DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 100,040

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07636-1080

Attention: Frederick De Brito, PhD
Associate Director, Drug Regulatory Affairs (U.S.A)

Dear Dr. De Brito:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ACZ-885.

We also refer to the meeting between representatives of your firm and the FDA on February 5, 2008. The purpose of the meeting was to your Phase 3 clinical development program.

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, MS
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

16 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 2

Linked Applications	Sponsor Name	Drug Name
IND 100040	NOVARTIS PHARMACEUTICALS CORP	IND —— ACZ885

b(4)

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
03/06/2008

Gregory King
06/02/2006 11:48 AM

To: _PH.O.DEV.PJM AB.IPT.ACZ_RA@PH
cc: DRA Archive/G/PH/Novartis@PH
Subject: —— FYI: FDA Fax-PIND100040-Meeting Minutes

b(4)

FYI - Official FDA minutes from April 13 2006 meeting attached.

Best regards,

Greg King
phone: 862-778-0495
cell (emergencies): 908-752-8441
fax: 973-781-3966
----- Forwarded by Gregory King/PH/Novartis on 06/02/2006 11:46 AM -----

Carmel Marengo
05/31/2006 05:07 PM

To: Gregory King/PH/Novartis@PH
cc:
Subject: Re;FDA Fax-PIND100040-Meeting Minutes

Greg,

Here is scanned fax.

FDA Fax-PIND 10040-Meeting Minutes.PDF

Carmel Marengo
Drug Regulatory Affairs
ABGU
Novartis Pharmaceuticals Corporation
405/2008A
Phone#862-778-0036
Fax #973-781-3966

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

PIND 100040

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

Attention: Greg King
Senior Therapeutics Area Manager
Drug Regulatory Affairs

Dear Mr. King:

Please refer to your Pre-Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ACZ885.

We also refer to the teleconference held on April 13, 2006, between representatives of your firm and this agency. The purpose of the meeting was to discuss development issues associated with ACZ885 ——— b(4)

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

Pratibha Rana, 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: April 13, 2006

TIME: 11:00-12:00 pm

LOCATION: Teleconference, Conference Room 3270

APPLICATION: PIND 100040

DRUG NAME: ACZ885

INDICATION: b(4)

TYPE OF MEETING: Type B

MEETING CHAIR: Jeffrey Siegel, MD, Clinical Team Leader, Rheumatology Biologics Products
Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

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

ATTENDEES:

Novartis Pharmaceuticals Corporation	Title
John Cutt, PhD	Drug Regulatory Affairs
Martin Koenig, PhD	Drug Regulatory Affairs
Debra Aleknavage	Drug Regulatory Affairs
Reinhold Janocha, PhD	Project Management
Heike Schwende, PhD	Project Management
Timothy Wright, MD	Exploratory Clinical Development
Professor Ulrich Trechsel, MD	Clinical Development
Erich Kilchherr, PhD	Technical Project Management, Biopharmaceutical Operations
Jutta Look, PhD	Regulatory CMC
Hermann Gram, PhD	Research
Nathalie Ezzet, PhD	Biostatistics
George Yancopoulos	Regeneron Pharmaceuticals
William Roberts	Regeneron Pharmaceuticals
Neil Stahl	Regeneron Pharmaceuticals
Randall Rupp	Regeneron Pharmaceuticals
Scott Mellis	Regeneron Pharmaceuticals

FDA	Title
Bob A. Rappaport, MD	Division Director, (DAARP)
Jeffrey Siegel, MD	Team Leader, Rheumatology Biologics Products
Dan Mellon, PhD	Supervisor, Pharmacology/Toxicology, DAARP
Sarah Okada, MD	Medical Officer, DAARP
Jerry Cott, PhD	Pharmacology/Toxicology Reviewer, DAARP
Dionne Price, PhD	Statistics Reviewer
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer
Pratibha Rana, MS	Regulatory Project Manager, DAARP
Ruth Cordoba-Rodriguez, PhD	Product Reviewer
Patrick Swann, PhD	Division Director, Division of Monoclonal Antibodies
Atul Bhattaram, PhD	Pharmacometrics

BACKGROUND:

Novartis Pharmaceuticals, Inc. submitted a Type-B meeting request dated December 23, 2005, to discuss the plans for developing ACZ885 for the treatment of ——— Novartis also submitted a briefing package dated March 9, 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 April 7, and April 12, 2006. Any discussion that took place at the teleconference is captured directly under the relevant original response including any changes in our original position. Novartis' questions are in ***bold italics***; FDA's response is in *italics*; meeting discussion is in normal font.

b(4)

REGULATORY QUESTIONS

Question 1: Novartis intends to file the IND for ACZ885 around the end of April 2006. In the IND, Novartis will provide ACZ885 batch analysis data from previous batches which used ——— Novartis has switched HSA supplier to a US-licensed facility and would be able to provide the certificate of analysis (CofA) for this clinical batch by the end of May 2006. Does the Agency agree with the timing of the receipt of the CofA?

b(4)

FDA Response:
Yes, it is acceptable, provided the Human Serum Albumin certificate of analysis is submitted prior to the 30-day IND decision date. Please include all specifications and acceptance criteria and information about the lots of HSA used in the manufacture of ACZ885 for use in US clinical trials and a statement that this HSA is sourced from a US-licensed blood facility when filing the IND.

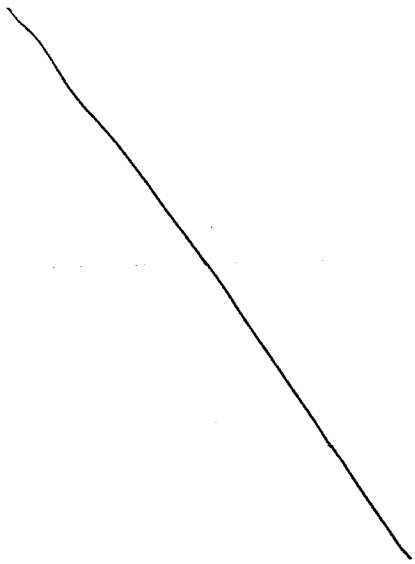
Sponsor's Follow-up Question: We would like to clarify that the CoA for the HSA will be submitted with the IND and the CoA for the clinical batch will be provided prior to the 30-day IND decision date. Is this in line with the Agency's expectation?

Discussion:
The Division stated that the CoA submission prior to the 30-day IND decision date is acceptable.

Question 2: The Quality Section of this Briefing Package describes various program elements to be used to show comparability of pre- and post-change drug substance and drug product. Novartis intends to submit the results of the various studies and analyses as they become available in the form of amendments to the IND. Novartis is seeking agreement from the Agency that, assuming the results of the comparability analyses are in-line with expectations as described in this briefing package, Novartis will transition to the new drug substance or product soon after submission of the amendments to the Agency. Does the Agency agree with this approach?

FDA Response:
No. The information submitted in the pre-IND package is not sufficient to assess the adequacy of the proposed comparability plan. The comparability report should be submitted to the IND for review and concurrence of comparability prior to the use of post-change drug product in clinical trials. Comparability data for each process change should be submitted to the IND as a single amendment. Please also refer to the Agency's reply to your question number 8 in the January 18, 2006 pre-IND meeting minutes.

Discussion:
There was no discussion other than the information presented in response section.



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_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 3

b(4)

CMC QUESTIONS

Question 1: Between phases I/II and III in MWS, Novartis intends to switch expression of ACZ885 from an — production cell line to an — production cell line. Concurrently, drug substance (DS) production will be transferred to a different site which will include a scale-up. Prior to the introduction of — derived ACZ885 in patients, Novartis will demonstrate comparability of pre- and post-change material with physico-chemical and biological analyses, a PK study in marmosets, and an assessment of human tissue cross reactivity. Does the Agency agree with this approach?

b(4)

FDA Response:
Yes. Physico-chemical and biological analyses should be sufficiently comprehensive to address all aspects of product quality that can impact safety/efficacy. For the IND submission, please provide a table summarizing the existing and planned nonclinical toxicology studies, the source of the drug product employed for each study, and how the drug product tested compares to the proposed clinical and final drug product batches. You should specifically address any differences between the new/final product and those used for toxicology studies and provide your rationale regarding the relevance of the toxicology data obtained using earlier drug product batches with respect to the proposed clinical formulations.

Discussion:
There was no discussion other than the information presented on FDA Response section.

Clinical Comments to Quality Questions 1-6

1. *You are proposing two cell line changes, a scale-up, site change, and formulation change during the course of your clinical development program. These are all major changes that may significantly affect the drug substance/product. If, in addition to meeting CMC*

requirements, you can demonstrate the — and — derived products are sufficiently similar to the — derived product, e.g., within the 80-125 percent confidence interval on two of three PK parameters, then it would be acceptable to use the newly derived products in your clinical trials. Human PK/PD studies may be warranted, depending on the results of your comparability testing. b(4)

2. *It is possible that a given subject could have been exposed to 3 different ACZ885 derivations. The immunogenic potential of these exposures, and its potential impact on safety and efficacy, must be carefully considered and monitored. You should track the number of different ACZ885 derivations given subjects receive, and assess whether these changes have affected the rate of anti-ACZ885 antibody development, and whether these antibodies cause a loss of efficacy and/or increase the chances of infusion/injection site reactions.*

Sponsor's follow up to FDA Clinical Comment # 2 to Quality Questions 1-6:
In order to implement these recommendations, Novartis would appreciate receiving advice regarding the number of patients, in particular for adult — that should be exposed to the final formulation. b(4)

FDA Response:
Assuming you determine that the final formulation is comparable to the previously studied product then, ideally, an adequate number of patients would be treated in the phase 3 trials to qualitatively assess whether safety, efficacy, and immunogenicity are comparable in patients receiving the two formulations. For example, if half the patients in the phase 3 trials receive the previous formulation and half receive the final formulation, this may be adequate.

Discussion:
The Sponsor requested clarification with respect to how firm the "50 percent rule" was. The Division re-iterated the primary issue as being able to qualitatively assess whether the safety, efficacy and immunogenicity of the final formulation is comparable to previous formulations. This ideally would be assessed, at the latest, during the Phase 3 trials, in order to have safety and efficacy data of the final formulation evaluable in the BLA, prior to a marketing approval decision. However, there is no definitive rule regarding the necessary number of subjects required to have used the final formulation.

Question 2: Novartis also intends to switch ——— patients to the — derived ACZ885 between phases II and III. In addition to the above mentioned comparability program, Novartis will have clinical data from MWS patients to further support comparability. Does the Agency agree with this approach? b(4)

FDA Response:
Please see response for CMC question 1

Discussion: Please see discussion for CMC question 1.

Question 3: Novartis also intends to start ——— patients with the — derived ACZ885. In addition to the above mentioned comparability program, Novartis will have clinical data from MWS and SJIA patients to further support comparability. Does the Agency agree with this approach? b(4)

FDA Response:
Please see response for CMC question 1.

Discussion: Please see discussion for question 1.

Question 4: Novartis also intends to switch adult — patients to the — DS in the extension phase of each of the three phase II studies. In addition to the above mentioned comparability program, Novartis will have clinical data from MWS patients to further support comparability. Does the Agency agree with this approach? b(4)

FDA Response:
Please see response for CMC question 1.

Discussion: Please see discussion for CMC question 1.

Question 5: Just prior to phase III for both — and adult — Novartis intends to change the — This change will be implemented using — drug substance, for which comparability to — will already have been demonstrated. For demonstration of comparability of pre- and post-change drug product, Novartis plans to perform physico-chemical and biological analyses, a non-clinical PK study in marmosets, and a comparative PK/PD study in humans. Does the Agency agree with this approach? b(4)

FDA Response:
Please see response for CMC question 1.

Discussion: Please see discussion for CMC question 1.

Question 6: The preferred type of cell line for generation of ACZ885 is — Therefore, Novartis is considering the possibility of an additional change in the production cell line from — to — Novartis could switch the DS during Phase III trials for both — — To demonstrate comparability of the pre- and post-change DS, Novartis would perform the same physico-chemical and biological analyses and non-clinical assessments as specified in Quality Question 1, as well as an assessment of clinical comparability in patients. Once comparability is demonstrated, this material would then be introduced into the latter part of the Phase 3 programs for all patients. Does the Agency agree with this approach? b(4)

FDA Response:
Please see response for CMC question 1

Appropriateness of comparability studies are influenced by the stage of clinical development, the extent of product and process knowledge, manufacturing experience for lots used in your clinical trials, as well as other parameters described in ICH Q5E. Therefore, the adequacy of the quality component of your comparability protocol for the — change will have to be re- b(4)

assessed in light of the advanced stage of clinical development, and cannot be based solely on the comparability protocol used during the upcoming ——— change. b(4)

Specific changes made to the drug product during the development of the final formulation should be supported by a clear delineation of comparability. Pending review of the comparability data, additional nonclinical bridging studies may be required. The nature of such studies will depend upon the magnitude of the changes made to the product and the overall impact of such changes on the relevance of the existing nonclinical studies.

Discussion: Please see discussion for CMC question 1.

ADDITIONAL CMC COMMENTS

1. *Please submit with your IND a comprehensive description of release assays for ACZ885 drug substance and drug product. These should include a ——— should have a numerical range for acceptance criteria.* b(4)

Novartis Follow-up to FDA's Additional CMC Comment # 1

Novartis will include a ——— for phase 3 drug substance and drug product. A ——— will be performed as additional test for the phase 2 ——— aterial and the data will be submitted with the IND.
Novartis will also include numerical specifications for the ——— for phase 3 drug substance. Specifications for the ——— to assess purity are included in the briefing book table 3-7, page 40. b(4)

Novartis proposes the ——— to assess the biological potency. This assay may also be considered as a binding assay (see slide 14 and slides 15 and 16 with excerpt from IND document, summarizing the assay principle). Given the higher variability of the binding assay by ——— does the Agency agree that the described ——— also covers binding activity and that therefore an additional binding assay is not necessary? b(4)

Discussion:
The Sponsor stated that the ——— binding assay will be included in the comparability testing, but not for release, as they feel that the ——— is sufficient as a binding assay. The Agency expressed concern that the ——— would not be sufficient to establish identity, however Novartis felt that in their hands, these tests are sufficient. The Agency then expressed that the IND should include the Sponsor's justification for why they feel these tests are sufficient as identity tests. The Sponsor will submit a summary of all toxicology lots. b(4)

2. *Your comparability package should include detailed acceptance criteria for the assays used to demonstrate comparability, as well as the basis for setting these acceptance criteria.*

3. *Your stability program should include a detailed set of acceptance criteria for the assays used to demonstrate stability. In addition, please identify stability indicating assays for ACZ885.*

4. *Product manufacturing changes described in this package occur at different timelines within clinical development of each indication. Please be aware that any manufacturing changes that may occur after licensing ACZ885 for the first indication are outside the scope of our current comments on comparability.*

Discussion: There was not discussion other than the information presented in the response section above.

PRECLINICAL QUESTIONS

Question 1: Novartis has recently completed the in-life phase of a marmoset embryo fetal development study. At the time of IND submission, interim data comprising maternal and fetal toxicity data and fetal ACZ885 exposure data from the control and high dose animals will be available. Novartis proposes to summarize the available data in a toxicological recommendation in the IND b(4)

FDA Response:

The Division strongly recommends that final study reports be submitted to support clinical trials.

b(4)

1

Discussion:
There was no discussion other than the information presented in the response section above.

Question 2: The minutes of the previous Pre-IND meeting (minutes from FDA dated February 17, 2005) stated Novartis was developing a surrogate mouse model to address the issue of immune function effects from early exposure to ACZ885 in neonatal/young offspring prior to the enrollment of children into clinical trials. Novartis would like to clarify its position on

immune function investigations in laboratory animals, as this differs slightly from the minutes of the previous meeting and seeks the agreement of the Agency.

FDA Response: We understand that you are developing a surrogate mouse model to investigate reproductive safety and immunotoxicity. It now appears that you do not intend to submit these data until registration. However, since we have no direct information on how ACZ885 may affect these safety parameters, you should complete and submit these studies prior to large-scale enrollment (i.e., Phase 3). In general, the Division will evaluate the results of the nonclinical and clinical studies during the development program to determine if there are signals that suggest the need for further developmental immunotoxicity studies to support the product application. If signals suggestive of immunotoxicity arise during drug development, further studies may be required to be completed. The Division is committed to work with you during your development program and will evaluate the potential need for additional studies.

Discussion:
There was no discussion other than the information presented in the response section above.

CLINICAL QUESTIONS

b(4)

Discussion:
There was no discussion other than the information presented in the response section above.

b(4)

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

PIND 100,040

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, ND 07936

Attention: Gregory King
Senior therapeutic Area Manager

Dear Mr. King:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ACZ885.

We also refer to the meeting between representatives of your firm and the FDA on January 18, 2006. The purpose of the meeting was to discuss the development issues associated with the Muckle Wells Syndrome (MWS) indication.

The official minutes of that meeting are enclosed. You are responsible for notifying 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: January 18, 2006

TIME: 2:00-3:30 pm

LOCATION: White Oak Conference Room 1419

APPLICATION: PIND 100,040

DRUG NAME: ACZ885

INDICATION: Muckle Wells Syndrome (MWS)

TYPE OF MEETING: Type B

MEETING CHAIR: Jeffrey Siegel, MD, Clinical Team Leader, Rheumatology Biologics Products
Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

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

ATTENDEES:

Novartis Pharmaceuticals Corporation	Title
John Cutt, PhD	Regulatory
Miriam Donaldson, MBA	
Hermann Gram, PhD	Research
Reinhold Janocha, PhD	Project Management
Gregory King	Regulatory
Paul Knights	Toxicology
Philip Lowe, PhD	Modeling & Simulation
William Roberts, PhD	Regulatory, Regeneron
Christiane Rordorff, MD	Clinical
Ulrich Trechsel, MD	Clinical
Albert Widmer, MSc	Statistics
Thasia Woodworth, MD	Clinical
Debra Aleknavage	Regulatory
FDA	**Title**
Bob A. Rappaport, MD	Division Director, (DAARP)
Jeffrey Siegel, MD	Team Leader, Rheumatology Biologics Products
Josie Yang, PhD	Supervisor, Pharmacology/Toxicology, DAARP
Sarah Okada, MD	Medical Officer, DAARP
Thomas J. Permutt, PhD	Team Leader, Statistics
Jerry Cott, PhD	Pharmacology/Toxicology Reviewer, DAARP

Dionne Price, PhD	Statistics Reviewer
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer
Pratibha Rana, MS	Regulatory Project Manager, DAARP
Ruth Cordoba-Rodriguez, PhD	Product Reviewer
Chana Fuchs	Product Team Leader
Atul Bhattaram, PhD	Pharmacometrics

BACKGROUND:

Novartis Pharmaceuticals, Inc. submitted a Type-B meeting request dated October 19, 2005, to discuss the plans for developing ACZ885 for the treatment of Muckle Wells Syndrome (MWS). Novartis also submitted a briefing package dated December 14, 2005, 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 January 17, 2006. The content of that email is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Novartis' questions are in ***bold italics***; FDA's response is in *italics*; meeting discussion is in normal font.

CMC QUESTION

Question 8: Novartis plans to make a cell line switch and concurrently to introduce manufacturing process changes to realize a more efficient drug substance production. Novartis intends to switch material at the transition from phase II to phase III within the Muckle-Wells and [redacted] indications. Novartis plans to demonstrate comparability of the pre and post change drug substance by conducting physico-chemical and biological analyses and nonclinical studies as appropriate. Does the agency agree with this approach?

b(4)

FDA RESPONSE

- *The general approach proposed by Novartis seems reasonable. However, the information submitted in the pre-IND package is not sufficient to fully assess the proposed changes and the adequacy of the comparability plans. A change in the producer cell line represents a major manufacturing change that could impact the safety, efficacy and identity of the ACZ885 drug substance and drug product.*

- *Novartis should develop a detailed comparability protocol in advance of implementation, and base acceptance criteria on historical data for the pre-change lots. The comparability protocol should also include an assessment of product stability, which should encompass identified stability-indicating parameters. In addition, the comparability protocol should include an assessment of in-process testing parameters.*

- *Viral load and removal should be re-assessed as appropriately required.*

- *Data should be submitted to FDA for assessment of comparability prior to the use of post-change drug product in clinical trials. Depending on the information submitted, some clinical studies, such as comparative PK assessment, may be required.*

ADDITIONAL CMC COMMENTS

The following comments are based on the sponsor intention to submit an IND package requesting approval of initiation of pivotal studies:

- *The FDA strongly suggests that Novartis set up an End-of-Phase 2 CMC meeting prior to initiating pivotal studies. Please refer to www.fda.gov/cder/guidance/3683fnl.htm for issues you should address for monoclonal antibodies prior to the conduct of pivotal studies.*

- *No information regarding the immunogenicity of this agent is included in the meeting package. A validated assay (or assays) for the detection of immune responses to ACZ885 must be in place prior to analysis of samples from a trial intended to support market approval.*

- *A qualified potency assay should be in place for a product that is going to be used in pivotal studies. Please submit the appropriate supporting information to the IND.*

- *Your IND submission should include information regarding the source of all animal or human-derived components used in the manufacture of ACZ885 cell banks, drug substance and drug product, as well as certifications showing that these products are from transmissible spongiform encephalopathy (TSE) free sources.*
  - *In addition, please provide the results of any virus testing done on these components.*

Discussion:

The Sponsor acknowledged the CMC/Product comments and had no questions. They plan to have more extensive CMC discussion at the next pre-IND meeting for ACZ885 for the _____ b(4)

Preclinical Questions

Question 1: Novartis believes that the current non-clinical package supports entry into a pivotal study and registration in MWS for both the IV and the SC formulations. Does the Agency agree?

FDA RESPONSE

The studies in the package appear to be sufficient to support the proposed Phase 2 trial in MWS. However, it is premature at this point to determine whether the overall toxicology program would support the registration of ACZ885 for this or other indications. Additional nonclinical studies could be required depending on the review of the submitted non-clinical toxicology studies

Discussion:
The Sponsor clarified that the proposed trial in MWS will be a Phase 3/pivotal study.

Question 2: Novartis believes that the toxicology data from the marmoset, including an early fetal development study and the available clinical safety data in adults is sufficient to support eventually inclusion of patients of ages 2 years and older in the proposed pivotal studies in MWS and in — patients. Does the Agency agree? b(4)

FDA RESPONSE

- *Your proposal appears acceptable provided that the effect of anti-IL1β on immune functions in F1 juvenile animals was assessed in the embryo-fetal development study. The final decision will be made upon reviewing the complete submission. If safety concerns are identified, additional nonclinical studies may be necessary.*

Discussion:

There was discussion regarding the meaning of F1 juvenile animals (that is, offspring of mothers who have been treated) and the meaning of "immune functions" which Dr. Yang clarified to be general cellular and humoral immune response studies to usual antigens. The Sponsor pointed out that such studies are difficult to perform in the marmoset due to litter loss (from stress) and limited volume of blood that can be obtained due to the pup size. They have in development a surrogate mouse model to address the issue of immune function effects from early exposure to ACZ885 in neonatal/young offspring. In addition to the mouse surrogate studies, the Sponsor will have the full results of the embryo-fetal development study, and full toxicology data (including blood and histopathology) from both mature and sexually immature animals, prior to the initiation of the pivotal study in MWS, and will submit these data prior to the submission of that protocol. Supportive published literature on the effect of IL-1 blockade on immune function in humans may also be submitted. The Division agreed that submission of the full immune function package will not be required at the time of the IND submission, planned for April 2006, b(4)

Clinical Questions

Question 1: Novartis believes that the safetv. tolerability and PK/PD results from Phase I/II in healthy subjects, — , and MWS patients together with the non-clinical package, provide sufficient information to proceed directly into a pivotal registration study in MWS patients. Does the Agency agree? b(4)

FDA RESPONSE

- *For a pivotal trial in MWS, with respect to safety, there is sufficient information to suggest the risks of ACZ885 are acceptable to proceed.*
- *With respect to efficacy, the data submitted, suggesting clinical responses out to 101-178 days in all four MWS patients studied, are limited but provide sufficient information to proceed to a pivotal study in this population.*
- *The usual requirement for two adequate and well controlled trials arises from the possibility that lack of independent substantiation leaves room for error, including bias or inherent biological variability. However, Muckle Wells Syndrome is a rare disorder with serious morbidity, so in principle, a single efficacy study with clear and robust*

evidence of efficacy and a favorable risk-benefit ratio could be adequate for an approval in the indication of MWS. Whether the results of this study will be sufficient to prove a claim of efficacy will be based on review of the data.

Discussion:

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

Question 2: Novartis plans to derive the dose and dose regimen for the pivotal study in MWS using the results from the ongoing MWS PoC study and the PK/PD model developed from the — study data. Does the Agency agree? b(4)

FDA RESPONSE

In principle, this approach and the described PK/PD model, are reasonable. We cannot comment in detail on the suitability of the model to a specific dose/dose regimen or disease with the information provided thus far. If detailed comment on or evaluation of the model for specific diseases or age ranges is desired, the data and NONMEM codes should be submitted for review.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Discussion:

The Sponsor stated that they plan to provide the data from the model and all parameters prior to the initiation of the pivotal study in MWS, and to discuss this at an EOP2 meeting (planned for approximately the end of 2006). The Division recommended that the Sponsor request an EOP2a and EOP2 meeting, which may be combined, but will allow for the submission of the modeling data and program earlier to allow more time for pharmacometrics review (ideally, at least 6 weeks).

Question 3: Novartis plans to conduct a phase III pivotal trial in MWS using a withdrawal study design in 20 patients with genetically characterized MWS. In order to enroll 20 patients in the pivotal trial, Novartis intends to roll over patients from the ongoing PoC-trial into the pivotal trial. Does the Agency agree with this approach?

FDA RESPONSE

- *In general terms, a randomized withdrawal design has certain limitations compared to a standard randomized induction design. Since patients are initially exposed to drug in an open-label fashion, it does not provide blinded data on the magnitude of treatment response. To optimize the interpretability of the results of the open label period it would be important to have pre-specified criteria for the definition of response. It also does not*

provide randomized controlled data on adverse event rates. Nonetheless, a randomized withdrawal trial can provide evidence of efficacy and would be an acceptable way to assess the efficacy of ACZ885 in MWS.

- *The ongoing PoC trial, A2102, has currently enrolled 4 subjects with a plan for 6 to 8 additional subjects. Due to the rarity of MWS, it is reasonable to include the patients from the PoC trial in the pivotal trial as well. However, rollover patients should be stratified at randomization to ensure equal distribution into both the placebo and active treatment arms.*

- *Additionally, enough data from the group of initially treatment naïve patients should be obtained to assess whether the effects in this group are similar to those seen in the rollover patient group. Ideally, baseline disease activity pattern (e.g., frequency, severity, and type of symptoms) of all pivotal study patients should be assessed prior to treatment, since there may be significant inter-individual variability, in order to have context regarding the response, and what might be expected in terms of recurrence of disease activity.*

Discussion:

The Sponsor presented several slides to clarify the proposed MWS pivotal trial protocol design and endpoints. In Part 1 of the protocol, subjects will receive one, open-label injection of ACZ885 to identify responders. Responders, while in remission, will proceed to Part 2, and be randomized to placebo or active treatment. The plan is to stratify at randomization the patients rolled over from the proof of concept study. Efficacy will be assessed by occurrence of flare. Relapse will be defined as recurrence of at least 2 symptoms of skin rash, joint or muscle pain, eye discomfort or redness, fatigue or malaise, or fever or chills, along with C-reactive protein (CRP) and/or serum amyloid A (SAA) values >30 mg/L, on two occasions in 1 week. Patients flaring will proceed directly to Part 3, which is open-label, continuous dosing using a regimen to be determined. Clinical endpoints will be rapid onset (within 2 days) of absence of skin rash, normalization of body temperature, and 30% reduction of CRP and SAA, and remission at 7 days, defined as absence of symptoms and skin rash, normal body temperature and normalization of CRP, SAA and leukocyte count. Plan is to enroll 20 of 50 known MWS patients in the European Union and US. The Division pointed out that the endpoint is a high hurdle, and asked whether lesser levels of response have been defined. The Sponsor plans to address this if results of the proof of concept study suggest this will be necessary.

b(4)

Question 4: After Novartis has obtained safety data in approximately 10 adults and 4 children (aged 4 to 17) the plan is to include children between 2 and 3 years. Does the Agency agree?

FDA RESPONSE:

- *As MWS is a serious disorder, with no approved therapies, that can present in infancy/early childhood, it is reasonable to include children between 2 and 3 years to assess for efficacy in this age range, conditional upon an interim assessment of results in adults and older children that demonstrates no serious safety signals.*

- *Increasing the safety experience by additional numbers of adults and older children exposed to ACZ885 first would be desirable, and we recommend you consider increasing the planned number of subjects for the pivotal study.*

- *The PK/PD data from the older children will need to be assessed to determine whether the dose and dose regimen of ACZ885 (derived from the PK/PD model developed using adult data, and PoC study data) remains appropriate for smaller children, prior to expansion of enrollment to the 2 and 3 year old children.*

Discussion:

The Sponsor acknowledged these comments and stated they "...would take as many patients as they could get." They then presented a slide on the estimated safety database across all indications that they plan to have at the time of the MWS BLA submission. This pooled data base will include approximately 554 subjects exposed for any period of time, 300 treated for 6 months, and 166 treated for at least 12 months. The Division agreed that this would likely be adequate for the MWS indication.

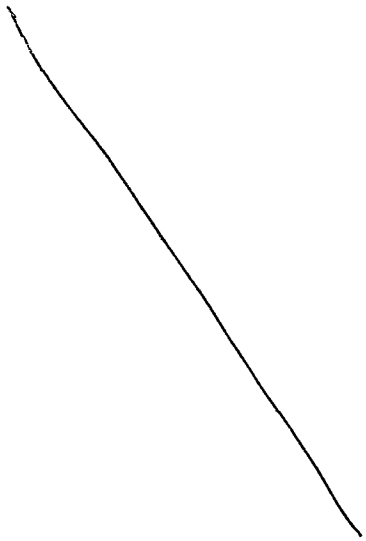
Question 5: A regimen to maintain MWS patients in remission can be predicted according to current clinical experience in adults. Such a regimen would be a 150 mg SC dose administered every 2 to 3 months. Novartis believes that this regimen can be expected to have a low immunogenic potential. Does the Agency agree?

FDA Response:

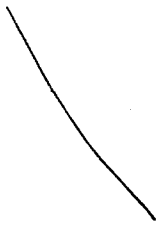
We do not agree; it is impossible to predict the immunogenic potential of dosing ACZ885 every 2 to 3 months. Some immunosuppressive biologics are more immunogenic when given periodically than when given on a continuous basis. The immunogenic potential of ACZ885 can only be determined from clinical trial data.

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

b(4)



b(4)



b(4)

Question 7: Novartis intends to seek labeling for other related conditions known to be linked to NALP3 mutations such as — FCAS. To achieve label extensions Novartis proposes to conduct appropriately-sized open label PK/PD, safety and tolerability studies. Novartis believes that this bridging approach is adequate to show safety and efficacy of ACZ885 in these rare and severe conditions. Does the Agency agree with this approach? b(4)

FDA RESPONSE

- *For approval of ACZ885 —, you would need to provide evidence of efficacy. Because — is rare, affects children, is related genetically and clinically to MWS,* b(4)

and has serious morbidity, it would be acceptable to perform a prospective open label study in ——, that builds upon the data from the pivotal trial in MWS, to assess the clinical benefits/effects, as well as PK/PD, safety and tolerability of ACZ885 in —— so long as the clinical benefit is clear and consistent across patients. For the uncontrolled studies, appropriate prospective selection of endpoints would be important. b(4)

- *In contrast to MWS and ——, FCAS, though also arising from NALP3 mutations, is less severe. Although age of onset is in childhood, many of the affected are adults, and the disease does not usually cause significant end organ damage. Performing a controlled trial in this population would not be unethical. Therefore, evidence of efficacy from at least one adequate and controlled trial will be necessary for approval in the indication of FCAS.* b(4)

Discussion:
With respect to Novartis requested clarification as to whether the open-label study in —— could be run concurrently with the pivotal trial in MWS, and if they could submit this study concurrently with the MWS registration to seek approval in both indications simultaneously. b(4)

Dr. Rappaport responded that this seemed acceptable, but wanted time for further consideration and discussion prior to a formal commitment. This will be provided to Novartis in a post-meeting note.

Post Meeting Note:

The Sponsor's proposal for submitting the study concurrently with MWS registration will be acceptable to the Division.

ADDITIONAL CLINICAL COMMENTS

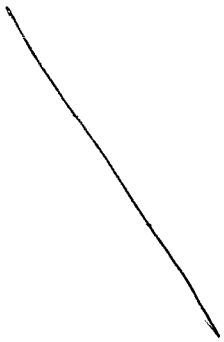
1. *The pre-meeting package included only a brief summary of the trial outline for the MWS pivotal trial. Review of this summary (included in the Novartis position statement to clinical question 3) and the phase 1 / 2 protocol for —— raises questions regarding how ACZ885 will be proposed to be used for these indications. In formulating your clinical development program, it will be important to determine whether the dosing will be intermittent, and given on first signs of flare, or continuous, i.e. given as a standing dose every 2 to 3 months for MWS.* b(4)

2. *In principle, if the development plan calls for proposed intermittent use, then the trial design should be a randomized re-treatment study, in which, after the open label treatment period, the patients should show signs of disease activity before being randomized to placebo or active re-treatment, then assessed for response.*

3. *If the development plan instead calls for proposed continuous use, then the trial design could be a randomized withdrawal study, in which case, after the open label treatment period, the patients should be in response at time of randomization to placebo or active treatment, then assessed for flares.*

4. *You do not comment in detail how you are finding the appropriate dose for use in MWS. Please address in the IND how you are planning to find the appropriate dose and whether more than one dose will be assessed in the pivotal randomized withdrawal study.*

5.



b(4)

6

7. *A complete protocol for the MWS pivotal trial must be submitted in the IND, and should include:*
   a. *Inclusion/Exclusion criteria for both study entry and in randomization*
   b. *Endpoints for both the open-label and randomized portions*
   c. *A description of imputation techniques for missing data. This technique should be conservative.*
   d. *A model informed consent that adequately describes the risks of this potentially immunosuppressive product.*

Discussion:
The Division inquired about the dosing for MWS and the Sponsor stated the planned dose for MWS will be 150 mg SC for adults, and will be based on weight for children, details to be determined upon further information from data modeling.

Dr. Nallani noted the sponsor's plans for exploration of pharmacogenomic biomarkers in the ongoing studies. He encouraged Novartis to submit their pharmacogenomic data as a voluntary genomic data submission. He also mentioned that an EOP2 meeting might be an appropriate time to submit/discuss a plan for biomarker and pharmacogenomic data for the MWS indication.

Post Meeting Comment:
Please find the procedure to submit Pharmacogenomic Data in the CDER guidance website under the procedural guidance # 22.

The Sponsor inquired about the likelihood of having the MWS and — indications receiving fast track status. The Division suggested that, on face, these indications are appropriate candidates for fast track status, but that Novartis should pay particular attention in its application to addressing the role ACZ885 in addressing the serious aspects of the diseases as delineated in the fast track guidance document.

b(4)

b(4)

At the conclusion of the meeting, Dr. Rappaport informed the Sponsor that all communication should occur via the Regulatory Project Manager.

Action Items:

- The Division agreed to clarify whether the Sponsor could submit the open-label study in ——— concurrently with MWS registration to seek approval in both indications simultaneously as a post meeting note. b(4)

Linked Applications	Sponsor Name	Drug Name
IND 100040	NOVARTIS GRIMSBY LTD	IND — ACZ885 b(4)

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
02/17/2006 00:00:00 AM

PMR/PMC Development Template

BLA 125319

PMR/PMC Title:

Establishment of a new working cell bank (WCB) using human serum albumin obtained from a US-licensed source.

- To develop a protocol for establishing new Working Cell Banks that uses human serum albumin obtained from a US-licensed source. The protocol should include acceptance criteria for cell culture metrics and canakinumab quality attributes, and provide limits which assure that validated cell generation time from the Master Cell Bank will be maintained. The protocol will be submitted as a Prior-Approval Supplement. A new Working Cell Bank to be used for the manufacture of all future canakinumab lots will be developed.

1. PMR/PMC Schedule Milestones:

Protocol Submission: February 28, 2010
WCB establishment Date: July 31, 2010
Final Report Submission: July 31, 2010

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 3.***

- **Which regulation?**
  - ☐ Accelerated approval
  - ☐ Animal efficacy confirmatory studies
  - ☐ Pediatric requirement
  - ☒ FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

During review of the BLA, it was noted that the current Working Cell Bank was manufactured using human serum albumin (HSA) sourced from non-US licensed sources. A safety risk evaluation by the FDA concluded that the risk for transmissible spongiform encephalopathy (TSE) was extremely low and that this should not prevent approval of the BLA. However, to further reduce the risk of possible TSE transmission, the FDA has determined that a new working cell bank using US-licensed human serum albumin must be established prior to manufacturing future lots of canakinumab.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

see paragraph above

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable.

4. If not required by regulation, characterize the review issue leading to this **PMC**

Not applicable

5. What type of study or clinical trial is required or agreed upon (describe)?

Required:

☐ Pharmacoepidemiologic study (list risk to be evaluated)
☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)
☐ Subpopulation (list type)
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials

☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)
☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation) Establishment of a new working cell bank (WCB) using human serum albumin obtained from a US-licensed source

Agreed upon:
☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)
☐ Other (provide explanation)

6. Is the PMR/PMC clear and feasible?
☒ Are the schedule milestones and objectives clear?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Larissa Lapteva, M.D., M.H.S.
Deputy Director for Safety
CDER/OND/ODE II/DAARP

PMR/PMC Development Template

BLA 125319

PMR/PMC Title:

1. Complete and report the ongoing, open-label, clinical trial D2306 investigating the safety of higher doses of Ilaris (canakinumab). Patients in trial D2306 who are non-responders to 2 mg/kg subcutaneously for patients weighing 15-40 kg or 150 mg subcutaneously for patients weighing >40 kg will receive escalating doses to 4 mg/kg subcutaneously for patients weighing 15-40 kg or 300 mg subcutaneously for patients weighing >40 kg.

PMR/PMC Schedule Milestones:

Trial Completion Date: June 2010,
Final Report Submission: September 2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

   Prior clinical experience with other immunosuppressive agents indicates there may be a safety concern with higher doses of Ilaris. Patients who fail to attain an adequate clinical response to the approved dose of Ilaris are expected to take higher doses, but the safety of higher doses is not fully characterized.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 3.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☒ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

     Patients who did not attain an adequate clinical response to initial dosing of Ilaris were treated with higher doses, but the safety of these higher doses was not fully studied.

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

The risk is that patients who fail to attain a clinical response to the recommended doses will be treated with higher doses and suffer toxicites such as serious infections due to the immunosuppressive effects of Ilaris.

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

   Not applicable.

4. If not required by regulation, characterize the review issue leading to this **PMC**

   Not applicable

5. What type of study or clinical trial is required or agreed upon (describe)?

   Required:
   - ☐ Pharmacoepidemiologic study (list risk to be evaluated)
   - ☐ Registry studies
   - ☒ Primary safety study or clinical trial (list risk to be evaluated) Risk of toxities with higher doses, such as serious infections related to the immunosuppressive effects of Ilaris.
   - ☐ Subpopulation (list type)

- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing studies
- ☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- ☐ Dose-response study performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other (provide explanation)

6. Is the PMR/PMC clear and feasible?
   - ☒ Are the schedule milestones and objectives clear?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Larissa Lapteva, M.D., M.H.S.
Deputy Director for Safety
CDER/OND/ODE II/DAARP

PMR/PMC Development Template

BLA 125319

PMR/PMC Title:

1. Complete and report the ongoing, multicenter, open-label, 6-month, clinical trial D2201 investigating the safety of higher doses of Ilaris (canakinumab). Patients in trial D2201 will receive a dose of 4 mg/kg subcutaneously for patients weighing less than 15-40 kg.

PMR/PMC Schedule Milestones:

Trial Completion Date: November 2010,
Final Report Submission: January 2011

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

   Prior clinical experience with other immunosuppressive agents indicates there may be a safety concern with higher doses of Ilaris. Patients who fail to attain an adequate clinical response to the approved dose of Ilaris are expected to take higher doses, but the safety of higher doses is not fully characterized.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to*** *3.*

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☒ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

     Children of body weight 15-40 kg who did not attain an adequate clinical response to initial dosing of Ilaris were treated with higher doses, but the safety of these higher doses was not fully studied.

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

     The risk is that children of body weight under 40 kg who fail to attain a clinical response to the recommended doses will be treated with higher doses and suffer toxicites such as serious infections due to the immunosuppressive effects of Ilaris.

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

   Not applicable.

4. If not required by regulation, characterize the review issue leading to this **PMC**

   Not applicable

5. What type of study or clinical trial is required or agreed upon (describe)?

   Required:
   - ☐ Pharmacoepidemiologic study (list risk to be evaluated)
   - ☐ Registry studies
   - ☒ Primary safety study or clinical trial (list risk to be evaluated) Risk of toxities with higher doses, in children under 40 kg, such as serious infections related to the immunosuppressive effects of Ilaris.
   - ☐ Subpopulation (list type)

- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing studies
- ☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- ☐ Dose-response study performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other (provide explanation)

6. Is the PMR/PMC clear and feasible?
   - ☒ Are the schedule milestones and objectives clear?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Larissa Lapteva, M.D., M.H.S.
Deputy Director for Safety
CDER/OND/ODE II/DAARP

PMR/PMC Development Template

BLA 125319

PMR/PMC Title:

Qualification of additional biochemical characterization assays to be used in support of establishing a new Canakinumab reference standard.

"To qualify the additional biochemical characterization assays that will be used in support of establishing a new canakinumab reference standard. Qualification of currently used assays will be submitted. "

PMR/PMC Schedule Milestones:

Study Completion Date: December 31, 2009
Final Report Date: February 28, 2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

   Canakinumab current reference standard has been characterized, with primary data reviewed to assure current reference standard is sufficiently controlled. The assays to be used on future reference standards need to be qualified to assure release of quality (as it pertains to safety and efficacy) drug.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to*** *3.*
   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

   No pharmacokinetic data, efficacy or safety available for the pediatric population

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

   Not applicable.

4. If not required by regulation, characterize the review issue leading to this **PMC**

   Canakinumab reference standards are implemented using release assays and additional biochemical characterization assays. The current reference standard has been tested and compared to the previous reference standard, and primary data was reviewed by FDA. However, to gain assurance that the future reference standards will be appropriately characterized, the assays need to be qualified, and these qualification studies need to be reviewed by FDA to assure appropriateness for intended

5. What type of study or clinical trial is required or agreed upon (describe)?

   Required:
   - ☐ Pharmacoepidemiologic study (list risk to be evaluated)
   - ☐ Registry studies
   - ☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)
☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:
☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)
☒ Other (provide explanation) Qualification of additional biochemical characterization assays to be used in support of establishing a new Canakinumab reference standard.

6. Is the PMR/PMC clear and feasible?
☒ Are the schedule milestones and objectives clear?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Larissa Lapteva, M.D., M.H.S.
Deputy Director for Safety
CDER/OND/ODE II/DAARP

PMR/PMC Development Template

BLA 125319

PMR/PMC Title:

Evaluation of the adequacy of the equilibration time required for thawed bulk drug substance to prevent excursions of drug product turbidity.

" To provide an evaluation, summary, and data that confirm the adequacy of the proposed equilibration time required for thawed bulk drug substance to prevent excursions of drug product turbidity."

PMR/PMC Schedule Milestones:

Study Completion Date: December, 2009
Final Report Submission: February, 2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

   Drug product lots that experienced in-process turbidity excursions of the thawed drug substance bulk were released within approved release specifications.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to*** *3.*
   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial
   - **Describe the particular review issue leading to the PMR**

     No pharmacokinetic data, efficacy or safety available for the pediatric population
   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**
   - **If the PMR is a FDAAA safety study/clinical trial, does it:**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable.

4. If not required by regulation, characterize the review issue leading to this **PMC**

During review of the BLA, it was observed that some drug product lots experienced turbidity excursions during in-process testing of the thawed drug substance bulk. This observation did not prevent approval as the release testing results of these lots were within specification. However, the manufacturer proposed a 24 hour thawed bulk drug substance equilibration time to remedy in-process turbidity excursions. FDA has determined that the proposed equilibration time should be supported by a study that evaluates its adequacy. The report with the evaluation, summary and data should be provided to FDA as a PMC.

5. What type of study or clinical trial is required or agreed upon (describe)?

Required:

☐ Pharmacoepidemiologic study (list risk to be evaluated)
☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

- ☐ Subpopulation (list type)
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing studies
- ☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- ☐ Dose-response study performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

6. Is the PMR/PMC clear and feasible?
   - ☒ Are the schedule milestones and objectives clear?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Larissa Lapteva, M.D., M.H.S.
Deputy Director for Safety
CDER/OND/ODE II/DAARP

PMR/PMC Development Template

BLA 125319

PMR/PMC Title:

Validation studies on a ——— for Canakinumab drug substance.

"To perform validation studies on a ——— for Canakinumab drug substance. The protocol, final report, and the proposed specification will be submitted as a CBE-0." b(4)

PMR/PMC Schedule Milestones:

Study Completion Date:	October, 2009
Final Report and specification Submission:	November, 2009

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

   Canakinumab drug substance is tested at release for purity, which does not include this assay. Lots manufactured for marketing were additionally characterized for the purposes of the BLA using this assay, so this was sufficient for approval. However, to assure quality of lots manufactured in the future which only require lot release assays and not additional characterization, an additional quality parameter should be implemented post-approval for a more complete control and monitoring of Canakinumab drug substance purity.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 3.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

   No pharmacokinetic data, efficacy or safety available for the pediatric population

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

   Not applicable.

4. If not required by regulation, characterize the review issue leading to this **PMC**

   Characterization of drug substance evaluated during BLA review showed that Canakinumab has a complex impurity profile. The product related substances and impurities that characterize Canakinumab are controlled by the manufacturing process and monitored by a set of analytical testing methods sufficient for approval. The FDA concluded that although the proposed methods are adequate, an additional analytical method should be required to monitor Canakinumab impurity profile according to current scientific knowledge of this type of products.

5. What type of study or clinical trial is required or agreed upon (describe)?

   Required:
   - ☐ Pharmacoepidemiologic study (list risk to be evaluated)
   - ☐ Registry studies
   - ☐ Primary safety study or clinical trial (list risk to be evaluated)

- ☐ Subpopulation (list type)
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing studies
- ☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- ☐ Dose-response study performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other (provide explanation)

6. Is the PMR/PMC clear and feasible?
   - ☒ Are the schedule milestones and objectives clear?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Larissa Lapteva, M.D., M.H.S.
Deputy Director for Safety
CDER/OND/ODE II/DAARP

PMR/PMC Development Template

BLA 125319

PMR/PMC Title:

To monitor canakinumab drug product for the appearance of new bands when compared to reference standard during the ——— assessment of registration stability testing, and to set an appropriate ——— specifications relative to reference standard upon availability of 24 months of registration stability data for canakinumab drug product. The proposed specifications and stability data will be provided as a CBE-0 supplement. b(4)

PMR/PMC Schedule Milestones:

Study Completion Date:	September, 2010
Final Report Date:	November, 2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

   According to the current CMC standards

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 3.***
   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

   No pharmacokinetic data, efficacy or safety available for the pediatric population

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

   Not applicable.

4. If not required by regulation, characterize the review issue leading to this **PMC**

   According to the current CMC standards

5. What type of study or clinical trial is required or agreed upon (describe)?

   Required:
   - ☐ Pharmacoepidemiologic study (list risk to be evaluated)
   - ☐ Registry studies
   - ☐ Primary safety study or clinical trial (list risk to be evaluated)
   - ☐ Subpopulation (list type)
   - ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
   - ☐ Thorough Q-T clinical trial
   - ☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)

- ☐ Nonclinical study (laboratory resistance, receptor affinity)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing studies
- ☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- ☐ Dose-response study performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other (provide explanation)

6. Is the PMR/PMC clear and feasible?
   - ☒ Are the schedule milestones and objectives clear?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Larissa Lapteva, M.D., M.H.S.
Deputy Director for Safety
CDER/OND/ODE II/DAARP

PMR/PMC Development Template

BLA 125319

PMR/PMC Title:

Annual stability testing of one marketed drug product lot and one drug substance lot of Canakinumab.

To perform stability testing on at least one marketed drug product lot and one drug substance lot; annually, for each year in which drug substance and/or drug product is manufactured, using the post-approval stability protocol specified in the BLA. The first update will be included in an annual report to be submitted."

PMR/PMC Schedule Milestones:

First update completion date:	First Annual Report/ by June- 2010
Final report submission	by August 2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

   Only feasible to conduct post approval. Stability data on limited number of lots provided sufficient data to set an expiration date which will be extended per stability protocol. Annual stability testing to confirm maintenance of the approved state and for the extended times as defined by protocol need to be conducted.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 3.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

   No pharmacokinetic data, efficacy or safety available for the pediatric population

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

   Not applicable.

4. If not required by regulation, characterize the review issue leading to this **PMC**

   Stability data on limited number of lots provided sufficient data to set an expiration date which will be extended per stability protocol. Annual stability testing to confirm maintenance of the approved state and for the extended times as defined by protocol need to be conducted.

5. What type of study or clinical trial is required or agreed upon (describe)?

   Required:
   - ☐ Pharmacoepidemiologic study (list risk to be evaluated)
   - ☐ Registry studies
   - ☐ Primary safety study or clinical trial (list risk to be evaluated)

- ☐ Subpopulation (list type)
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing studies
- ☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- ☐ Dose-response study performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other (provide explanation)

6. Is the PMR/PMC clear and feasible?
   - ☒ Are the schedule milestones and objectives clear?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Larissa Lapteva, M.D., M.H.S.
Deputy Director for Safety
CDER/OND/ODE II/DAARP

PMR/PMC Development Template

BLA: 125319

PMR/PMC Title:

Assessment of release and shelf-life specifications for canakinumab drug substance (DS) and drug product (DP) after manufacture of 15 lots.

"To assess release and shelf-life specifications for canakinumab drug substance and drug product after manufacture of 15 lots. Specifications assessment and supporting data will be provided"

PMR/PMC Schedule Milestones:

DS specifications assessment Date:	After 15 lots manufactured or 5 y post-approval
DP specifications assessment Date:	After 15 lots manufactured or 5 y post-approval

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

   The DS and DP release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of canakinumab for the initial marketed product..

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 3.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

   No pharmacokinetic data, efficacy or safety available for the pediatric population

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

   - **If the PMR is a FDAAA safety study/clinical trial, does it:**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

   Not applicable.

4. If not required by regulation, characterize the review issue leading to this **PMC**

   Canakinumab DS and DP release and shelf-life specifications are based on clinical and manufacturing experience during BLA review, however, the number of lots to date do now allow for a robust statistical analysis of the data. These specifications have a statistical component that should be re-assessed once enough number of marketed product has been released.

5. What type of study or clinical trial is required or agreed upon (describe)?

   Required:
   ☐ Pharmacoepidemiologic study (list risk to be evaluated)
   ☐ Registry studies
   ☐ Primary safety study or clinical trial (list risk to be evaluated)
   ☐ Subpopulation (list type)

- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing studies
- ☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- ☐ Dose-response study performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other (provide explanation)

6. Is the PMR/PMC clear and feasible?
   - ☒ Are the schedule milestones and objectives clear?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Larissa Lapteva, M.D., M.H.S.
Deputy Director for Safety
CDER/OND/ODE II/DAARP

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # BLA# 125319	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Ilaris Established/Proper Name: Canakinumab Dosage Form: Injection Strengths: 180 mg/vial		
Applicant: Novartis Agent for Applicant (if applicable):		
Date of Application: December 15, 2008 Date of Receipt: December 17, 2008 Date clock started after UN:		
PDUFA Goal Date: June 17, 2009	Action Goal Date (if different):	
Filing Date: February 18 , 2009 Date of Filing Meeting: January 29, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): Cryopyrin Associated Periodic Syndrome (CAPS)		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	☐ Standard ☒ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐	☐ Drug/Biologic ☐ Drug/Device ☒ Biologic/Device
☐ Fast Track ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 100040	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments:**	☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).	
Exclusivity	
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	☒ YES ☐ NO ☐ YES ☒ NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) **Comments:**	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments:**	☐ YES # years requested: ☐ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☐ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☐ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☐ NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	☐ YES ☐ NO

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES ☒ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments:**	☐ All paper (except for COL) ☐ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments:**	☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	☒ YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments:**	☒ YES ☐ NO ☐ YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments:**	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments:**	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes,** BLA #	 ☐ YES ☒ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments:**	☐ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.***	☒ YES ☐ NO

Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it 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 this application." Applicant may not use wording such as, "To the best of my knowledge..." **Comments:**	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐ Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** *Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments:**	☒ YES ☐ NO
Pediatrics	
PREA *Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes,** does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments**: A request for a partial waiver and deferral is included but the Sponsor did not include a pediatric plan.	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☒ NO ☐ YES ☐ NO

BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments:**	☐ YES ☐ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not applicable** ☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use ☐ MedGuide ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments:**	☒ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments:**	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments:**	☒ YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments:**	☐ Not Applicable ☒ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments:**	☐ Not Applicable ☒ YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments:**	☒ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments:**	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	☒ YES Dates: February 5, 2008 ☐ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	☒ YES Date(s): October 21, 2008 ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments:**	☐ YES Date(s): ☒ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 02/13/09

NDA/BLA #: 125319

PROPRIETARY/ESTABLISHED NAMES: Ilaris (Canakinumab)

APPLICANT: Novartis

BACKGROUND:
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Ramani Sista	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Jeffery Siegel		
Clinical	Reviewer:	Carolyn Yancey	Y
	TL:	Jeffery Siegel	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Srikanth Nallani	Y
	TL:	Suresh Doddapaneni	N
Biostatistics	Reviewer:	David Petullo	Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kathy Young	Y
	TL:	Adam Wasserman	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Ruth Cordoba-Rodriguez Lixin Xu	Y
	TL:	Chana Fuchs	Y
Facility (*for BLAs/BLA supplements*)	Reviewer:	Anastasia Lolas	Y
	TL:	Patricia Hughes	N
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Roy Blay	N
	TL:	Constance Lewin	N
Other reviewers			

OTHER ATTENDEES:

505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? **If no,** explain:	☒ YES ☐ NO

Electronic Submission comments **List comments:**	☐ Not Applicable
CLINICAL **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments:** ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments:**	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	☐ Not Applicable ☐ YES. ☐ NO ☐ Not Applicable ☒ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? **(NDAs/NDA supplements only)**	☐ YES ☐ NO ☐ YES ☐ NO

FACILITY (BLAs only) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Dr. Curtis Rosebraugh

GRMP Timeline Milestones:

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☒	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # BLA # 125319	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: ILARIS Established/Proper Name: Canakinumab Dosage Form: Subcutaneous Injection		Applicant: Novartis Pharmaceuticals Agent for Applicant (if applicable):
RPM: Ramani Sista		Division: Anesthesia, Analgesia and Rheumatology Products

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	June 18, 2009
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application[2] Characteristics	
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☒ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	Orphan Designation
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☒ Yes, dated: June 12, 2009
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No June 02, 2009
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date: Approved on June 17, 2009
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	June 17, 2009
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	April 15, 2009
• Original applicant-proposed labeling	December 18, 2008
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	June 17, 2009
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	PPI and Instruction for Use: December 18, 2008
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	June 17, 2009
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	Will be updated to reflect review changes
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM June 16, 2009 ☒ DMEPA May 28, 2009 ☒ DRISK May 29, 2009 ☒ DDMAC May 8, 2009 ☐ CSS ☒ Other reviews OBP RPM-May 20, 2009
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	April 9, 2009 April 10, 2009
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	February 13, 2009
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included June 17, 2009
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☐ None 3 PMRs
• Outgoing communications *(if located elsewhere in package, state where located)*	June 11, 12, and 15 2009
• Incoming submissions/communications	June 15 (4), 16, and 17, 2009
❖ Postmarketing Commitment (PMC) Studies	☐ None 6 PMCs

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	Please see communication for PMRs
• Incoming submission documenting commitment	Please see communications for PMRs
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	December 30, 2008. January 15, 14, 13, 08, 2009, February 19, 18 (2), 13,11, 09, 06, and 05, March 31, 26, 13 (3), 11, 09, and 05 (2), April 29, 28, 23, 21, and 20, May 21 and 18, June 10, 08, 05, and 02,
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☒ Not applicable
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☐ Not applicable May 21, 2009
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg October 21, 2008
• EOP2 meeting *(indicate date)*	☐ No mtg February 5, 2008
• Other (e.g., EOP2a, CMC pilot programs)	April 13, 2006 and January 18, 2006
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None June 17, 2009
Division Director Summary Review *(indicate date for each review)*	☐ None June 17, 2009
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None May 18, and 25, 2009
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL
• Clinical review(s) *(indicate date for each review)*	May 11, 2009
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	In clinical review/May 11, 2009
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	In clinical review/May 11, 2009
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed

[5] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☐ None May 11, 2009 Not Applicable
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested May 12, 2009
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None May 08, 2009
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None May 12, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None June 17, 2009
• Supervisory Review(s) *(indicate date for each review)*	☐ None May 13, 2009
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None May 14, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None June 4, 2009
• CMC/product quality review(s) *(indicate date for each review)*	☐ None June 3, 2009
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None June 17, 2009
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each*	☒ Not needed

review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Addressed on page 44 of microbiology review by Anastasia Lolas
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER	Date completed: June 16, 2009 ☒ Acceptable ☐ Withhold recommendation
o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.