CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125294Orig1s000

MICROBIOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date: August 1, 2012
To: Administrative File, STN 125294/0/32
From: Kalavati Suvarna, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Resubmission of original BLA
US License: # 1803
Applicant: SICOR Biotech UAB
Mfg Facility: **Drug substance:** SICOR Biotech UAB, Moletu, Pl.5, Vilinus, Lithuania (FEI: 3008110727).
Drug product: TEVA Pharmaceutical Industries, Ltd, 64 Hashikma St., Industrial Zone, Kfar Saba, Israel 44102 (FEI: 3002721084).
Product: Proprietary Name to be determined (r-metHuG-CSF, XM02; (b) (4))
Dosage: Solution for injection (300 mcg/0.5 mL and 480 mcg/0.8 mL in a pre-filled syringe)
Indication: The reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer.
GRMP Date: August 2, 2012
PDUFA Date: August 30, 2012

Recommendation for Approvability: This submission was reviewed from a CMC microbiology and sterility assurance perspective and is recommended for approval with the following post-marketing commitments:

Post-marketing commitment 1: To submit data on (b) (4) accumulated after manufacture of 30 commercial batches and any changes to currently proposed (b) (4) action limits of (b) (4) prior to (b) (4) in a CBE-30 supplement by date (provided by applicant).

Post-marketing commitment 2: To submit winter shipment data from the shipping qualification study in a CBE-0 supplement by date (provided by applicant).

Post-marketing commitment 3: To submit the following data obtained after implementation of changes made to improve microbial control in the drug substance manufacturing process:

a. In-process and final filgrastim bioburden and endotoxin data for the (b) (4) following the proposed changes.
b. Microbial control data for storage (b) (4)

c. Any other changes and data that could affect microbial process control (for example, changes in hold times).

The information should be submitted as a CBE-30 supplement by September 30, 2012.

SUMMARY: The subject of this BLA is [redacted] (b) (4) a recombinant human granulocyte colony stimulating factor produced in *E. coli* without glycosylation and with an N-terminal methionyl extension (r-metHuG-CSF). The [redacted] (b) (4) presented in this BLA has the laboratory code of XM02 and the proposed trade name of NEUTROVAL™. The proprietary name has not been finalized at this time. The original BLA received a complete response letter on September 29, 2010. The applicant submitted responses to the deficiencies identified in the September 29, 2010 letter in a BLA resubmission (eCTD sequence number 0033). The re-submission and amendments to the re-submission (eCTD sequence numbers: 0033 dated 2/29/2012; 0034 dated 4/5/2012; 0039 dated 6/27/2012; and 0042 dated 7/31/2012) are reviewed here.

ASSESSMENT:

In the resubmission (eCTD sequence 0033 dated 2/29/2012), the sponsor responded to deficiencies in the complete response letter dated 9/29/2010 issued for BLA 125294 (Neutroval from Teva Pharmaceutical USA). Teva Pharmaceuticals USA informed the Agency of the change in BLA sponsor from Teva Pharmaceuticals USA to SICOR Biotech UAB (an indirect wholly-owned subsidiary of Teva Pharmaceuticals USA) in an amendment, eCTD sequence 0034 dated 4/5/2012.

The CMC microbiology information request for drug substance and drug product that were included in the complete response letter (in bold) and the applicant's response (normal font) are shown below:

Drug substance:

You have proposed several changes to the DS manufacturing process to improve microbial control. Submit the following data in support of the proposed changes:

a. In-process and final XM-02 bioburden and endotoxin data for the [redacted] (b) (4) following the proposed changes.

b. Microbial control data for storage [redacted] (b) (4)

c. Identify any additional changes that could affect microbial process control (for example, changes in hold times). The safety of such changes should be supported by appropriate testing and controls.

Applicant's response: The requested data along with updated Module 3 will be submitted to the Agency in the 3Q, 2012.

Review comments: The applicant was asked to provide an update with respect to the change implementation date, number of batches manufactured since implementation of the change, and timeline for submission of the data to the BLA.

Applicant's response: The changes to improve microbial control of the drug substance manufacturing process were implemented March 30, 2011. A total of (b) (4) have been manufactured between December 2010 and September 2012. The full data package will be submitted in September 2012 (eCTD sequence 0042 dated 7/31/2012).

Review comments: The microbial control data obtained after implementation of the changes should be requested as a post-marketing commitment.

Drug product:

Provide a written commitment to submit the results of the re-evaluation of the bioburden limit after 30 commercial batches are manufactured and to propose a new (b) (4) bioburden action limit that more accurately reflects process capability.

Applicant's response: Based on the limited manufacturing experience, the bioburden alert limit of (b) (4) and action limit of (b) (4) was set prior to (b) (4) Teva committed to adjust the alert and action limits according to accumulated commercial manufacturing data from 30 batches and submit the results to the Agency.

Review comment: The (b) (4) bioburden data from 30 commercial batches should be requested as post-marketing commitment.

Container Closure:
The primary container closure system components in contact with the (b) (4)-DP liquid formulation are:
- Type I glass syringe barrel
- (b) (4) rubber stopper
- Steel needle

Cardboard cartons are used for secondary packaging of the drug product (pack sizes of 1, 5 or 10 syringes). (b) (4)

An information request relating to the shipping validation that was not included in the original complete response letter was requested from the applicant.

Information request: Please provide data from your shipping qualification study which assessed shipment of minimum and maximum loads and worst case conditions (temperature, duration, shock impact) for shipment. The data on plunger movement, container closure integrity and package integrity after shipping of the (b) (4) drug product from Kfar Saba, Israel to the US distribution site should also be included for review.

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2.3.P.8. STABILITY

Commercial scale and small scale (b) (4) of commercial scale) batches of (b) (4) -DP (300 mcg/0.5 mL and 480 mcg/0.8 mL strengths), manufactured at Kfar Saba were entered into the stability program. For the purposes of the stability study, the syringes did not contain a plunger rod and were placed in horizontal position. A shelf-life of 36 months is proposed for the filgrastim-DP. Endotoxin (b) (4) and sterility test are performed initially and at 36 months. The batches FL5001 (300 µg/0.5 mL) and FL8001(400 µg/0.5 mL) met the endotoxin and sterility acceptance criteria at 36 months. Data supporting stability and expiry should be reviewed by OBP/DTP.

SATISFACTORY

Environmental Assessment

The applicant has stated that an Environmental Assessment is not required as:

- Filgrastim drug substance is a recombinant protein, which is very similar to naturally occurring human G-CSF. Therefore, no potentially harmful effects to the environment are expected.
- Filgrastim is a comparable product of existing G-CSF on the market. The approval of the filgrastim should not result in an increase of the total quantity released into the environment.

cGMP Status

The drug product manufacturing site TEVA, 64 Hashikma St., Industrial Zone, Kfar Saba, Israel 44102 was inspected (b) (4) and classified VAI. The CTX and SVS profiles were covered and are considered acceptable.

The drug substance manufacturing site SICOR Biotech UAB, Moletu pl. 5, LT-08409 Vilnius, Lithuania was inspected May 31, 2010 to June 4, 2010 and classified NAI and is acceptable. This inspection covered filgrastim drug substance.

Conclusion

I. The BLA resubmission, as amended, is recommended for approval from a CMC microbiology product quality perspective with the following post-marketing commitments:

(i) To submit data on (b) (4) accumulated after manufacture of 30 commercial batches and any changes to currently proposed (b) (4) action limits of (b) (4) prior to (b) (4) in a CBE-30 supplement by date (provided by applicant).

(ii) To submit winter shipment data from the shipping qualification study in a CBE-0 supplement by date (provided by applicant).

(iii) To submit the following data obtained after implementation of changes made to improve microbial control in the drug substance manufacturing process:

a. In-process and final figrastim bioburden and endotoxin data for the [redacted] (b) (4) following the proposed changes.

b. Microbial control data for storage [redacted] (b) (4)

c. Any other changes and data that could affect microbial process control (for example, changes in hold times).

The information should be submitted as a CBE-30 supplement by September 30, 2012.

II. CMC drug product specific information and data should be reviewed by OBP/DTP reviewer.

III. The drug product manufacturing site TEVA, 64 Hashikma St., Industrial Zone, Kfar Saba, Israel 44102 was inspected [redacted] (b) (4) and classified VAI. The CTX and SVS profiles were covered and are considered acceptable.

The drug substance manufacturing site SICOR Biotech UAB, Moletu pl. 5, LT-08409 Vilnius, Lithuania was inspected May 31, 2010 to June 4, 2010 and classified NAI and is acceptable. This inspection covered filgrastim drug substance.

Cc: OMPQ/BMAB/Building 51, Suvarna
OMPQ/BMAB/Building 51, Hughes
OMPT/CDER/OND/OHOP/DHP, Akinsanya, Lara
OMPQ/BMAB/Building 51, eCTD Files (STN:125294)

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/s/

KALAVATI C SUVARNA
08/01/2012

PATRICIA F HUGHES TROOST
08/01/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date: August 10, 2010
To: Administrative File, STN 125294/0
From: Patricia F. Hughes, Ph.D., Ph.D., Team Leader, CDER/OC/DMPQ/BMT 8/10/2010
Kalavati Suvarna, Ph.D., Peer Reviewer, CDER/OC/DMPQ/BMT
Anastasia Lolas, M.S., Peer Reviewer, CDER/OC/DMPQ/BMT 8/11/10
Subject: Team Leader Microbiology Product Quality Review of the Original BLA
US License: # 1803
Applicant: Teva Pharmaceuticals USA
Mfg Facilities: Drug substance: Sicor Biotech UAB, Vilnius, Lithuania (FEI 3008110727)
Drug product: TEVA Pharmaceutical Industries, Ltd, Kfar Saba, Israel 44102 (FEI: 3002721084).
Product: NEUTROVAL™ (r-metHuG-CSF, XM02; (b) (4))
Dosage: Sterile solution for subcutaneous injection in single-use pre-filled syringe (300 µg/0.5 mL and 480 µg/0.8 mL)
Indication: Reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer.
Due Date: September 30, 2010

Recommendation for Approvability:

1. Microbiology Product Quality

The original BLA and all relevant amendments were reviewed from a CMC microbiology product quality perspective by primary CMC microbiology reviewers Anastasia Lolas, M.S. and Kalavati Suvarna, Ph.D. The BLA, as amended, contains deficiencies listed below and is not recommended for approval. In addition, two post-marketing commitments will be communicated to the sponsor.

The Microbiology Product Quality deficiencies are as follows:

Due to several proposed changes to the filgrastim drug substance manufacturing process to improve microbial control, please submit the following data as soon as they are available:

a. In-process and final filgrastim bioburden and endotoxin data for the (b) (4) following the proposed changes.
b. Microbial control data for storage (b) (4).
c. Any other changes and data that could affect microbial process control (for example, changes in hold times).

The two post-marketing commitments are as follows:

PMC 1: Assess plunger movement, container closure integrity and package integrity after shipping of the filgrastim drug product from Kfar Saba, Israel to the US distribution site in the shipping qualification study. The data derived from the shipping qualification studies using worst case conditions (temperature, duration, shock impact) with minimum and maximum loads should be submitted in a CBE-30 supplement by date (provided by the applicant).

PMC 2: Submit data on [redacted] (b) (4) accumulated after manufacture of 30 commercial batches and any changes to currently proposed [redacted] (b) (4) action limits of [redacted] (b) (4) prior to [redacted] (b) (4). The data should be submitted in a CBE-30 supplement by date (provided by applicant).

2. Establishment Acceptability:

The drug substance manufacturing facility, Sicor Biotech UAB, was inspected May 31-June 4, 2010 by a CDER team of investigators from OC/DMPQ/BMT and OBP/DTP and was classified as NAI and is considered acceptable from a CGMP perspective.

The commercial manufacturing site for NEUTROVAL™ (XM02, [redacted] (b) (4) drug product is TEVA Pharmaceutical Industries, 64 Hashikma St., Industrial Zone, Kfar Saba, Israel 44102. This site was inspected [redacted] (b) (4) and is considered acceptable from a CGMP perspective.

SECONDARY REVIEW:

3.2.S DRUG SUBSTANCE:

[redacted] (b) (4)

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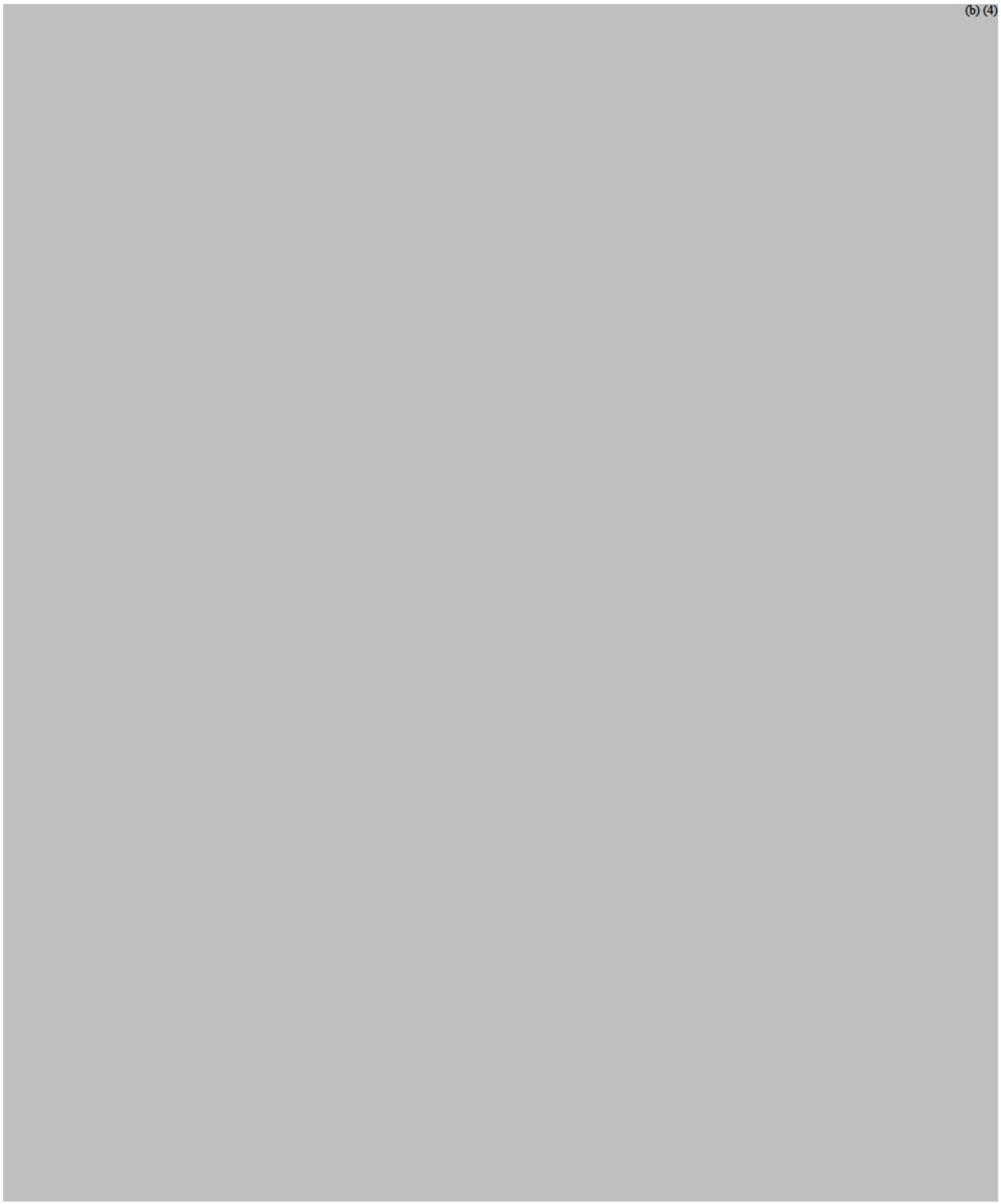

Environmental Assessment

The applicant has stated that an Environmental Assessment is not required as:

- Filgrastim drug substance is a recombinant protein, which is very similar to naturally occurring human G-CSF. Therefore no potentially harmful effects to the environment are expected.
- Filgrastim is a comparable product of existing G-CSF on the market. The approval of the filgrastim should not result in an increase of the total quantity released into the environment.

Conclusion

I. The BLA, as amended, is not recommended for approval from a CMC microbiology product quality perspective. The CMC microbiology deficiencies are as follows:

Due to several proposed changes to the filgrastim drug substance manufacturing process to improve microbial control, please submit the following data as soon as they are available:

a) In-process and final filgrastim bioburden and endotoxin data for the (b) (4) following the proposed changes.
b) Microbial control data for storage (b) (4).
c) Any other changes and data that could affect microbial process control (for example, changes in hold times).

The following two post-marketing commitments should be communicated to the sponsor:

PMC 1: Assess plunger movement, container closure integrity and package integrity after shipping of the filgrastim drug product from Kfar Saba, Israel to the US distribution site in the shipping qualification study. The data derived from the shipping qualification studies using worst case conditions (temperature, duration, shock impact) with minimum and maximum loads should be submitted in a CBE-30 supplement by date (provided by the applicant).

PMC 2: Submit data on (b) (4) accumulated after manufacture of 30 commercial batches and any changes to currently proposed (b) (4) action limits of (b) (4) prior to (b) (4). The data should be submitted in a CBE-30 supplement by date (provided by applicant).

II. CMC product specific information and data should be reviewed by OBP/DTP reviewer.

III. There are no inspectional follow-up items.

Cc:

OND/OODP/DBOP (HFD-107), Chaudhry, Danyal
DMPQ/BMT/Building 51, Blue Files (STN:125294)

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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: 02 August 2010

To: Administrative File, STN 125294/0

From: Anastasia G. Lolas, Microbiologist, OC/DMPQ/MAPCB/BMT AL 8/2/10

Through: Patricia Hughes, Ph.D., Team Leader, OC/DMPQ/MAPCB/BMT PFH 8/2/10

Subject: Original BLA – Drug substance review

US License: #1803

Applicant: TEVA Pharmaceuticals USA

Facility: DS – SICOR Biotech UAB, Vilnius, Lithuania (FEI 3008110727)
DP – TEVA Pharmaceutical Industries, Ltd, Kfar Saba, Israel (FEI 3002721084)

Product: Neutroval™ (b) (4)

Dosage: Sterile solution in a single-use pre-filled syringe (300 µg/0.5 mL & 480 µg/0.8 mL) for subcutaneous injection, 5 µg/Kg/day

Indication: Reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer

Due date: 30 September 2010

Recommendation for Approvability: BLA STN 125294 is not recommended for approval from a microbial control and CMC microbiology product quality perspective. There is one microbiology deficiency (see last page of this review). The SICOR Biotech UAB facility was inspected May 31-June 4, 2010 and classified acceptable (NAI).

Review Summary

TEVA Pharmaceuticals USA submitted BLA STN 125294/0 (seq 0000) on 30-Nov-2009 to license Neutroval™ (b) (4) and the associated manufacturing processes. Code XM02 was also used during development. The application is electronic in CTD format and is a standard review with a PDUFA user fee date of 30-Sep-2010. A pre-IND/pre-BLA meeting was held with the applicant on 25-Nov-2008 to discuss the submission and contents of this BLA. The meeting minutes are also provided in the submission.

The drug product is already marketed in Europe (since September 2008) as a biosimilar of Neupogen®. SICOR Biotech UAB in Vilnius, Lithuania is an indirect wholly-owned subsidiary of TEVA Pharmaceuticals USA, Inc. and markets the product in Europe along with RatioPharm GmbH in Germany as Biograstim®, Filgrastim-Mepha, Filgrastim ratiopharm, Ratiograstim® or TEVAGRASTIM®.

The drug substance filgrastim is manufactured by SICOR Biotech UAB in Vilnius, Lithuania (FEI 3008110727). The site has never been inspected by the Agency. A pre-license inspection was conducted May 31-June 4, 2010. Several recommendations were made to the firm but there were no 483 observations. Initial classification is NAI.

The drug product is provided in a single-use pre-filled syringe as a sterile solution of 300 µg/0.5 mL or 480 µg/0.8 mL for subcutaneous injection (b) (4) (b) (4) The recommended dose is 5µg/Kg/day for reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer. The drug product is manufactured by TEVA Pharmaceutical Industries, Ltd in Kfar Saba, Israel (FEI 3002721084). (b) (4)

This review addresses only the drug substance microbiological product quality and manufacturing process. A separate assessment has been written for the drug product. The application is not recommended for approval due to one microbiology deficiency regarding microbial control of the drug substance manufacturing process (see last page of review). The applicant has submitted information on how to address these concerns. However, the proposed changes and validation for these changes will not be complete until after the PDUFA date for this application. The applicant should submit data from these validation studies.

Following an information request from the Division of Biologic Oncology Products (sent 15-Jan-2010), an amendment was submitted on 22-Jan-2010 (seq 0005) to address inspection readiness for the drug substance and drug product manufacturing facilities, provide FEI numbers, provide more detailed manufacturing schedules and a list of other products manufactured at the drug substance and drug product facilities. The previous amendment (seq 0004) did not contain sufficient detail regarding the manufacturing schedule for the SICOR Biotech UAB facility (b) (4) . Seq 0005 identified (b) (4) . Additional amendments were submitted in response to CMC and microbiology questions (seq 0014, 0016 and 0017).

The following amendments related to CMC-microbiology were reviewed: 08-Dec-2009 (seq 0001), 11-Jan-2010 (seq 0004), 22-Jan-2010 (seq 0005), 30-Apr-2010 (seq 0011), 03-Jun-2010 (seq 0014), 15-Jun-2010 (seq 0016), 24-Jun-2010 (seq 0017), and 20-Jul-2010 (seq 0022).

Review Narrative

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

S DRUG SUBSTANCE

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(b) (4)

Conclusion

I. BLA STN 125294/0 was reviewed from a microbial control and CMC microbiology product quality perspective and is not recommended for approval. There is one microbiology deficiency.
II. The submission should be reviewed in its entirety by an OBP/DTP reviewer.
III. No additional inspection follow-up items were identified.

Cc: OPS/OBP/WO Bldg 21, Rawls

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CMC Microbiology Deficiencies

1. Due to several proposed changes to the filgrastim drug substance manufacturing process to improve microbial control, please submit the following data as soon as they are available:
    a. In-process and final filgrastim bioburden and endotoxin data for the (b) (4) following the proposed changes.
    b. Microbial control data for storage (b) (4).
    c. Any other changes and data that could affect microbial process control (for example, changes in hold times).

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

Date: July 30, 2010
To: Administrative File, STN 125294/0
From: Kalavati Suvarna, Ph.D., CDER/OC/DMPQ/MAPCB/BMT 8/6/2010
Endorsement: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT 8/6/2010
Subject: Original BLA
US License: # 1803
Applicant: Teva Pharmaceuticals USA
Mfg Facility: TEVA Pharmaceutical Industries, Ltd, 64 Hashikma St., Industrial Zone, Kfar Saba, Israel 44102 (FEI: 3002721084).
Product: NEUTROVAL™ (r-metHuG-CSF, XM02; (b) (4)
Dosage: Solution for injection (300 mcg/0.5 mL and 480 mcg/0.8 mL in a pre-filled syringe)
Indication: The reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer.
Due Date: September 30, 2010

Recommendation for Approvability: This submission was reviewed from a CMC microbiology and sterility assurance perspective and is recommended for approval with the following post-marketing commitments:

Post-marketing commitment 1: To assess plunger movement, container closure integrity and package integrity after shipping of the (b) (4) drug product from Kfar Saba, Israel to the US distribution site in the shipping qualification study. The data derived from the shipping qualification studies using worst case conditions (temperature, duration, shock impact) with minimum and maximum loads should be submitted in a CBE-30 supplement by date (provided by the applicant).

Post-marketing commitment 2: Submit data on (b) (4) accumulated after manufacture of 30 commercial batches and any changes to currently proposed (b) (4) action limits of (b) (4) prior to (b) (4). The data should be submitted in a CBE-30 supplement by date (provided by applicant).

SUMMARY: The subject of this BLA is (b) (4), a recombinant human granulocyte colony stimulating factor produced in *E. coli* without glycosylation and with an N-terminal methionyl extension (r-metHuG-CSF). The (b) (4) presented in this BLA has the laboratory code of XM02 and the proposed trade name of NEUTROVAL™. The BLA was submitted in eCTD format. This review covers the evaluation of the drug product aspects of the application from a

microbial control and sterility assurance perspective. The commercial manufacturing site for NEUTROVAL™ (XM02, filgrastim) drug product is TEVA Pharmaceutical Industries located in Kfar Saba, Israel.

The original submission and amendments to the original submission (eCTD sequence numbers: 0001 dated 12/8/2009; 0002 dated 12/21/2009; 0004 dated 1/11/2010; 0008 dated 3/26/2010; 0011 dated 4/30/2010; 0015 dated 6/11/2010; 0017 dated 6/24/2010; and 0022 dated 7/20/2010) are reviewed here.

ASSESSMENT:

3.2.P. DRUG PRODUCT:

The (b) (4)-DP is presented in (b) (4) glass, single-use, pre-filled syringes with permanently attached stainless steel needle in two dosage strengths of 300 µg/0.5 mL and 480 µg/0.8 mL of filgrastim-DS. Both strengths will be supplied in packs of one, five or ten pre-filled syringes. The liquid formulation is an (b) (4) (pH 4.2), sterile, (b) (4) solution for subcutaneous injection. It has no preservatives. (b) (4)-DP solution for injection requires no reconstitution with any diluent. (b) (4) . The recommended dose of XM02 is 5µg/kg/day given daily as a subcutaneous injection (b) (4).

Table 1: Composition of the (b) (4)-DP.

Ingredient	Concentration (mg/mL)	Quantity per syringe (mg)	Function	Standard
Filgrastim-DS	(b) (4)			In-house
Excipients				
Acetic acid, glacial				USP
Polysorbate 80				NF
Sodium Hydroxide				NF
Sorbitol				NF
Water for injection				USP
1				

(b) (4)

Description of the container closure:

The primary container for (b) (4)-DP pre-filled syringes consists of a (b) (4) glass

[redacted] syringe barrel with fixed needle and needle shield, [redacted] rubber plunger stopper [redacted] and a [redacted] The syringes may or may not have a needle guard safety device attached to it during packaging and labeling.

3.2.P.2. Pharmaceutical Development

3.2.P.2.1. Components

[redacted]

3.2.P.2.2. Formulation:

Formulation developmental studies should be reviewed by OBP/DTP.

3.2.P.2.3. Manufacturing Process Development

Information pertaining to batches manufactured at pilot scale and full scale at [redacted] and transfer of manufacturing from [redacted], should be reviewed by OBP/DTP reviewer.

The [redacted]-DP manufacturing process at Kfar Saba employs [redacted]

Container Closure:

The primary container closure system components in contact with the [redacted]-DP liquid formulation are:

- Type I glass syringe barrel
- [redacted] rubber stopper
- Steel needle

Cardboard cartons are used for secondary packaging of the drug product (pack sizes of 1, 5 or 10 syringes). [redacted] The stability of filgrastim-DP decreases following exposure to light in the primary package. No such effect was seen in samples protected by the secondary packaging.

[redacted]

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• Filgrastim drug substance is a recombinant protein, which is very similar to naturally occurring human G-CSF. Therefore no potentially harmful effects to the environment are expected.
• Filgrastim is a comparable product of existing G-CSF on the market. The approval of the filgrastim should not result in an increase of the total quantity released into the environment.

cGMP Status

The drug product manufacturing site TEVA, 64 Hashikma St., Industrial Zone, Kfar Saba, Israel 44102 was inspected (b) (4) and classified VAI. The CTL, SVS, and (b) (4) profiles were covered and are considered acceptable (check performed on 7/27/2010). Inspection waiver memo included.

Conclusion

I. Sections 3.2.P of the BLA pertaining to microbial control and sterility assurance of the drug product manufacturing process were reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective with the following post-marketing commitments:

(i) Please assess plunger movement, container closure integrity and package integrity after shipping of the filgrastim drug product from Kfar Saba, Israel to the US distribution site in the shipping qualification study. The data derived from the shipping qualification studies using worst case conditions (temperature, duration, shock impact) with minimum and maximum loads should be submitted in a CBE-30 supplement by date (provided by the applicant).

(ii) Please submit data on (b) (4) accumulated after manufacture of 30 commercial batches and any changes to currently proposed (b) (4) (b) (4) bioburden action limits of (b) (4) prior to (b) (4) in a CBE-30 supplement by date (provided by applicant).

II. CMC drug product specific information and data should be reviewed by OBP/DTP reviewer.

III. The drug product manufacturing site TEVA, 64 Hashikma St., Industrial Zone, Kfar Saba, Israel 44102 was inspected (b) (4) and classified VAI. The CTL, SVS, and (b) (4) profiles were covered and are considered acceptable (Check performed on 7/27/2010). The inspection of this facility was waived (inspection waiver memo included).

Cc: DMPQ/BMT/Building 51, Suvarna
DMPQ/BMT/Building 51, Hughes
OND/OODP/DBOP (HFD-107), Chaudhry, Danyal
DMPQ/BMT/Building 51, Blue Files (STN:125294)

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

Inspection Waiver Memorandum

Date: 26 March 2010
From: Kalavati Suvarna, Ph.D., CDER/OC/DMPQ/BMT
Jee Chung, Ph.D., OPS/OBP/DTP
To: BLA File – STN 125294/0
Subject: Recommendation to waive a pre-approval inspection
Sponsor: Teva Pharmaceuticals USA
Manufacturing Facility: TEVA Pharmaceutical Industries, Ltd, 64 Hashikma St., Industrial Zone, Kfar Saba, Israel 44102 (FEI: 3002721084).
Product: NEUTROVAL™ (r-metHuG-CSF, XM02; (b) (4))
Indication: The reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer.
Through: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/BMT 3/24/10

Waiver Recommendation

Based on the compliance history of the firm, the current GMP status, and the fact that TEVA Pharmaceutical Industries has been approved to manufacture multiple CDER products using the same manufacturing process, we recommend that the pre-approval inspection of the TEVA Pharmaceutical Industries drug product manufacturing facility in Kfar Saba, Israel 44102 (FEI: 3002721084) be waived for STN 125294/0 (submission dated November 30, 2009.

Clearance Routing

CONCUR / DO NOT CONCUR DATE 4-30-10

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

CONCUR / DO NOT CONCUR DATE 4-15-10

Amy Rosenberg, M.D.
Director, Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER

Summary

BLA 125294/0 is an original submission for [redacted] (Proposed name: NEUTROVAL™; other names: XM02) for the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer. The [redacted] drug product [redacted]-DP) is a solution for injection presented in [redacted] glass, single-use, pre-filled syringes in two dosage strengths of 300 µg/0.5 mL and 480 µg/0.8 mL. The liquid formulation [redacted] The drug product is stored at 2 – 8°C for 36 months.

The primary container for filgrastim-DP comprises a [redacted] glass syringe barrel with fixed needle and needle shield, [redacted], [redacted] rubber plunger stopper and a [redacted] plunger rod. The syringes may or may not have a needle guard safety device attached during packaging and labeling.

Drug substance is shipped from Sicor Biotech Vilnius Lithuania to Teva [redacted]

The drug product manufacturing takes place in [redacted] and involves the following steps:

[redacted]

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 Teva Pharmaceuticals USA with License #1803. Teva will market Filgrastim product which is the subject of BLA 125294 that is currently under review at the Agency under this license.
b. TEVA Pharmaceutical Industries produces multiple CDER approved products using (b) (4).

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

A compliance check of the TEVA Pharmaceutical Industries, Ltd, facility in Kfar Saba, Israel indicates that it was inspected from (b) (4). The most recent inspection was a GMP/pre-approval inspection for several ANDA products including the following injectable products: (b) (4) area was covered during this inspection. The inspection was classified VAI:acceptable for profiles SVS and (b) (4). A two-item FDA 483 was issued regarding failure to submit an NDA-Field Alert Report for (b) (4), failure to establish and follow procedures designed to prevent microbiological contamination of drug product (b) (4) The inspection covered in depth equipment qualifications for (b) (4) operations, cleaning validations, environmental monitoring, and conduct of investigations.

Previous inspections include a GMP/pre-approval inspection conducted in April 2005 classified as NAI and a pre-approval inspection conducted in August 2003 classified as VAI. The 2009 inspection noted that all previous deficiencies had been corrected.

3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

The last inspection was classified VAI:acceptable. The deficiencies were related to failure to submit an NDA-Field Alert Report for (b) (4), and failure to establish and follow procedures designed to prevent microbiological contamination of drug product (b) (4)

[redacted] (b) (4) These deficiencies do not reveal significant process problems or systematic problems.

4. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.*

   TEVA Pharmaceutical Industries, Ltd, facility in Kfar Saba, Israel is approved to manufacture multiple drug products using [redacted] (b) (4)

5. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.*

   There are no significant differences between the [redacted] (b) (4) processes used for other approved products and the [redacted] (b) (4) process used for Filgrastim drug product.

Signed:

Kalavati Suvarna, Ph.D.
Microbiologist, OC/DMPQ/BMT

DATE 3/24/2010

Jee Chung, Ph.D.
Biologist, OPS/OBP/DTP

DATE 4/14/2010

Regulatory Filing Review Memo for BLAs and Supplements

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

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

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

STN: 125294/0 Product: (b) (4)/XM02 Applicant: Teva Pharmaceuticals USA

Final Review Designation (circle one): (Standard) Priority

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

Submission organization (circle one): Traditional (CTD)

Filing Meeting: Date January 12, 2010
Committee Recommendation (circle one): (File) RTF

RPM: _____
(signature/date)

Attachments:

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

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		
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		
❑ Novel Excipients		N	No novel excipients
❑ Executed Batch Records	Y		
❑ Method Validation Package	Y		
❑ Comparability Protocols	Y	N	Defer to OBP

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	Defer to OBP
o nomenclature			
o structure (e.g. sequence, glycosylation sites)			
o properties			
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y		
❑ description of manufacturing process	Y		
o batch numbering and pooling scheme			
o cell culture and harvest			
o purification			
o filling, storage and shipping			
❑ control of materials	Y	N	Defer to OBP
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	Defer to OBP. No discussion of microbial control (bioburden and endotoxin)
o justification of specifications			
o analytical method validation			
o reference standards			
o stability			
❑ process validation (prospective	Y		Microbial control is discussed and data are

CTD Module 3 Contents	Present?		If not, justification, action & status
plan, results, analysis, and conclusions)			presented
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	N	Defer to OBP
❑ characterization of drug substance	Y	N	Defer to OBP
❑ 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		Microbiology only
❑ reference standards	Y	N	Defer to OBP
❑ container closure system	Y		Description, Container-closure integrity, sterilization
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y		Bioburden and endotoxin testing only
Drug Product [3.2.P]			
❑ description and composition	Y		
❑ pharmaceutical development	Y		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y		OBP Lead
❑ batch formula	Y		
❑ 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		
❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o other needed validation data	Y	N	Microbial controls included. (b) (4) bioburden limits high for bulk solution. Data from 2 full scale PV lots included; one lot from each strength. Pilot scale batch evaluations included. Media fill information included

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	OBP Lead
❑ control of drug product (justification of specifications; analytical method validation)	Y	Endotoxin and sterility included. Others OBP Lead.
❑ container closure system [3.2.P.7] ○ specifications (vial, elastomer, drawings) ○ availability of DMF ○ closure integrity ○ administration device(s)	Y	Reference to CBER Master File (b) (4) (b) (4) for (b) (4)
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	Y	OBP Lead
Diluent (vials or filled syringes) [3.2P']		Liquid formulation; (b) (4)
❑ 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: ○ 3 consecutive lots ○ 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	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
validation, batch analysis, characterization of impurities) ❑ reference standards ❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	 Y N Y N Y N	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	 Y Y N	UltraSafe Passive™, (b) (4), Needle Guard and plunger rod
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment 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.: 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 Y N Y N	 Multi-product DS site. List of other products manufactured at DS and DP sites not included. DP equipment is dedicated to (b) (4) DP. OBP Lead

CTD Module 3 Contents	Present?		If not, justification, action & status
USA Regional Information [3.2.R]			
❑ executed batch records	Y		
❑ method validation package	Y		
❑ comparability protocols	Y	N	No comparability protocols proposed
Literature references and copies [3.3]	Y	N	Not applicable

Examples of Filing Issues	Yes?		If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	Y		Not applicable
❑ legible	Y		
❑ English (or translated into English)	Y		
❑ compatible file formats	Y		
❑ navigable hyper-links	Y		
❑ interpretable data tabulations (line listings) & graphical displays	Y		
❑ summary reports reference the location of individual data and records	Y		
❑ all electronic submission components usable	Y		
includes appropriate process validation data for the manufacturing process at the commercial production facility?	Y		Media fill information included.
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	OBP Lead
includes complete description of product lots and manufacturing process utilized for clinical studies	Y	N	OBP Lead
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y	N	OBP Lead
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	OBP Lead
certification that all facilities are ready for inspection		N	Facilities listed; Production schedule and certification that they are ready for inspection not included. DP site was inspected in June 2009 and classified VAI. Production schedule for DS site requested on 17-Dec-2009 to be submitted prior to 14-Jan-2010

Examples of Filing Issues	Yes?	If not, justification, action & status
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	OBP
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 Y N Y N Y N	Endotoxin (b) (4)
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	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	N	Dedicated equipment for DP; List of other products manufactured at the same site not included.
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	Not applicable; original BLA

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).

Fileable

Recommendation (circle one): (File) RTF 1/4/2010 1/4/2010

Reviewer: Kalavati Suvarna; Anastasia Lolas Type (circle one): Product (Chair) Facility (DMPQ)

(signature/ date)

Concurrence:

Branch/Lab Chief: 1/4/2010 Division Director: Acting DD 01/04/2010