CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125319

MICROBIOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: June 17, 2009
To: Administrative File, STN 125319
From: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/BMT
Subject: Amendment to the Team Leader Review Memo of May 29, 2009
US License: # 1244
Applicant: Novartis Pharmaceuticals Corporation.
Manufacturing Facilities:
Drug Substance: Novartis Pharma S.A.S., Huningue, France (FEI 3004864869)
Drug Product: Novartis Pharma Stein AG, Stein, Switzerland (FEI 3002653483)
Product: Ilaris® (canakinumab)
Dosage: Sterile lyophilized powder in a glass vial (150 mg) for subcutaneous injection following reconstitution
Indication: Treatment of cryopyrin-associated periodic syndromes
Due Date: 18 June 2009

Recommendations for Approvability:

STN 125319 is recommended for approval from a microbial control, sterility assurance and microbiology product quality perspective. The establishments listed in the BLA have an acceptable cGMP compliance status.

The team leader review memo of May 29, 2009 is being amended here to reflect an addendum made to the original primary microbiology product quality review by Anastasia Lolas, M.S. OC/DMPQ/MAPCB/BMT on June 16, 2009 on endotoxin safety level calculations and to provide a final compliance status assessment of the establishments listed in the BLA.

This Team Leader concurs with the conclusions provided in the June 16, 2009 by Anastasia Lolas, M.S.

Cc: WO Bldg 51, Hughes
WO Bldg 51, Lolas
WO Bldg 22, Sista
WO Bldg 51, Blue Files (STN125319)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date:	16 June 2009
To:	Administrative File, STN 125319
From:	Anastasia G. Lolas, Microbiologist, OC/DMPQ/MAPCB/BMT AL 6/17/09
Through:	Patricia Hughes, Ph.D., Team Leader, OC/DMPQ/MAPCB/BMT PH 6/17/09
Subject:	Addendum to original review for new Biologics License Application
US License:	#1244
Applicant:	Novartis Pharmaceuticals Corporation
Facilities:	DS – Novartis Pharma S.A.S., Huningue, France (FEI 3004864869) DP – Novartis Pharma Stein AG, Stein, Switzerland (FEI 3002653483)
Product:	Ilaris® (canakinumab)
Dosage:	Sterile lyophilized powder in a glass vial (150 mg) for subcutaneous injection following reconstitution
Indication:	Treatment of cryopyrin-associated periodic syndromes
Due date:	18 June 2009

Recommendation for Approvability: STN 125319/0 is recommended for approval from a microbial control, sterility assurance and microbiology product quality perspective. The Novartis Pharma S.A.S. (Huningue, France) drug substance manufacturing site and the Novartis Pharma AG (Basel, Switzerland) testing site were inspected on May 4-12, 2009. There were two FDA483 observations for the Basel site. The firm's response to these observations has been reviewed by BMT and the International Compliance Team and found acceptable. There were no observations for the Huningue site.

The addendum is being written to provide clarification regarding the bacterial endotoxin specification for the final drug product and to provide an update on the GMP status of the facilities with a final assessment for the Basel, Switzerland testing site.

Based on a maximum human of 10 mg/Kg, the amount of endotoxin that could potentially be delivered to a patient at —— (proposed specification) is —— for a total of —— for a 70 Kg patient. In the case of children, the amount of total endotoxin that could potentially be delivered is —— for a 15 Kg patient and —— for a 40 Kg patient. These levels are —— than the safety threshold. The proposed dose is 2 mg/Kg and the clinical division is considering 3 b(4)

mg/Kg for certain cases. The potential for delivering product with bacterial endotoxins above the safety threshold is minimal at these levels with a final product specification of —— b(4)

cGMP Status

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the submitted establishments. There are no pending or ongoing compliance actions to prevent approval of STN 125319/0 at this time. An updated TB-EER is attached to this addendum. The status for the establishments is:

Establishment	FEI	Inspection Date	Classification	Profile
Novartis Pharma S.A.S. Centre de Biotechnologie 8 rue de l'Industrie 68330 Huningue France	3004864869	May 4-7, 11-12, 2009	NAI	— b(4)
Novartis Pharma AG Lichtstrasse 35 CH-4056 Basel Switzerland	3002807772	May 8, 2009	VAI	CTB
Novartis Pharma Stein AG Schaffhausestrasse 4332-Stein Switzerland	3002653483	Sep 13-21, 2007	NAI	— CHG, ——, —, CTX, SVL, SVS, — TCM, TCT, TTR b(4)
		Sep 5-6, 2005	NAI	CTL
		An inspection assignment has been issued to be covered in conjunction with other inspections in the future.		
		No inspectional history. An inspection assignment has been issued to be covered in conjunction with other inspections in the future.		b(4)
		Sep 24-25, 2007	NAI	CTL
		Feb 3-4, 2005	VAI	CTL

Novartis Pharmaceuticals Corporation 25 Old Mill Road Suffern, NY 10901	2416082	Nov 17-20, 2008	NAI	ADM, CHG, CTX, TCM, TCT, TDP, TTR
		Nov 19-21, 2007	NAI	CHG, CSG, CTR, LIQ, POW, SNI, SUP, SVL, SVS, [redacted], TCM, TCT, TTR, TDP
		Feb 5-6, 2009	NAI	CHG, CSG, CTR, TCM, TCT, TTR
		Mar 12-20, 2009	NAI	ADM, CHG, CSG, CTR, NEC, POW, TCM, TCT, TTR

b(4)

Conclusion

STN 125319/0 was reviewed from a microbial control, sterility assurance and microbiology product quality perspective and is recommended for approval.

Cc: OC/DMPQ/WO Bldg 51, Lolas
OC/DMPQ/WO Bldg 51, Hughes
OC/DMPQ/WO Bldg 51, Blue Files (STN 125319)
OND/ODEII/DAARP/WO Bldg 22, Sista

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: May 29, 2009
To: Administrative File, STN 125319
From: Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/BMT
Endorsement: Concepcion Cruz, Branch Chief, CDER/OC/DMPQ/MAPCB
Subject: Team Leader Review Memo
US License: # 1244
Applicant: Novartis Pharmaceuticals Corporation.
Manufacturing Facilities:
Drug Substance: Novartis Pharma S.A.S., Huningue, France (FEI 3004864869)
Drug Product: Novartis Pharma Stein AG, Stein, Switzerland (FEI 3002653483)
Product: Ilaris® (canakinumab)
Dosage: Sterile lyophilized powder in a glass vial (150 mg) for subcutaneous injection following reconstitution
Indication: Treatment of cryopyrin-associated periodic syndromes
Due Date: 18 June 2009

Recommendations for Approvability:

CMC Microbiology Product Quality Assessment:
The BLA, as amended, is recommended for approval from a microbial control, sterility assurance and microbiology product quality perspective. Data and information supporting the recommendation for approval are presented in the review memo from Anastasia Lolas, M.S., OC/DMPQ/BMT.

Issues that were encountered in the course of this review included the presence of [redacted] in drug substance samples before and after filling at levels of [redacted] b(4)

[redacted] The firm recommends that ACZ885 should not be given parenterally to premature babies or neonates. This should be considered in labeling decisions.

Consideration should be given to the endotoxin limit if dosing changes to the [redacted] for patients with body weight of ≥15 kg and ≤40 kg are recommended by the review team. The safety threshold for [redacted] for 15 kg body weight and [redacted] for 40 kg body weight) could be exceeded. b(4)

The vial and carton label state appropriately that the product is sterile. Aseptic techniques for reconstitution of the lyophilized product are described in the package insert. The label should state that the in use storage time for the reconstituted solution not exceed 4 hours at 2-8°C in the absence of supporting microbiological data for a longer storage time.

CGMP Facilities Assessment:
The final assessment of the Novartis Pharma AG potency testing laboratory in Basel Switzerland (FEI=3002807772) is pending. The facility was inspected on May 8, 2009 and a 2 item 483 was presented to the management of the testing lab regarding a lack of sufficient detail in the SOPs for the potency assay and deficiencies in the timeliness of closing deviations. The inspection team is recommending a "Voluntary Action Indicated" (VAI) classification to the inspection. The firm has responded to the 483 observations and a final decision from the Office of Compliance is pending.

Pre-License inspection of the drug substance manufacturing site, Novartis Pharma S.A.S., Huningue, France was conducted on May 4-7, 11-12, 2009. No 483 observations were made at the conclusion of the inspection of the Huningue manufacturing site and the facility was deemed acceptable from a CGMP perspective.

The inspection of the drug product manufacturing site was waived.

All other facilities listed in the BLA are in compliance with the requirements prescribed in the applicable regulations (21 CFR 210, 211, and 600) based on the outcome of pre-license inspections of the drug substance manufacturing site and other recent surveillance inspections.

Conclusions:

I. Microbial control, sterility assurance validation data and information and microbiology product quality aspects of the CMC section of this application were assessed. The BLA, as amended, is recommended for approval.

II. All other sections of the BLA should be reviewed by OBP/DMA reviewer from a CMC perspective.

III. All establishments listed in the BLA, with the exception of the Novartis potency testing lab in Basel Switzerland, have been determined to comply with standards listed in the application and with requirements prescribed in applicable regulations, including but not limited to the good manufacturing practice requirements set forth in parts 210, 211, and 600. The official determination of the Novartis potency testing laboratory in Basel Switzerland is pending.

Cc: WO Bldg 51, Hughes
WO Bldg 51, Lolas
WO Bldg 22, Sista
HFD-123, Cordoba-Rodriguez
HFD-123, Xu
WO Bldg 51, Blue Files (STN125319)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES — Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date:	21 May 2009
To:	Administrative File, STN 125319
From:	Anastasia G. Lolas, Microbiologist, OC/DMPQ/MAPCB/BMT AL 5/21/09
Through:	Patricia Hughes, Ph.D., Team Leader, OC/DMPQ/MAPCB/BMT PH 5/22/09 Concepcion Cruz, Acting Branch Chief, OC/DMPQ/MAPCB Sdg for C. Cruz 5/22/09
Subject:	New Biologics License Application
US License:	#1244
Applicant:	Novartis Pharmaceuticals Corporation
Facilities:	DS – Novartis Pharma S.A.S., Huningue, France (FEI 3004864869) DP – Novartis Pharma Stein AG, Stein, Switzerland (FEI 3002653483)
Product:	Ilaris® (canakinumab)
Dosage:	Sterile lyophilized powder in a glass vial (150 mg) for subcutaneous injection following reconstitution
Indication:	Treatment of cryopyrin-associated periodic syndromes
Due date:	18 June 2009

Recommendation for Approvability: STN 125319/0 is recommended for approval from a microbial control, sterility assurance and microbiology product quality perspective. The Novartis Pharma S.A.S. (Huningue, France) drug substance manufacturing site and the Novartis Pharma AG (Basel, Switzerland) testing site were inspected on May 4-12, 2009. There were two FDA483 observations for the Basel site. The firm's response to these observations has been reviewed by BMT and found acceptable. The final recommendation will be provided by ICB/DMPQ. There were no observations for the Huningue site. An inspection waiver memo is attached to this review for the drug product site, Novartis Pharma Stein AG (Stein, Switzerland).

Review Summary

Novartis Pharmaceuticals Corporation submitted STN 125319/0 on 17-Dec-2008 to license Ilaris® (canakinumab) and the associated drug substance and drug product manufacturing processes. The application has an orphan drug status and is a priority review with a PDUFA user fee date of 18-Jun-2009. STN 125319/0 is an electronic submission in CTD format. A pre-BLA meeting (IND 100,040) was held on 21-Oct-2008 that included BMT's comments.

The manufacturing schedule submitted initially by the applicant did not include any production plans for the subject drug substance within the review cycle. Following internal discussions and meetings with the review team and Novartis (after the filing meeting on 29-Jan-2009 and at later times), a preliminary schedule was set for April 10-May 18, 2009. Additional communications led to moving the production schedule one week earlier so that purification would start on May 6th at the Huningue site. The revised production schedule was submitted to the application file on 02-Feb-2009. Novartis indicated that production could not be moved further due to availability of raw materials. Reviews are due on 18-May-2009.

An information request was sent to the applicant on 31-Mar-2009 and an amendment was submitted on 08-Apr-2009. An additional information request was sent on 21-Apr-2009 and an amendment was submitted on 29-Apr-2009. A third information request was sent in May 2009 and a response provided on 15-May-2009. The following amendments related to CMC and product quality microbiology were reviewed:

2-Feb-2009 (seq 0002)	01-Apr-2009 (seq 0021)	29-Apr-2009 (seq 0029)
09-Feb-2009 (seq 0006)	06-Apr-2009 (seq 0022)	15-May-2009 (seq 0033)
13-Mar-2009 (seq 0016)	08-Apr-2009 (seq 0024)	
20-Mar-2009 (seq 0019)	15-Apr-2009 (seq 0025)	

A pre-approval inspection of the drug substance manufacturing site, Novartis Pharma S.A.S. (Huningue, France) and the QC testing site Novartis Pharma AG (Basel, Switzerland) was conducted May 4-12, 2009. There were two FDA483 observations for the Basel site: insufficient detail of SOPs and deviations not being closed in a timely manner. There were no FDA483 observations for the Huningue site. Several recommendations were offered to the firm.

An inspection waiver memo is attached to this review for the drug product manufacturing site Novartis Pharma Stein AG in Stein, Switzerland.

Review Narrative

1. COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3

S DRUG SUBSTANCE

S.1 General Information

Canakinumab or ACZ885 is a recombinant human monoclonal antibody (anti-human interleukin-1β) of the Immunoglobulin G1/κ isotype. It is comprised of two 447- or 448- residue heavy chains and two 214-residue light chains with a molecular mass of 145157 Daltons. The production strain is a murine cell line identified as —— Sp2/0-Ag14. Canakinumab is a clear to opalescent aqueous solution of pH 6.2-6.8 containing —— of active and —— L-histidine HCl in WFI. It is stored at ——

b(4)

S.2 Manufacture

S.2.1 Manufacturers

Manufacturing	*Quality Control (release and stability for potency)*
Novartis Pharma S.A.S.	Novartis Pharma AG
Centre de Biotechnologie	Lichtstrasse 35
8 rue de l'Industrie	CH-4056 Basel
68330 Huningue	Switzerland
France	FEI 3002807772
FEI 3004864869/3007198645	

The Huningue site has two registration numbers. Inspections have been recorded under FEI 3004864869. However, the site presented the inspection team with an updated registration form dated 09/01/2008 with FEI 3007198645. This issue has been brought up to the attention of MAPCB/DMPQ and the two numbers will be merged. The operational number is 3004864869. b(4)

The master cell and working cell banks are stored at the above two locations and

Viral clearance and *Mycoplasma* testing are performed by two contract laboratories:

b(4)

Reviewer's Comments: The above two sites were submitted in the 15-May-2009 amendment as they were not in the original submission. During the inspection, it was determined that they are being used for testing and BPO Huningue was requested to submit them to the BLA.

S.2.2 Description of the Manufacturing Process and Process Controls

b(4)

40 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Microbiology- 1

2. COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

The vial and carton labels state appropriately that the product is sterile. Aseptic technique is described in the package insert for reconstituting the lyophilized product. The label states that the in-use storage time for the reconstituted solution is —— at 2-8°C. Following communications with Novartis, it was agreed that the in-use storage time will not exceed 4 hours at 2-8°C in the absence of data to support —— — and considering that studies performed with the bulk solution demonstrated strong microbial growth-promoting properties. See Sections P.3.5 and P.8 for more information. Labeling should be revised accordingly. b(4)

Reviewer's Comments: The label (vial, carton labels and package insert) should state that the in-use storage time for the reconstituted product solution is not to exceed 4 hours at 2-8°C in the absence of microbiological data to support longer storage periods.

Environmental Assessment

Question to the Applicant:

As provided for by 21 CFR 25.31, submit an Environmental Assessment.

Applicant's Response:

A claim for categorical exclusion from preparing an Environmental Assessment under 21 CFR 25.31(c) is provided by the applicant in the 08-Apr-2009 amendment on the grounds that no extraordinary circumstances exist that that would require an environmental assessment. Even though the amino acid sequence of canakinumab does not occur naturally, all the amino acids are naturally occurring and would be expected to react as other naturally occurring proteins. It is not expected that use of this moiety will result in changes in the distribution of naturally occurring proteins, their metabolites or degradation products in the environment.

SATISFACTORY

cGMP Status

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the submitted establishments. There are no pending or ongoing compliance actions to prevent approval of STN 125319/0 at this time. The status for the establishments is: b(4)

Establishment	FEI	Inspection Date	Classification	Profile
Novartis Pharma S.A.S. Centre de Biotechnologie 8 rue de l'Industrie 68330 Huningue France	3004864869	May 4-7, 11-12, 2009	NAI	—
Novartis Pharma AG Lichtstrasse 35 CH-4056 Basel	3002807772	May 8, 2009	VAI	CTB

Switzerland				
Novartis Pharma Stein AG Schaffhausestrasse 4332-Stein Switzerland	3002653483	Sep 13-21, 2007	NAI	CHG, CTX, SVL, SVS, TCM, TCT, TTR
		Sep 5-6, 2005	NAI	CTL
		An inspection assignment has been issued.		
		No inspectional history. An inspection assignment has been issued.		
		Sep 24-25, 2007	NAI	CTL
		Feb 3-4, 2005	VAI	CTL
		Nov 17-20, 2008	NAI	ADM, CHG, CTX, TCM, TCT, TDP, TTR
		Nov 19-21, 2007	NAI	CHG, CSG, CTR, LIQ, POW, SNI, SUP, SVL, SVS, TCM, TCT, TTR, TDP
		Feb 5-6, 2009	NAI	CHG, CSG, CTR, TCM, TCT, TTR
		Mar 12-20, 2009	NAI	ADM, CHG, CSG, CTR, NEC, POW, TCM, TCT, TTR

b(4)

Conclusion

I. STN 125319/0 was reviewed from a microbial control, sterility assurance and microbiology product quality perspective and is recommended for approval.

II. Aspects other than microbial control and sterility assurance should be reviewed by OBP/DMA.

III. No additional inspection follow-up items were identified.

Cc: OC/DMPQ/WO Bldg 51, Lolas
OC/DMPQ/WO Bldg 51, Hughes
OC/DMPQ/WO Bldg 51, Cruz
OC/DMPQ/WO Bldg 51, Blue Files (STN 125319)
OPS/OBP/NIH Bldg N29B, Cordoba-Rodriguez
OPS/OBP/NIH Bldg N29B, Xu
OND/ODEII/DAARP/WO Bldg 22, Sista

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Determining When Pre-License / Pre-Approval Inspections are Necessary

Inspection Waiver Memorandum

Date:	15 May 2009
From:	Anastasia Lolas, M.S., Microbiologist, OC/DMPQ/BMT Ruth Cordoba-Rodriguez, Ph.D., Product Reviewer, OPS/OBP/DMA Lixin Xu, Ph.D., Product Reviewer, OPS/OBP/DMA
To:	BLA File – STN 125319/0
Subject:	Recommendation to waive a pre-license inspection
Sponsor:	Novartis Pharmaceuticals Corporation
Facility:	Novartis Pharma Stein AG, Stein, Switzerland (FEI 3002653483)
Product:	Ilaris® (canakinumab)
Indication:	Treatment of cryopyrin-associated periodic syndromes
Through:	Patricia Hughes, Ph.D., Team Leader, OC/DMPQ/BMT

Waiver Recommendation

Based on the compliance history of the firm, the current GMP status, and the fact that Novartis Pharma Stein AG has been approved to manufacture many CDER products using the same manufacturing process, we recommend that the pre-approval inspection of the Novartis Pharma Stein AG manufacturing facility in Stein, Switzerland (FEI: 3002653483) be waived for STN 125319/0 submitted 17-DEC-2008.

Clearance Routing

CONCUR / DO NOT CONCUR DATE 5/28/09

Richard L. Friedman, M.S.
Director, Division of Manufacturing and Product Quality, Office of Compliance, CDER

Kathleen Clouse CONCUR / DO NOT CONCUR DATE 05/21/2009

Kathleen Clouse, Ph.D.
Director, Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER

Summary

BLA 125319 is a new biologics application for Ilaris® (canakinumab), a recombinant human monoclonal antibody, produced in a murine cell line (Sp2/0) for the treatment of cryopyrin-associated periodic syndromes (CAPS). This electronic submission in CTD format was submitted by Novartis Pharmaceuticals Corporation and has a priority and orphan drug status. The drug product Ilaris® (canakinumab) is a sterile, lyophilized powder (150 mg) in a 6 mL glass vial for subcutaneous injection following reconstitution.

The drug product manufacturing site is Novartis Pharma Stein AG in Stein, Switzerland (FEI: 3002653483). This facility is also responsible for packaging and some release and stability testing. Canakinumab drug substance is [redacted] b(4)

Supporting Information

The following information is provided in support of waiving the pre-approval inspection:

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

    a. The holder of the BLA is Novartis Pharmaceuticals Corporation. The firm holds a license for Simulect® (basiliximab), another recombinant monoclonal antibody produced in a murine cell line for the prophylaxis of acute organ rejection in patients receiving renal transplantation. This product is a lyophilized powder supplied in a 6 mL glass vial for intravenous infusion following reconstitution and/or dilution. The license for Novartis is #1244 for currently approved STN 103764.

    b. The Novartis Pharma Stein AG facility has been approved to manufacture multiple products including NDAs and Simulect® (basiliximab).

2. *FDA has not inspected the establishment in the past 2 years.*

    A compliance check of the Stein, Switzerland facility indicates that it has been inspected in the past 2 years. The last inspection was in September 2007 (9/13-9/21) by the District in response to a foreign inspection request for a CGMP inspection. Profiles CHG, [redacted] TTR, SVL, SVS, [redacted], TCM, TCT [redacted] and CTX were covered and found acceptable. The inspection was classified as NAI without any observations. The facility is a Tier 1 inspection priority for FY 2009. b(4)

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	Not required by CFR601.2
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Quality overall summary [2.3]	(Y) N	
❑ Drug Substance	(Y) N	
❑ Drug Product	(Y) N	
❑ Facilities and Equipment	(Y) N	
❑ Adventitious Agents Safety Evaluation	(Y) N	
❑ Novel Excipients	(Y) N	
❑ Executed Batch Records	(Y) N	
❑ Method Validation Package	(Y) N	
❑ Comparability Protocols	(Y) N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	(Y) N	
Drug Substance [3.2.S]		
❑ general info	(Y) N	
o nomenclature		
o structure (e.g. sequence, glycosylation sites)		
o properties		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y) N	
❑ description of manufacturing process	(Y) N	
o batch numbering and pooling scheme		
o cell culture and harvest		
o purification		
o filling, storage and shipping		
❑ control of materials	(Y) N	
o raw materials and reagents		
o biological source and starting materials		
o cell substrate: source, history, and generation		
o cell banking system, characterization, and testing		
❑ control of critical steps and intermediates	(Y) N	
o justification of specifications		
o analytical method validation		
o reference standards		
o stability		
❑ process validation (prospective	(Y) N	

CTD Module 3 Contents	Present?	If not, justification, action & status
plan, results, analysis, and conclusions)		
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	(Y) N	
❑ characterization of drug substance	(Y) N	
❑ control of drug substance	(Y) N	
o specification		No qualification or validation of appearance, color, pH, quantity assay and HCP methods. This will be a review issue.
o justification of specs.		
o analytical procedures		
o analytical method validation		
o batch analyses		
o consistency (3 consecutive lots)		
o justification of specs.		
❑ reference standards	(Y) N	
❑ container closure system	(Y) N	
❑ stability	(Y) N	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		No method qualification or validation of appearance, color, pH, and quantity assay. This will be a review issue.
o results		
o method validation		
Drug Product [3.2.P]		
❑ description and composition	(Y) N	
❑ pharmaceutical development	(Y) N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y) N	
❑ batch formula	(Y) N	Yes
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	(Y) N	No information on process and controls for the labeling and packaging of vialed DP. This will be a review or inspection issue
❑ controls of critical steps and intermediates	(Y) N	
❑ process validation including aseptic processing & sterility assurance:	(Y) N	
o 3 consecutive lots		
o other needed validation data		
❑ control of excipients (justification of specifications; analytical method	(Y) N	

CTD Module 3 Contents	Present?	If not, justification, action & status
validation; excipients of human/animal origin)		
☐ control of drug product (justification of specifications; analytical method validation)	(Y) N	Qualification of compendial methods will be a review issue
☐ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity o administration device(s)	(Y) N	
☐ stability ☐ summary ☐ post-approval protocol and commitment ☐ pre-approval o protocol o results o method validation	(Y) N	
Diluent (vials or filled syringes) [3.2P']		
☐ description and composition of diluent	Y N	No use of diluent. Use of WFI
☐ pharmaceutical development	Y N	
☐ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
☐ batch formula	Y N	
☐ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
☐ controls of critical steps and intermediates	Y N	
☐ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o other needed validation data	Y N	
☐ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
☐ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ reference standards	Y N	
❑ container closure system	Y N	
o specifications (vial, elastomer, drawings)		
o availability of DMF		
o closure integrity		
❑ stability	Y N	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
Other components to be marketed (full description and supporting data, as listed above):		
❑ other devices	Y N	N/A
❑ other marketed chemicals (e.g. part of kit)	Y N	
Appendices for Biotech Products [3.2.A]		
❑ facilities and equipment	(Y) N	
o manufacturing flow; adjacent areas		
o other products in facility		
o equipment dedication, preparation and storage		
o sterilization of equipment and materials		
o procedures and design features to prevent contamination and cross-contamination		
❑ adventitious agents safety evaluation (viral and non-viral) e.g.:	(Y) N	
o avoidance and control procedures		
o cell line qualification		
o other materials of biological origin		
o viral testing of unprocessed bulk		
o viral clearance studies		
o testing at appropriate stages of production		
❑ novel excipients	(Y) N	None
USA Regional Information [3.2.R]		Subsections do not have granularity
❑ executed batch records	(Y) N	
❑ method validation package	(Y) N	

CTD Module 3 Contents	Present?	If not, justification, action & status
◻ comparability protocols	Y N	No comparability protocols proposed
Literature references and copies [3.3]	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review? ◻ legible ◻ English (or translated into English) ◻ compatible file formats ◻ navigable hyper-links ◻ interpretable data tabulations (line listings) & graphical displays ◻ summary reports reference the location of individual data and records ◻ all electronic submission components usable	(Y) N (Y) N (Y) N (Y) N (Y) N (Y) N (Y) N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	(Y) N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	(Y) N	
includes data demonstrating consistency of manufacture	(Y) N	
includes complete description of product lots and manufacturing process utilized for clinical studies	(Y) N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	(Y) N	
certification that all facilities are ready for inspection	Y N	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	(Y) N	
if not using a test or process specified by regulation, data is provided to show the	Y N	N/A

Examples of Filing Issues	Yes?	If not, justification, action & status
alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: □ LAL instead of rabbit pyrogen □ mycoplasma □ sterility □ □	 Y N Y N Y N	
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	N/A

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

Recommendation (circle one): (File) RTF

Reviewer: [signature] 2/12/09 Type (circle one): (Product) (Chair) Facility (DMPQ)
(signature/ date)

Concurrence:
Branch/Lab Chief: [signature] 2/12/09 Division. Director: [signature] 02/12/09
(signature/ date) (signature/ date)

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	N		Each section has its own table of contents
Introduction to the summary documents (1 page) [2.2]	Y		
Quality overall summary [2.3]	Y		
❑ Drug Substance	Y		
❑ Drug Product	Y		
❑ Facilities and Equipment	Y		
❑ Adventitious Agents Safety Evaluation	Y	N	Defer to OBP
❑ Novel Excipients	Y	N	Defer to OBP
❑ Executed Batch Records	Y	N	Defer to OBP
❑ Method Validation Package	Y		Refers to Module 3
❑ Comparability Protocols	N		

CTD Module 3 Contents	Present?		If not, justification, action & status
Module Table of Contents [3.1]	Y	N	Each section has its own table of contents
Drug Substance [3.2.S]			
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	Y	N	Defer to OBP
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y		
❑ description of manufacturing process o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	Y		
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	Y	N	Defer to OBP
❑ control of critical steps and intermediates o justification of specifications o analytical method validation o reference standards o stability	Y		
❑ process validation (prospective plan, results, analysis, and conclusions)	Y		

CTD Module 3 Contents	Present?		If not, justification, action & status
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y Y	N N	Defer to OBP Defer to OBP
❑ characterization of drug substance	Y		Microbiology only
❑ control of drug substance o specification o justification of specs. o analytical procedures o analytical method validation o batch analyses o consistency (3 consecutive lots) o justification of specs.	Y	N	Defer to OBP
❑ reference standards	Y	N	Defer to OBP
❑ container closure system	Y	N	Defer to OBP (no microbiological tests, DS is stored frozen)
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation			
Drug Product [3.2.P]			
❑ description and composition	Y		
❑ pharmaceutical development	Y		Container-closure integrity test only
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y		
❑ batch formula	Y	N	Defer to OBP
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y		
❑ controls of critical steps and intermediates	Y		Microbiology only
❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o Filter validation o Component, container, closure depyrogenation and sterilization validation o Validation of aseptic processing (media	Y Y Y Y		

CTD Module 3 Contents	Present?	If not, justification, action & status
simulations) o Environmental Monitoring Program o Lyophilizer validation o Other needed validation data (hold times)	Y N Y	b(4)
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	Defer to OBP
❑ control of drug product (justification of specifications; analytical method validation)	Y	Microbiology only
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity o administration device(s)	Y	Container-closure integrity only
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y	Microbiology only
Diluent (vials or filled syringes) [3.2P']		N/A
❑ description and composition of diluent	Y N	
❑ pharmaceutical development	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o Filter validation o Component, container, closure depyrogenation and sterilization	Y N Y N Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
validation o Validation of aseptic processing (media simulations) Y N o Environmental Monitoring Program Y N o Lyophilizer validation Y N o Other needed validation data (hold times) Y N ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) Y N ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) Y N ❑ reference standards Y N ❑ container closure system Y N o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity ❑ stability Y N ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results		
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices Y N ❑ other marketed chemicals (e.g. part of kit) Y N		N/A
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment Y o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety Y N		Defer to OBP

CTD Module 3 Contents	Present?	If not, justification, action & status
evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	Y N	Defer to OBP
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	Y N Y N	Defer to OBP Microbiology only
Literature references and copies [3.3]	Y N	Defer to OBP

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review? ❑ legible ❑ English (or translated into English) ❑ compatible file formats ❑ navigable hyper-links ❑ interpretable data tabulations (line listings) & graphical displays ❑ summary reports reference the location of individual data and records ❑ all electronic submission components usable	Y Y Y Y Y Y Y Y	Mostly yes, several links don't work
includes appropriate process validation data for the manufacturing process at the commercial production facility?	Y	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	Y	
includes data demonstrating consistency of manufacture	Y N	Defer to OBP
includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	Defer to OBP
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	Defer to OBP

Examples of Filing Issues	Yes?	If not, justification, action & status
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	
certification that all facilities are ready for inspection	Y	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	Microbiology only
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility ❑ ❑	 Y N Y N Y N	 Rabbit pyrogen test not provided Defer to OBP N/A
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	Defer to OBP
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	b(4)
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y	—
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	N/A

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

I contacted Novartis on 16-Jan-2009 to confirm that there are no plans to manufacture DS during the review cycle at the Huningue site. I indicated that the site needs to be inspected during the review cycle. I also asked regarding the ——— and the rabbit pyrogen test and in their response, they indicate that they have the data and can submit them to the BLA. After the filing meeting on 29-Jan-2009, OBP, BMT and DAARP called Novartis to inform them about b(4)

issues. We indicated that some of these issues could be considered filing issues. One of them was regarding the production schedule and inspection. On 30-Jan-2009, they responded to the DAARP PM that they can manufacture April 10 – May 22, 2009. Therefore, I recommend filing of the BLA based on this additional information.

Recommendation (circle one): File RTF

Reviewer: [signature] Type (circle one): Product (Chair) Facility (DMPQ)
(signature/ date)
1/30/09

Concurrence:
Branch/Lab Chief: [signature] 1/30/09 Division. Director: [signature] 1/30/09
(signature/ date) (signature/ date)