide a Word document of the PLR-formatted label, in addition to the draft labeling already provided in the BLA.

If you have any questions, we can discuss them further on Monday.

Regards,
Kathleen

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 Draft Labeling

 Deliberative Process

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CDER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (<http://www.fda.gov/cber/regsopp/8404.htm>). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see <http://www.fda.gov/cber/ich/ichguid.htm>).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications. ~~You cannot have multiple indications under supplement submissions. If the sponsor submits multiple indications under a supplement, you must unbundle the submission.~~

CDER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125249

Product: Rilonacept
(IL-1Trap)

Applicant: Regeneron
Pharmaceutical

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 6/21/07 Committee Recommendation (circle one): File RTF

RPM: KmCavids
(signature/date)

Attachments:

- Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
 - 1 Part A – RPM
 - Part B – Product/CMC/Facility Reviewer(s): _____
 - Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____
 - Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____
- Memo of Filing Meeting

Part A. Regulatory Project Manager (RPM)

Cover Letter	<input checked="" type="radio"/> Y	<input type="radio"/> N	
Form 356h completed	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> If foreign applicant, US Agent signature.	Y/N/A/N		
Comprehensive Table of Contents	<input checked="" type="radio"/> Y	<input type="radio"/> N	
Debarment Certification with correct wording (see * below)	<input checked="" type="radio"/> Y	<input type="radio"/> N	
User Fee Cover Sheet	<input checked="" type="radio"/> Y	<input type="radio"/> N	
User Fee payment received	<input type="radio"/> Y	<input checked="" type="radio"/> N	Orphan designation
Financial certification &/or disclosure information	<input checked="" type="radio"/> Y	<input type="radio"/> N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	<input checked="" type="radio"/> Y	<input type="radio"/> N	request for categorical exclusion
Pediatric rule: study, <u>waiver</u> or deferral	<input checked="" type="radio"/> Y	<input type="radio"/> N	waiver request - orphan designation
Labeling:	<input checked="" type="radio"/> Y	<input type="radio"/> N	label in PLR; SPL submitted
<input type="checkbox"/> PI -non-annotated	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> PI -annotated	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> PI (electronic)	<input checked="" type="radio"/> Y	<input checked="" type="radio"/> N	
<input type="checkbox"/> Medication Guide	<input type="radio"/> Y	<input checked="" type="radio"/> N	
<input type="checkbox"/> Patient Insert	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> package and container	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> diluent	<input type="radio"/> Y	<input checked="" type="radio"/> N	
<input type="checkbox"/> other components	<input type="radio"/> Y	<input checked="" type="radio"/> N	
<input type="checkbox"/> established name (e.g. USAN)	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> proprietary name (for review)	<input checked="" type="radio"/> Y	<input type="radio"/> N	

* The Debarment Certification must have correct wording, e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,..."

Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> English (or translated into English)	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> summary reports reference the location of individual data and	<input checked="" type="radio"/> Y	<input type="radio"/> N	

records			
<input type="checkbox"/> protocols for clinical trials present	<input checked="" type="radio"/> Y	N	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	<input checked="" type="radio"/> Y	N	
companion application received if a shared or divided manufacturing arrangement	Y	N	
	N/A		
if CMC supplement:			
<input type="checkbox"/> description and results of studies performed to evaluate the change	Y	N	
	N/A		
<input type="checkbox"/> relevant validation protocols	Y	N	
<input type="checkbox"/> list of relevant SOPs	Y	N	
if clinical supplement:			
<input type="checkbox"/> changes in labeling clearly highlighted	Y	N	
	N/A		
<input type="checkbox"/> data to support all label changes	Y	N	
<input type="checkbox"/> all required electronic components, including electronic datasets (e.g. SAS)	Y	N	
if electronic submission:			
<input type="checkbox"/> required paper documents (e.g. forms and certifications) submitted	Y	<input checked="" type="radio"/> N	eCTD guidance states no paper copies needed.

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Comparability Reports (CR) not in BLA. were requested & received July 6 2007.

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? NO.

Does this submission relate to an outstanding PMC? No.

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: N/A
- Dates: _____

Recommendation (circle one): File RTF

RPM Signature: [Signature]

Branch Chief concurrence: _____



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125249/0

BLA ACKNOWLEDGEMENT

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

JUN 13 2007

Attention: Mierette R. Stocker
Associate Director, Regulatory Affairs

Dear Ms. Stocker:

We have received your final piece of your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

Our Submission Tracking Number (STN): BL 125249/0

Name of Biological Product: Riloncept (IL-1 Trap)

Indication: Treatment for cryopyrin-associated periodic syndromes (CAPS)

Date of Application: May 25, 2007

Date of Receipt: May 29, 2007

If you have not already done so, promptly submit the *content of labeling* (21 CFR 601.14(b)) in electronic format as described at the following website:
<http://www.fda.gov/oc/datacouncil/spl.html>.

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. 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, please contact me at (301) 796-2205.

Sincerely,

A handwritten signature in black ink that reads "Kathleen Davies". The signature is written in a cursive style with a large, prominent initial "K".

Kathleen Davies, M.S.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

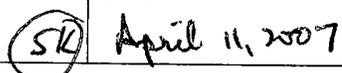
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list "Form FDA 3454 Attachment 1"	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Murray Goldberg	TITLE Senior VP, Finance and Administration, CFO, Treasurer and Assistant Secretary
FIRM / ORGANIZATION Regeneron Pharmaceuticals, Inc.	
SIGNATURE 	DATE 

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Certification: Financial Interests and Arrangement of Clinical Investigators**Listing of Investigators in Pivotal Study IL1T-AI-0505**

Principle Investigator	(Site Location)	Sub-Investigators
1) N.J. Amar, MD	(Waco, TX)	--
2) Bruce Berwald, MD	(St. Louis, MO)	
3) Robert Cartwright, MD	(Columbus, GA)	
4) Stanley B. Cohen, MD	(Dallas, TX)	
5) William Travis Ellison, MD	(Greer, SC)	
6) Lansing G. Ellsworth, MD	(Cedar City, UT)	
7) Darrell N. Fiske, MD	(Stuart, FL)	
8) Ronald P. Fogel, MD	(Chesterfield, MI)	
9) Santosh K. Gill, MD	(Aurora, IL)	
10) Susanna Goldstein, MD	(New York, NY)	
11) Maria Greenwald, MD	(Palm Desert, CA)	

Principle Investigator	(Site Location)	Sub-Investigators
12) Joe L. Hargrove, MD	(Little Rock, AR)	
13) Arthur Kavanaugh, MD	(LaJolla, CA)	
14) Alan J. Kivitz, MD	(Duncansville, PA)	
15) Wayne E. Larson, MD	(Lakewood, WA)	
16) Steven D. Mathews, MD	(Jacksonville, FL)	
17) Harold A. Moore, MD	(Columbia, SC)	
18) Michael Noss, MD	(Cincinnati, OH)	
19) Stephen J. Pollard, MD	(Louisville, KY)	
20) Dennis S. Riff, MD	(Anaheim, CA)	

Principle Investigator	(Site Location)	Sub-Investigators
21) J. Wesley Robertson, MD	(Forest, VA)	--
22) John Rubino, MD	(Raleigh, NC)	
23) Mohamed Bassam Sebai*, MD	(Upland, CA)	
24) William Hoyt Smith**, MD	(Chattanooga, TN)	
25) Martin L. Throne, MD	(Atlanta, GA)	
26) Philip D. Toth, MD	(Indianapolis, IN)	
27) Willard F. Washburne, MD	(Shreveport, LA)	--

*Replaced Eugene P. Boling, MD

**Replaced Fitzhugh Lee Hamilton, MD

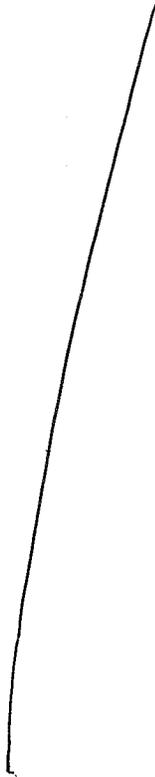
†Sub-investigator was either removed from the study or left the site during the course of the study.

Listing of Investigators in Pilot Study IL1T-AI-0406*:

Principle Investigator:

- Raphaela Goldbach-Mansky, MD

Sub-Investigators:



* Study IL1T-AI-0406 was conducted at a single site at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) located in Bethesda, MD.

† Sub-investigator was either removed from the study or left the site during the course of the study.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125249/0

PRESUBMISSION ACKNOWLEDGEMENT

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

FEB 23 2007

Attention: Mierette R. Stocker
Associate Director, Regulatory Affairs

Dear Ms. Stocker:

We have received your presubmission of your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

Submission Tracking Number (STN): BL 125249/0

Name of Biological Product: Riloncept (IL-1 Trap)

Indication: Treatment for cryopyrin-associated periodic syndromes (CAPS)

Date of Submission: February 13, 2007

Date of Receipt: February 15, 2007

We acknowledge your schedule for submission of the remaining portions of this application, as described in our letter of December 21, 2006, regarding BB-IND 11781. In accordance with provision (c) of the act, our review clock will not start until the date on which you submit the final portion and inform us that your application is complete.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact me at (301) 796-2205.

Sincerely,

A handwritten signature in black ink, appearing to read "K.M. Davies". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

Kathleen Davies, M.S.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
And Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BL 125249/0

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

JAN 18 2007

Attention: Mierette R. Stocker
Associate Director, Regulatory Affairs

Dear Ms. Stocker:

We have received your presubmission of your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

Submission Tracking Number (STN): BL 125249/0

Name of Biological Product: Rilonecept (IL-1 Trap)

Indication: Treatment for cryopyrin-associated periodic syndromes (CAPS)

Date of Submission: January 3, 2007

Date of Receipt: January 4, 2007

We acknowledge your schedule for submission of the remaining portions of this application, as described in our letter of December 21, 2006, regarding BB-IND 11781. In accordance with provision (c) of the act, our review clock will not start until the date on which you submit the final portion and inform us that your application is complete.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact me at (301) 796-2205.

Sincerely,

A handwritten signature in black ink, appearing to read "K. Davies". The signature is written in a cursive style with a large initial "K" and a long, sweeping underline.

Kathleen Davies, M.S.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
And Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE
COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>REGENERON PHARMACEUTICALS INC Mierette Stocker 777 Old Saw Mill River Road Tarrytown NY 10591 US</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>STN 125249/0</p>
--	---

<p>2. TELEPHONE NUMBER</p> <p>914-345-7590</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p>
--	---

<p>3. PRODUCT NAME</p> <p>rilonacept</p>	<p>6. USER FEE I.D. NUMBER</p> <p>PD3006907</p>
--	---

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
<input checked="" type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
--	--	--

<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> 	<p>TITLE</p> <p>Director, Regulatory Affairs</p>	<p>DATE</p> <p>04 Dec 2006</p>
---	--	--------------------------------

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION

\$.00



U.S. Food and Drug Administration



[FAQ](#)



[User Fees](#)



[Draft Cover Sheet](#)



[Previous Cover Sheets](#)



[Profile](#)



[Sign Out](#)

[Prescription Drug User Fee](#)



Confirmation

**YOUR PAYMENT IDENTIFICATION
NUMBER IS: PD 3006907**

Your Cover Sheet has been submitted electronically. You must print two copies and sign the original. Please include the original with your application and include a copy with your payment.

[\(Create Another Cover Sheet\)](#)

Coversheet

PRESCRIPTION USER FEE COVER SHEET

[\(Print/View Final Coversheet\)](#)

1 Fee: \$0.00

Total: \$0.00

Applicant Information

Applicant: REGENERON
PHARMACEUTICALS INC
Mierette Stocker
914-345-7590
mierette.stocker@regeneron.com

Applicant Contact Information

Submitter: Mierette Stocker
REGENERON PHARMACEUTICALS
INC
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591
UNITED STATES



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

BB IND 11781

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

Attention: Mierette R. Stocker
Associate Director, Regulatory Affairs

Dear Ms. Stocker:

Please refer to your Investigational New Drug Application (BB IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IL-1 Trap.

We also refer to the teleconference held on December 12, 2006, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Kathleen Davies, M.S.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

SPONSOR MEETING AGENDA

MEETING DATE: December 12, 2006

TIME: 1:00 – 2:00 PM (EST)

LOCATION: Teleconference from Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD. 20993

APPLICATION: BB IND 11781,

PRODUCT: IL-1 Trap

INDICATION: _____

SPONSOR: Regeneron Pharmaceuticals, Inc.

TYPE OF MEETING: Type B, pre-BLA CMC

MEETING CHAIR: Rigoberto A. Roca, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

MEETING RECORDER: Kathleen Davies, Regulatory Health Project Manager

FDA Attendees	Title
Rigoberto A. Roca, MD	Deputy Division Director, Division of Anesthesia, Analgesia and Rheumatology Products
Jeff Siegel, MD	Clinical Team Leader
Keith Hull, MD PhD	Clinical Reviewer
Mamata De, PhD	Pharmacology/ Toxicology Reviewer
Kathleen Clouse, PhD	Director, Division of Monoclonal Antibodies (Acting)
Chana Fuchs, PhD	Product Team Leader
Ruth Cordoba-Rodriguez, PhD	Product Reviewer
Gilbert Salud	Therapeutic Facilities Review Branch
Kathleen Davies, MS	Regulatory Health Project Manager

Regeneron Pharmaceuticals, Inc. Attendees	Title
Katherine Boeskin	Manager, Technical Operations
Thomas Daly, PhD	Vice President, Preclinical Development and Protein Chemistry
Stephen Holst	Vice President, Quality and Regulatory Affairs
Randall Rupp, PhD	Sr. Vice President, Manufacturing
William Roberts, MD	Vice President, Regulatory Development

Mierette Stocker	Director, Regulatory Affairs
Neil Stahl, PhD	Sr. Vice President, Therapeutics and Clinical Development
William Trompeter, PhD	Director, Process and Analytical Sciences
Gerald Underwood	Vice President, Manufacturing
Ron Wang, PhD	Sr. Director, Quality Control
Patricia Gilooly	Director, Quality Assurance
Lenh Mong, MS	Regulatory Affairs Associate

BACKGROUND:

Regeneron submitted a request for a Pre-BLA CMC meeting to discuss the proposed filing and formatting of Quality Module 3. Regeneron included a detailed table of contents for discussion and at the meeting.

No specific questions were submitted by Regeneron for this meeting.

The following comments are derived from the meeting package review and were sent to the sponsor on November 28, 2006. The sponsor submitted responses to the comments in anticipation of the teleconference; the sponsor's responses are attached at the end of the minutes. Any discussion stated below is additional discussion based upon the responses given by Regeneron. Regeneron specifically requested further clarification from the Division on I.8, II.4, II.11, III.1 and III.9.

FDA Comments:

I. Manufacturing

1. You state that manufacturing process P4 is the intended process for commercial manufacturing and it is currently used for IL1T-AI-0406 and IL1T-AI-0505 clinical studies. In a previous meeting, you identified two manufacturing processes for the drug product (DP), P4A and P4B. The two processes are not clearly identified in the pre-BLA meeting package (e.g., Table 23 and 26). The BLA submission should clearly define the two processes and identify which manufacturing process was used to generate DP used in each clinical trial and if patients received product from more than one manufacturing process. Association of lot numbers to patients should be included in the clinical section, with a linkage from the CMC section.

Discussion:

There was no additional discussion on this point.

2. Figure 1 of the meeting package seems to indicate that you have _____ you should provide information on all the _____ used for IL-1 Trap manufacturing process and assure that the process is appropriately validated based on the intended use.

Discussion:

There was no additional discussion on this point.

3. **The BLA should clearly indicate if the manufacturing process, or parts thereof, are**

Discussion:

There was no additional discussion on this point.

4. **In addition to data from conformance lots, the BLA should contain all data supporting the assignments and acceptance criteria of critical, key and non-key operational and performance process parameters. These data should include specific studies to identify such parameters as well as an analysis of all manufactured lots in support of these parameters and acceptance criteria. Analysis of failed batches should also be included.**

Discussion:

There was no additional discussion on this point.

5. **You should clarify if the parameters listed for the**

Discussion:

There was no additional discussion on this point.

6. **The BLA submission needs to include validation for all of the manufacturing process.**

Discussion:

There was no additional discussion on this point.

7. **Be aware that failing pre-set acceptance criteria in validation protocols indicates a failure of the validation study. Concurrence with the justification to a failed validation is at discretion of the Agency.**

Discussion:

There was no additional discussion on this point.

(X)

3 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

12. The BLA should identify which stability assays are stability-indicating assays and provide supporting data.

Discussion:

There was no additional discussion on this point.

III. Additional Comments and Recommendations

1. You should provide confirmation that all facilities are ready for inspection at the time of the BLA-CMC module submission.

Discussion:

The Sponsor asked the Division what timeline is acceptable for readiness of facilities to be inspected. The Division stated that, when the last reviewable unit of the BLA is submitted by the Sponsor, the facilities must be ready for inspection and this must be stated in the administrative section of the last reviewable unit. Facility readiness is a component of the filing review process for a BLA. The Division also stated that the Sponsor can contact the Project Manager within the Division three to four months prior to submission of the final reviewable unit to submit a manufacturing schedule and initiate discussions regarding the timeline for the inspections.

The Division reiterated to the Sponsor that if the last reviewable unit is planned for May 2007, the manufacturing facility must be available for inspection in May 2007, and not from June to August 2007. The Sponsor stated that they would ensure that the facility will be ready for inspection when the final reviewable unit is submitted to the Division. The Sponsor also stated that they would notify the Division of a proposed manufacturing schedule so that the Division can plan a site inspection.

2. A planned manufacturing schedule should be submitted with the BLA for the purpose of scheduling the pre-approval inspection.

Discussion:

There was no additional discussion on this point.

3. Please assure that all links in the e-CTD BLA submission are operational.

Discussion:

There was no additional discussion on this point.

4. Immunogenicity assay validation should be included and should link to the immunogenicity data in the clinical module.

Discussion:

There was no additional discussion on this point.

- 5. Provide a summary table that lists the stability data per lot as well as per assay.**

Discussion:

There was no additional discussion on this point.

- 6. You should submit all stability data from previous processes that are intended for use in support of the to-be-licensed process**

Discussion:

There was no additional discussion on this point.

- 7. Provide a table summarizing all lots manufactured and the results of lot release testing. The table should clearly identify the manufacturing process associated with each lot.**

Discussion:

There was no additional discussion on this point.

- 8. Please make sure that all regulatory activities related to the BLA including full and timely cooperation of DMF holders, contractors and suppliers will be properly coordinated by the time of the BLA submission.**

Discussion:

There was no additional discussion on this point.

- 9. For a rolling BLA, you should provide a schedule for submission of all units of the BLA and receive agreement from the FDA on the schedule prior to submitting any portion of the BLA. Refer to "Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review" for additional information.**

Discussion:

The Division asked the Sponsor to clarify the comment regarding submission of nonclinical results from a full length IL-1 Trap antibody assay. The Sponsor stated that this was mislabeled and refers to the clinical results from a full length IL-1 Trap antibody assay planned for a September 2007 submission. The Division acknowledged this and stated that they were still reviewing the proposed rolling submission schedule and would notify the Sponsor by letter of the acceptability of the schedule.

Post-meeting notes:

1. The Division denied the proposed rolling submission schedule and notified the Sponsor via letter. The Sponsor submitted an amended schedule for review by the Division, which was accepted.

2. Although the briefing package was reviewed by the Division, it is still the Sponsor's responsibility to make sure that they have addressed every aspect of their manufacturing process.

ACTION ITEMS:

1. The Sponsor will submit all _____ data available with the CMC reviewable unit.
2. The shelf-life determination of the product will be determined after stability data are reviewed by the Division.
3. Assays used for characterization and for future comparability studies should be well qualified with controls.
4. The Sponsor understands that manufacturing facilities must be ready for inspection when the final reviewable unit is submitted to the Division.

④

19 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Linked Applications

Sponsor Name

Drug Name

IND 11781

REGENERON PHARMS

Interleukin-1 Receptor Fc Fusion Protein (IL-1 Trap) (human recombinant, CHO cells, Regeneron)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kathleen M Davies

01/16/2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

BB IND 11781

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

Attention: Mierette R. Stocker
Associate Director, Regulatory Affairs

Dear Ms. Stocker:

Please refer to your Investigational New Drug Application (BB IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IL-1 Trap.

We also refer to the meeting held on September 19, 2006, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Kathleen Davies, M.S.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Tuesday, September 19, 2006

TIME: 1:30 – 3:00 p.m. (EST)

LOCATION: Food and Drug Administration, White Oak, Conference Rm 1311,
10903 New Hampshire Ave, Silver Spring, MD 20993-0002

APPLICATION: BB IND 11,781

PRODUCT: IL-1 TRAP

INDICATION: Treatment of _____

SPONSOR: Regeneron Pharmaceuticals, Inc.

TYPE OF MEETING: Type B, pre-BLA

MEETING CHAIR: Rigoberto A. Roca, MD, Division of Anesthesia, Analgesia and
Rheumatology Products (DAARP)

MEETING RECORDER: Kathleen Davies, Regulatory Health Project Manager

MEETING OBJECTIVE: To discuss the planned submission of a BLA for IL-1 Trap in
eCTD format and to confirm the acceptability of the safety and
efficacy data package to support the proposed labeling claims.

Meeting request: May 31, 2006, received June 1, 2006

Meeting package: August 3, 2006, received August 4, 2006

A type B meeting was granted on July 17, 2006.

FDA Attendees	
Bob A. Rappaport, MD	Director, Division of Anesthesia, Analgesia and Rheumatology Products
Rigoberto Roca, MD	Deputy Director (Rheumatology Team)
Jeff Siegel, MD	Medical Team Leader (Rheumatology)
Keith Hull, MD	Clinical Reviewer
Ruth Cordoba-Rodriguez	Product Reviewer
Dan Mellon, PhD	Pharmacology/Toxicology Team Leader
Suresh Doddapaneni, PhD	Clinical Pharmacology Team Leader
Dionne Price, PhD	Biostatistics Acting Team Leader
Kate Meaker, MS	Biostatistics Reviewer
Kathleen Davies, MS	Regulatory Health Project Manager
Chana Fuchs, PhD	Product Team Leader
Kathleen A. Clouse, PhD	Director, Division of Monoclonal Antibodies (Acting)

Peter Vaccari	Reviewer, Orphan Products
Joette Meyer	Clinical Reviewer

Regeneron Pharmaceuticals Inc.	
Administration	
Stephen Holst	Vice President, Quality and Regulatory Affairs
Imogene Grimes, PhD	Vice President, Biostatistics, Data Management, Informatics
Scott Mellis, MD, PhD	Vice President, Clinical Pharmacology and Experimental Medicine
Lenh Mong, MEng	Regulatory Affairs Associate
William Roberts, MD	Vice President, Regulatory Development
Neil Stahl, PhD	Senior Vice President, Preclinical Development And Biomolecular Medicine
Mierette Stocker	Director, Regulatory Affairs
Stephen Weinstein, MD PhD	Executive Director, Clinical Sciences
Thomas Daly, PhD	Vice President, Protein Chemistry Sciences

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BACKGROUND:

Regeneron submitted a Pre-BLA meeting request to discuss their planned submission of IL-1 Trap to treat *CLASI*-Associated Periodic Syndromes (CAPS). IL-1 Trap for the treatment of CAPS has been granted Orphan Product Designation and Fast Track Designation. Currently there are no therapies approved for the treatment of CAPS. IL-1 Trap is a cytokine agonist that binds to and blocks the bioactivity of the cytokine interleukin-1 (IL-1), which is overproduced in patients with CAPS. Preliminary data from an ongoing pilot study of IL-1 Trap in subjects with CAPS indicate that IL-1 Trap relieves symptoms associated with the syndromes and reduces the levels of acute phase reactants. The proposed BLA submission will include data through the six-month time point of a CAPS pivotal study and additional safety data submitted with the 120-day update, which will together provide up to one year of IL-1 Trap exposure data for subjects in the CAPS pivotal study trial. Regeneron plans to submit the BLA in eCTD format.

1. Does the Agency agree that the timing for provision of the long term safety data from the open-label extension phase of the pivotal trial is acceptable?

FDA Response:

You have proposed including data through the six-month time point of the CAPS pivotal study in the original BLA submission with additional safety data from the open-

label extension phase being submitted with the 120-day safety update, thereby providing up to one year of IL-1 Trap exposure data for patients. The Division does not find this proposal acceptable. A complete safety database which will permit the assessment of the safety of IL-1 Trap will need to be submitted at the time of the original BLA submission, and this will need to include the one-year safety data.

Discussion:

The Sponsor proposed that for the one-year safety data of 45 patients in the pivotal CAPS study, safety data for one-year's worth of exposure on approximately 30 patients would be submitted with the BLA and the remaining patients' safety data with the 120-day safety update. The Division explained that a complete safety database from the pivotal study is required at the time of submission. If the BLA is submitted without a complete safety database, it is not probable that time will permit review of the latter data during the review cycle, meaning that the data submitted initially is expected to be the complete data package. The Division strongly advised the Sponsor against submitting the clinical portion of the BLA until the one-year safety database of the 45 patients was completed. The Sponsor asked if the partial safety database would be complete enough to consider for the BLA submission and the Division reiterated that a nearly complete submission is unacceptable and that one-year safety data on all patients from the pivotal study is key information for this submission and is thus required prior to or at the time of the BLA submission.

2. *Does the Agency agree that this is an acceptable organization of the safety data?*

FDA Response:

You have proposed providing safety data from all IL-1 Trap study groups in three separate tiers:

- A. Tier 1: Pivotal Study (IL1T-AI-0505) Part A
- B. Tier 2: All data from patients with CAPS
- C. Tier 3: Data from patients in the completed clinical studies, excluding healthy volunteers, who will be included separately in an additional section.

The Division agrees that the three proposed tiers are acceptable, but also requests that you include a fourth tier that combines all three tiers and reflects patients treated with IL-1 Trap compared to placebo.

Discussion:

The Sponsor agreed with the Division on including a fourth tier of safety data. The Sponsor proposed that the fourth tier have double-blind, placebo-controlled, randomized portions of all completed studies, including Part A of the pivotal study, double-blind, locked portions of the Systemic Juvenile Idiopathic Arthritis (SJIA) study, and double-blind portions of all other controlled studies. This data would exclude the healthy volunteer pharmacokinetic (PK) studies, the withdrawal portion of the pivotal study and the open-label studies. The Division agreed that this was an acceptable fourth tier for the organization of the safety data.

3a. Does the Agency agree that there is no requirement to conduct studies in the pediatric patients for the Orphan Product indication, CAPS?

3b. Does the Agency agree that if the requirements of 21 CFR 201.57(f)(9)(iv) were met, that pediatric use may be included in the product label for patients with CAPS?

FDA Response to 3a. and to 3b.:

Although it is true that since CAPS is an orphan indication that there is no formal requirement to conduct pediatric studies under the Pediatric Research Equity Act (PREA), it is strongly recommended that you conduct studies in children. The Division expects there to be considerable use in children if your product is approved.

Discussion:

The Sponsor stated that the proposed BLA submission will contain placebo-controlled safety data from approximately 20 pediatric patients, aged 5 to 18 years. Approximately six pediatric patients with CAPS, aged 7 to 16 years, are anticipated to enroll in the open-label study. The Sponsor stated that they feel there is potential to add pediatric labeling information based on this data.

4. Does the Agency agree that the proposed post-marketing safety monitoring plan for IL-1 Trap is adequate?

FDA Response:

You have proposed a post-marketing mechanism whereby healthcare professionals and patients can report adverse events (AEs) directly to Regeneron. Experience with spontaneous healthcare professional- and patient-reporting of AEs has shown that underreporting and incomplete clinical data on AEs are frequent deficiencies in the database. Due to the limited patient experience with IL-1 Trap at the time of your BLA submission, it will be important to adequately collect post-marketing safety data, assuming approval, to gain a further understanding of the safety risks of IL-1 Trap. Consequently, the Division recommends you develop a more active plan for collection of safety data, such as a Phase 4 study enrolling patients for long-term safety follow-up.

The Sponsor stated that a detailed safety monitoring plan will be submitted with the proposed BLA submission.

5a. Does the Agency agree that the characteristics of the new binding antibody assay are adequate to support the BLA?

FDA Response:

The information provided in the pre-BLA meeting package is insufficient to assess the adequacy of the new binding assay. Adequacy can only be assessed based on review of the full validation package and corresponding patient data. In general, an

ELISA assay should be an appropriate format for detection of antibodies against IL-1 Trap. The Division has the following additional comments regarding the information provided for this assay:

Discussion:

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6. *Does the Agency agree with this approach of including both the CAPS subjects and subjects from other clinical studies of IL-1 Trap in the population pharmacokinetic analyses?*

FDA Response:

In general, the proposed approach to include both the CAPS subjects and subjects from other clinical studies of IL-1 Trap in the population PK analyses is acceptable. However, if the plasma/serum samples would have been analyzed using different bioanalytical assay methods, it will be critical that the different methods are adequately cross-validated for this approach to be successful.

In addition, factors affecting the PK of IL-1 Trap may vary in different populations. The Division recommends that you collect traditional PK data in CAPS patients for confirmatory PK characteristics of IL-1 Trap in CAPS patients.

Discussion:

The Sponsor noted that currently there are four standard operating procedures (SOPs) to evaluate clinical PK samples. Of the four SOPs, two of them have only minor differences; therefore, the Sponsor proposed evaluating each of the three relevant assays for concordance among a subset of

available serum samples. The Division requested that the Sponsor elaborate on the assay evaluation in the planned submission and present any data that shows equivalence or differences.

The Sponsor proposed an assessment of trough levels from patients in the pivotal trial by a measurement of consistency of trough levels from CAPS patients with complete PK profiles from rheumatoid arthritis patients and healthy volunteers. The Division indicated that measuring only trough levels may not provide adequate information. The Sponsor noted this and stated that based on available data they did not feel that using trough levels alone would be a concern and if this approach does not work then they may pursue intensive sampling scheme.

The Division asked if the Sponsor intended to obtain PK data in the pediatric patients and they stated they had trough levels in rheumatoid arthritis pediatric patients and planned to collect trough levels in CAPS pediatric patients as well.

7. *Does the Agency agree with the proposal to submit only validation reports on the critical and most current versions of the assays?*

FDA Response:

See response to Question 6. **If the population PK analyses include all the samples obtained in the development program, then validation data for all the assays needs to be submitted with the BLA submission.**

Discussion:

The Sponsor agreed to submit the validation data for all assays with the BLA submission.

- 8a. *Does the Agency agree with the proposed rolling BLA submission schedule?*

FDA Response:

Submission of a rolling BLA is appropriate. The Division has the following comments regarding the submission schedule:

- i. **We strongly recommend a CMC pre-BLA meeting be held prior to submission of the CMC portion of the BLA. In the meeting package, you mention that the CMC questions for this pre-BLA meeting were removed in order to focus on the clinical safety and biostatistical aspects of the BLA submission. Though you had a type B meeting with the FDA on February 16, 2006 in which certain aspects of product development were discussed, the questions submitted and discussed at the February 16 meeting did not fully cover all components that are usually discussed, clarified and agreed upon at a CMC pre-BLA meeting.**
- ii. **For agreement on a submission schedule of a rolling BLA, you should provide a comprehensive schedule for the reviewable units (RU) you plan to submit. This schedule should include identification of the specific items that will be part of each RU and the dates of submission for each unit. The**

timeline should also identify dates for submissions of additional information not available during the submission of the initial RU, such as stability updates.

Discussion:

The Sponsor stated that they plan to submit Quality Module 3 as the first module of the proposed rolling BLA submission in October or November, 2006. The Sponsor stated that, at this time, they feel all their CMC questions have been adequately answered by the Division at the End-of-Phase 2 meeting held in February 2006, and do not feel a pre-BLA CMC meeting is necessary. The Division reiterated that a CMC meeting prior to the BLA submission would be helpful to make sure all pertinent information is covered and to allow the participation of representatives from the facilities branch and a comprehensive discussion of what the Division expects and what the Sponsor plans to submit to the BLA. However, the Division concurred that the Sponsor does not need to have a pre-BLA CMC meeting; it is at the discretion of the Sponsor. The Sponsor also agreed to submit a comprehensive outline of the proposed submission schedule for the reviewable units of the rolling BLA prior to the first Module submission.

Post-meeting note: On September 25, 2006 Ms. Stocker contacted Ms. Davies to request a CMC pre-BLA meeting per the Division's recommendation at the pre-BLA meeting on September 19, 2006.

8b. Does the Agency agree that the IL-1 Trap BLA for CAPS is eligible for the Pilot 1 program?

FDA Response:

The Division discourages the use of a Pilot 1 program for the IL-1 trap BLA. Our experience has been that the Pilot 1 program is not beneficial to a full and comprehensive review of the submitted data because it does not permit the interaction between review disciplines on issues where cross-discipline communication of data is required. This significantly reduces the efficiency of review and our ability to assess the safety and efficacy of your product. Additionally, we have found that the Pilot 1 program requires significantly more resources than does a traditional or rolling BLA submission and the Division is not able to invest these resources when they may not yield an optimal review.

Discussion:

The Sponsor acknowledged the Division's reservations regarding the Pilot 1 program and does not plan to request participation in the program.

Additional Comments:

Pharmacology/Toxicology:

Your BLA submission should contain final study reports for all nonclinical pharmacology/toxicology studies. However, you should submit the final reports to your IND as soon as they are available. In particular, please submit final reports of the 6-month monkey subcutaneous (SC) and intravenous (IV) toxicology studies as these studies were designed to support the safety of your clinical trials. The study reports should include your evaluation of the degree of immunosuppression noted in the studies as well as any specific toxicity that may impact the clinical use of your product.

A juvenile animal study may be required to support a pediatric indication; however, final determination of the need for such a study can only be made upon review of the final reproductive toxicology study reports.

Definitive determination of the adequacy of the nonclinical studies that comprise your planned nonclinical portion of your BLA submission cannot be determined until the final study reports have been submitted for review.

Discussion:

The Sponsor submitted the final report for the 6-month monkey subcutaneous toxicity study on September 13, 2006, to the IND and will submit the final reports for the 6-month monkey intravenous toxicity studies as soon as possible. The Sponsor noted that the chronic monkey toxicity studies contained adolescent animals, and that these studies will also be submitted to the IND with the reproductive toxicity studies.

Clinical:

The Division requests you include the following analyses and tables in your BLA submission:

- A. Table of Clinical Studies: This data should include a table consisting of the individual clinical studies relevant to your BLA submission. For each clinical study the table should include the study number, study phase, an abbreviated description of the study design, background therapy (if any), the number of placebo control patients, the number of patients treated with IL-1 Trap and the total number of patients. For example:**

Study Phase	Study Design	Concomitant Therapy	Control Subjects (n)	IL-1 Trap-treated Patients (n)	Total
ILT-AI-0505 Phase 3	Randomized, placebo-controlled, double-blind	NSAIDs, Prednisone	100	100	200

- B. Patient Disposition:** Include a table with a detailed description of all patients enrolled in the CAPS pivotal trial and include a diagram outlining the distribution of patients randomized to each phase of the trial, the number (and percent) completing that phase and the number (and percent) not completing.
- C. Protocol Violations:** This should be separated for both Part A and Part B of the CAPS pivotal trial for both placebo and IL-1 Trap treatment arms.
- D. Reasons for Discontinuation:** Include a table outlining reasons for discontinuation based on treatment arm.
- E. Extent of Exposure to IL-1 Trap:** Include a table describing the extent of patient exposure to IL-1 Trap in the CAPS pivotal trial as well as for all patients in all studies based on grouping of days (e.g., 1-60 days, 61-120 days, etc.).
- F. Concomitant Medications:** This should include concomitant medications prior to enrollment and during the trial.
- G. Adverse Events and Serious Adverse Events:** Include separate analyses for infections including incidence rates based on 6 month intervals (i.e., 0-6 months, 6-12 months exposure).
- H. Total Number of Dropouts from All Clinical Trials:** Include for the placebo-controlled periods as well as the open-label periods.
- I. Pediatric Patients:** Perform separate safety analyses on the pediatric patients.
- J. Subset analyses:** For the primary endpoint include subset analyses based on key demographic features and relevant disease activity measures.
- K. Since this BLA will represent a new molecular entity your submission should include:**
- i. A section on drug-drug interactions.
 - ii. A section on special populations.
 - iii. A section on important regulatory actions in other countries or important information contained in any foreign labeling.

- iv. A section on less common adverse events, including AE's over the entire database, grouped by incidence and body system for events occurring at a rate less than 1%.
- v. A section on hepatotoxicity in the clinical trials.
- vi. A section with an overview of vital signs testing in the development program.
- vii. Analysis of vital signs focused on measures of central tendencies (e.g, means and standard deviations).
- viii. Analysis of vital signs focused on outliers or shifts from normal to abnormal.
- ix. Marked outliers for vital signs and dropouts for vital sign abnormalities.
- x. Overview of ECG testing in the development program, including brief review of preclinical results.
- xi. Standard analyses and explorations of ECG data.
- xii. Overdose experience.
- xiii. Tables of demographic information for phase 1 and phase 2-3 studies separately.

Discussion:

The Sponsor agreed to accommodate the Division's requests for the specified clinical analyses and tables.

Post-meeting Comment

If you wish, it may be worthwhile to submit "mock" data tables in the .XPT file format to permit the Division an opportunity to evaluate whether the data tables are being formatted in a reviewable manner. These tables would consist of a few column headings with several rows of data (which could be manufactured data for the purposes of this exercise), to see if the data can be manipulated.

ACTION ITEMS:

1. The Sponsor agreed to submit a comprehensive outline of the planned reviewable units of the BLA submission prior to submission of the first module.
2. The Sponsor acknowledged the Division's advice regarding submitting an incomplete safety database and understood that data submitted after the initial clinical module submission would not likely be reviewed.
3. The Sponsor will submit complete validation packages of their binding assays.

4. The Sponsor _____
5. The Sponsor agreed to _____ for Antibody binding assay _____
6. The Sponsor will submit validation reports for all bioanalytical assays.
7. The Sponsor will submit requested non-clinical final study reports to the IND as soon as they are completed.

ATTACHMENTS/HANDOUTS:

The Division requested that slides from Sponsor presentation at meeting on September 19, 2006 be submitted.

19 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Linked Applications

Sponsor Name

Drug Name

IND 11781

REGENERON PHARMS

Interleukin-1 Receptor Fc Fusion Protein (IL-1 Trap) (human recombinant, CHO cells, Regeneron)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kathleen M Davies

10/18/2006



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 11781

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

Attention: Mierette R. Stocker
Associate Director, Regulatory Affairs

Dear Ms. Stocker:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Interleukin-1 (IL-1) Trap.

We also refer to the meeting held on February 16, 2006, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1277.

Sincerely,

{See appended electronic signature page}

Pratibha Rana, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 16, 2006

TIME: 11:30-1:00 pm

LOCATION: White Oak Conference Room 1313

APPLICATION: IND 11,781

DRUG NAME: IL-1 Trap

INDICATION: Treatment of patients with *CIAS1* Associated Periodic Syndromes (CAPS)

TYPE OF MEETING: Type B

MEETING CHAIR: Rigoberto Roca, M.D., Deputy Director
Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

MEETING RECORDER: Pratibha Rana, MS, Regulatory Project Manager, DAARP

ATTENDEES:

Regeneron Pharmaceuticals, Inc.	Title
Hanne Bak, PhD	Research Engineer, Process Development
Thomas Daly, PhD	Vice President, Protein Sources
Stephen Holst, PhD	Sr. Vice President, Manufacturing
William Roberts, MD	Vice President, Regulatory Development
Mierette Stocker	Director, Regulatory Affairs
Gerald Underwood	Vice President, Manufacturing
Scott Carver, PhD	Director of Cell Culture Manufacturing
William Trompeter, PhD	Director of Process and Analytical Sciences
Randall Rupp, PhD	Sr. VP Manufacturing Operations
FDA	Title
Bob A. Rappaport, MD	Division Director, (DAARP)
Rigoberto Roca, MD	Deputy Director, (DAARP)
Keith Hull, MD	Medical Officer, (DAARP)
Pratibha Rana, MS	Regulatory Project Manager, (DAARP)
Ruth Cordoba-Rodriguez, PhD	Product Reviewer
Chana Fuchs, PhD	Team Leader, Product
Michelle Jessen	Product Reviewer

BACKGROUND:

Regeneron Pharmaceuticals, Inc. submitted a Type-B meeting request dated November 22, 2005, to discuss and reach an agreement with the Agency on the current Chemistry, Manufacturing, and Controls (CMC) development plans to support licensure of IL-1 Trap for treatment of patients with *CIAS1* Associated Periodic Syndromes (CAPS). The Sponsor also submitted a briefing package dated January 12, 2006, which contained a list of questions to be discussed at this meeting. Upon review of the briefing package, the Division responded to the Sponsor's questions via email on February 15, 2006. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. The Sponsor's questions are in ***bold italics***; FDA's response is in *italics*; meeting discussion is in normal font.

CMC QUESTIONS

Question 1: Regeneron has made changes to IL-1 Trap drug product in order to reduce the reconstitution time from approx. _____ to <1 min. The changes involved: _____

Regeneron is currently testing the new process (process B) and plans to introduce product manufactured following process B during the last two phases of the pivotal study IL1T-AI-0505. Product manufactured using the original lyophilization method (process A) will be administered to patients during the first two phases of the pivotal clinical trial IL1T-AI-0505.

Does the Agency consider all aspects of the strategy described above acceptable?

FDA Response:

The data submitted do not provide sufficient information to assess comparability of drug product manufactured using lyophilization method, P4-B, to drug product manufactured using lyophilization method P4-A.

- 1. Full comparability data between products manufactured by processes P4-A and P4-B should be submitted to the FDA for assessment prior to introducing DP manufactured by process P4-B into clinical trials.*
- 2. The comparability protocol for reconstituted DP should incorporate acceptance criteria that are set based on lot release data acquired from lots manufactured by process P4-A.*
- 3. Product manufactured following process P4-B should be placed under real time and accelerated stability, and stability data should be compared to stability data collected from lots manufactured by process P4-A.*
- 4. Comparability and stability testing should incorporate a quantitative assay based on _____ . In addition, parameters such as _____ levels should be used for comparability assessment.*

CLINICAL COMMENTS

- *You state that subjects will reconstitute study drug in a closed box for 15 minutes to avoid unblinding. For the placebo controlled portions of the clinical trial it is essential that there be proper blinding to avoid bias. If subjects can tell the difference between study drug and placebo based on the rate of dissolution this would represent an unblinding issue. Asking subjects not to look inside the closed box during reconstitution does not constitute adequate blinding. You will need to address this issue to make sure your study is adequate and controlled.*
- *During your clinical development you state that you will be making a switch to process B material. It will be essential to measure antibodies to the product separately for patients receiving the earlier material and those receiving process B material. In addition, you should assess the percent of patients who go from antibody-negative to antibody-positive when they switch to process B material.*

Discussion:

The Sponsor stated that they are still looking for the best method to monitor _____

The Sponsor stated that _____ the method is not validated. Alternatively, the Sponsor may send samples to a contract laboratory facility.

The Sponsor agreed _____ will be measured.

The Sponsor agreed to provide comparability data as advised.

The Sponsor acknowledged that they have initiated the enrollment of patients into their Phase 3 study without reaching agreement with the Division on their recently submitted Special Protocol Assessment (SPA) due to time considerations concerning the activity of disease in patients with CAPS. The Sponsor and Division discussed the possible introduction of bias using the blinding method described above and that additional analyses will need to be undertaken at the time of review of a BLA submission to assess for biasing of the results. The Division also requested the Sponsor to perform the appropriate antibody assessments for Process A and B in patients exposed to both formulations of IL-1 Trap.

Question 2: Does the Agency support the discontinuation of drug substance release testing for process-related impurities (specifically, _____) that have been consistently removed below an acceptable limit of quantification during the conformance lots?

FDA Response:

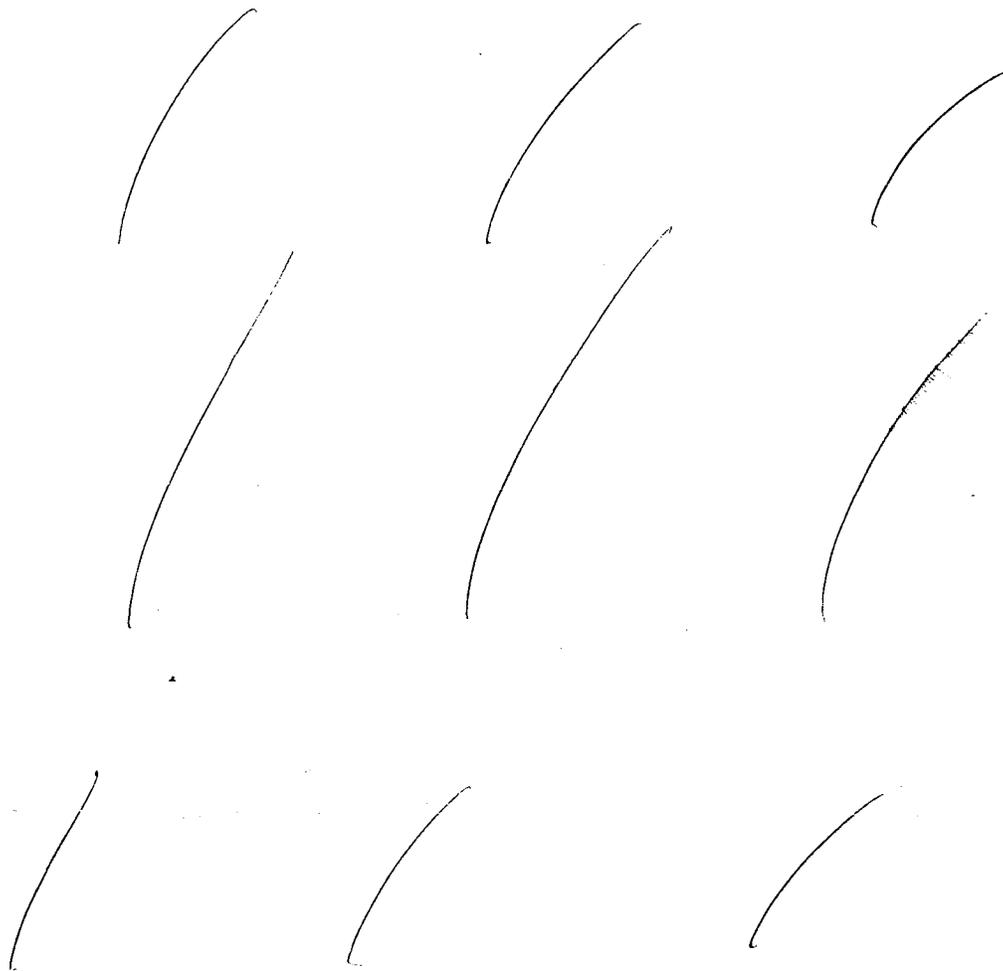
The determination for removal of testing for process-related impurities cannot be made until the relevant data has been submitted and reviewed to determine its acceptability. Removal of testing will depend on assessment of a comprehensive validation package with pre-defined acceptance

criteria that supports the consistent removal of impurities by the manufacturing process. We advise that process validation studies for removal of impurities be submitted for the to-be-marketed process.

Discussion:

There was no discussion other than the information presented on the slide above.

Question 3: Does the Agency agree that the methods and data are adequate to meet the requirements for



Question 4: Does the Agency agree with the strategy for revising the acceptance criteria for the release of DS, FDS and DP?

FDA Response:

Determination of acceptability regarding your proposed strategy for assignment of specifications at this time is premature. The complete dataset from IL-1 Trap lots used in clinical trials will have to be assessed prior to setting final specifications. Specifications are linked to the

manufacturing process, analytical procedures, preclinical studies, and clinical studies, and should account for the stability of the drug substance and drug product.

Discussion:

There was no discussion other than the information presented on the slide above.

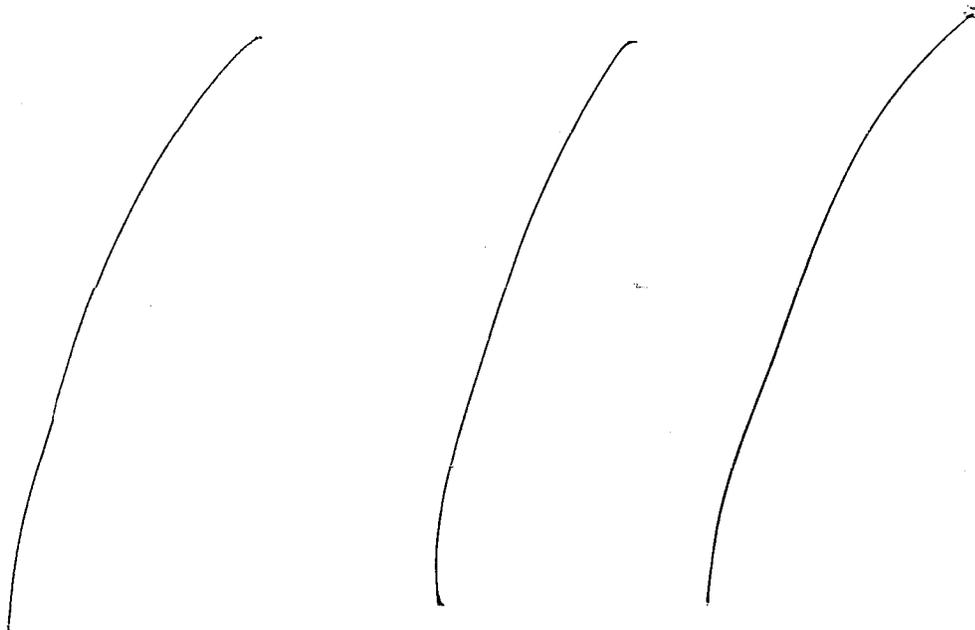
Question 5: Does the Agency agree with the strategy described for determining retest periods and expiration dating?

FDA Response:

- *Please refer to the response to question 4 regarding specifications and clinical experience.*
- *Please be advised that expiry dating and extrapolation of stability data for determination of expiry dating will be based upon review of stability data within the biologics license application, following ICH Q1 and ICH Q5C guidances.*

Discussion:

There was no discussion other than the information presented on the slide above.



Additional CMC Comments

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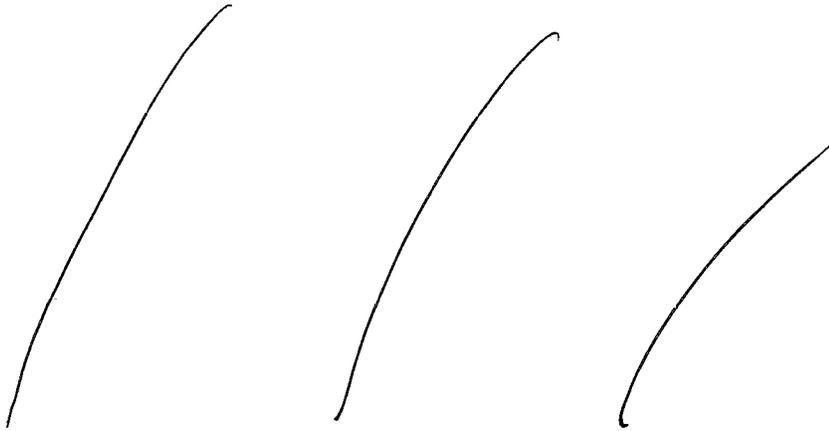
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Deliberative Process



Discussion:

There was no discussion other than the information presented on the slide above.

Action Items:

1. The Division requested the Sponsor officially submit the slides presented during the face-to-face meeting.

Sponsor's slides enclosed:

**APPEARS THIS WAY
ON ORIGINAL**

BB

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Draft Labeling

Deliberative Process

Linked Applications

Sponsor Name

Drug Name

IND 11781

REGENERON PHARMS

Interleukin-1 Receptor Fc Fusion Protein (IL-1 Trap) (human recombinant, CHO cells, Regeneron)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRATIBHA RANA

04/04/2006