

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125290

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 Ave.
Silver Spring, MD 20993

Date: 6/26/2009
To: Administrative File, STN 125290/0
From: Bo Chi, Ph.D., CDER/OC/DMPQ/MAPCB/BMT *BC 6/29/09*
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT *PFA 6/29/09*
Subject: Amendment to memo for New Biologic License Application (BLA) STN 125290/0
Applicant: Novartis Pharmaceuticals Corporation
US License: 1244
Facility: Bayer HealthCare Pharmaceuticals, Inc., Emeryville, CA 94662
FEI: 1000124057
Product: Extavia® (Interferon beta-1b)
Dosage: Lyophilized powder, 0.3 mg/vial, subcutaneous injection
Indication: Multiple sclerosis
PDUFA date: August 14, 2009

This is to amend the review memo for Novartis' BLA STN125290/0 to add the following post-market commitments (PMC):

1. Novartis has committed to monitor endotoxin for the (b) pool. Endotoxin data will be collected for the next 10 batches or for three years, whichever is shorter. Please provide endotoxin data and the proposed endotoxin limit for the (b) pool at the end of the study.
2. Novartis has committed to collect bioburden data for (b) pools maintained at 2-8 °C for thirty days. Once this data is collected and analyzed, the alert and action bioburden limits for the (b) pool will be assessed and based on this assessment, the adjustment of the limits will be evaluated. Please provide the collected data and the proposed new bioburden limits for the (b) pool at the end of the study.
3. Novartis has committed to use 100 mL sample volume instead of 10 mL for the pre-filtration bioburden test. Data will be collected for the next 10 batches or for 3 years and the bulk pre-filtration bioburden limit will be set based on the 100 mL sample volume. Please provide the collected data and the proposed new bulk pre-filtration bioburden limit at the end of the study.



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

Date: 4/30/2009
To: Administrative File, STN 125290/0
From: Bo Chi, Ph.D., CDER/OC/DMPQ/MAPCB/BMT *BC 4/30/09*
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT *PH 4/30/09*
Subject: New Biologic License Application (BLA)
Applicant: Novartis Pharmaceuticals Corporation
US License: 1244
Facility: Bayer HealthCare Pharmaceuticals, Inc., Emeryville, CA 94662
FEI: 1000124057
Product: Extavia® (Interferon beta-1b)
Dosage: Lyophilized powder, 0.3 mg/vial, subcutaneous injection
Indication: Multiple sclerosis
PDUFA date: June 5, 2009

Recommendation: This application is recommended for approval from product quality microbiology and sterility assurance perspective. A separate evaluation of the contract manufacturer of Extavia drug substance and drug product, Bayer HealthCare Pharmaceuticals, Inc. at Emeryville, CA, will be conducted by the compliance officer at San Francisco District Office.

Review Summary

Novartis has submitted this BLA for Extavia® (interferon beta-1b) for the treatment of relapsing forms of multiple sclerosis. The product, manufacturing process, and specifications are identical in all relevant respects to the currently-licensed interferon beta-1b product (Betaseron®) from Bayer Healthcare Pharmaceuticals. Included in this submission is a letter from Bayer, granting FDA authority to cross-reference the entirety of the Betaseron BLA (STN 103471/0) as it existed on December 31, 2006 in support of this new BLA. Bayer HealthCare Pharmaceuticals, Inc. at Emeryville, CA is the contract manufacturer of Extavia drug substance and drug product.

Updated information on process validation and in-process controls for the Extavia drug substance and drug product was requested. The BLA was amended on 11/7/2008, 2/12/2009, 3/20/2009, and 4/10/2009 to the CMC section. This review is an evaluation of the amendments.

Assessment
Drug Substance

Environmental Assessment:

Novartis Pharmaceuticals Corporation certifies that this submission for NVF233 / 250 µg powder qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(c). rINF-β is a naturally occurring protein and it is expected to be completely metabolized and absorbed in the body after application to the patient. It is expected that approval of the BLA for NVF233 / 250 µg powder will not alter the concentration or distribution of naturally occurring interferon beta-1b, its metabolites, or degradation products in the environment. Further, Novartis Pharmaceuticals Corporation states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment.

cGMP Status:

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below.

DS and DP manufacturing site
Bayer HealthCare Pharmaceuticals, Inc.
5650 Hollis Street, Emeryville,
CA 94662, USA
FEI: 3006481922

Inspected January 15 - February 5, 2009 and initially classified VAI. The [REDACTED] (b) (4) profiles were covered, however a final district decision has not yet been made.

Manufacture for the diluent in pre-filled syringe
Baxter Pharmaceutical Solution, LLC
927 S. Curry Pike,
Bloomington,
IN 47402, USA
FEI: 1000115571

Inspected April 14 - May 2, 2008 and classified NAI. The [REDACTED] (b) (4) profiles were covered and are acceptable.

Package site

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Conclusion

- I. The BLA is recommended for approval from a product quality microbiology and sterility assurance perspective.
- II. Information and data in this BLA not related to microbial control of the drug substance and sterility assurance of the drug product should be reviewed by an OBP reviewer.
- III. A separate evaluation of Bayer HealthCare Pharmaceuticals, Inc. at Emeryville, CA, the contract manufacturer of Extavia drug substance and drug product, will be conducted by

BLA STN 125290/0, Novartis, Extavia

the compliance officer at San Francisco District Office.

Cc: WO51: Chi
WO51: Hughes
WO22: Reese
HFD-123, Cherney
HFD-123, Bernstein
HFD-328, TFRB Blue Files (STN 125290)

Archived File: S:\archive\BLA\125290\125290.0.rev.mem.BLA.4.30.2009.doc



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: 4/28/2009
To: Administrative File, STN 125290/0
From: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/BMT *PRB 4/30/09*
Subject: Secondary Review Memo: New Biologic License Application (BLA)
Applicant: Novartis Pharmaceuticals Corporation
US License: 1244
Facility: Bayer HealthCare Pharmaceuticals, Inc., Emeryville, CA 94662
FEI: 1000124057
Product: Extavia® (Interferon beta-1b)
Dosage: Lyophilized powder, 0.3 mg/vial, subcutaneous injection
Indication: Multiple sclerosis
PDUFA date: June 5, 2009

Team Leader Recommendation:

BLA 125290, as amended, is recommended for approval from a microbiology product quality perspective.

The acceptability of the contract manufacturer for Extavia drug substance and drug product, Bayer Health Care Pharmaceutical, Inc. in Emeryville CA will be determined by The FDA San Francisco district office.

Review Summary

BLA 125290 for Extavia (Interferon beta-1b) was submitted by Novartis Pharmaceutical Corporation for the treatment of multiple sclerosis. Extavia® (interferon beta-1b) is a product expressed from recombinant *E. coli* cells during a (b) (4) process. Bayer HealthCare Pharmaceuticals, Inc. at Emeryville, CA holds BLA 103471 for Betaseron® (interferon beta-1b). Bayer is the manufacturer of Betaseron® and also the contract manufacturer of Extavia® drug substance and drug product for Novartis. Because the Extavia manufacturing process and specifications are similar to the currently-licensed interferon beta-1b product (Betaseron®, STN 103471) from Bayer Healthcare Pharmaceuticals, BLA 103471 was cross referenced in it's entirety in the assessment of the new BLA 125290 from Novartis for Extavia (interferon beta-1b). Authorization to cross reference the BLA 103471 was provided in the application.

Amendments to BLA 125290 for Extavia were submitted to update drug substance microbial controls and drug product sterility assurance data and information cross referenced in BLA 103471. The amendments were reviewed by Bo Chi, Ph.D., CDER/OC/DMPQ/BMT from microbiology product quality perspective and the BLA, as amended, is recommended for approval. The BMT Team Leader concurs with the recommendations of the primary reviewer.

Conclusions:

Item	Status
Environmental assessment	Acceptable
Facilities cGMP Status: 1. Bayer HealthCare Pharmaceuticals, Inc. (FEI 100012057) (b) (4) (b) (4) (b) (4)	1. Pending final district decision fro (b) (4) 2. Acceptable for (b) (4) 3. Acceptable for (b) (4)
Drug Substance Microbial Control	Acceptable
Drug Product Sterility Assurance	Acceptable
Microbial Product Quality	Acceptable
Facility information	Attached

Cc: WO51: Chi
WO22: Reese
HFD-328, TFRB Blue Files (STN 125290)

Archived File: S:\archive\BLA\125290\125290.0.TL.rev.mem.BLA.4.28.2009.doc