

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125294Orig1s000**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

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|--|---|
| <b>Date</b>                                | (electronic stamp)  |
| <b>From</b>                                | Ann. T. Farrell, M.D., Acting Division Director   |
| <b>Subject</b>                             | Division Director Summary Review  |
| <b>NDA/BLA #</b>                           | 125294  |
| <b>Supplement #</b>                        |   |
| <b>Applicant Name</b>                      | Teva Pharmaceuticals, Inc. changed to SICOR Biotech UAB   |
| <b>Date of Submission</b>                  | 02/29/12  |
| <b>PDUFA Goal Date</b>                     | 8/29/12   |
| <b>Proprietary Name / Established Name</b> | None/tbo-filgrastim/XM-02   |
| <b>Dosage Forms / Strength</b>             | Solution for subcutaneous injection in pre-filled syringes with and without needle guard 300mcg/0.5 mL and 480mcg/0.8mL   |
| <b>Proposed Indication(s)</b>              | to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia |
| <b>Action/Recommended Action for NME:</b>  | approval  |

|   |   |
|---|---|
| <b>Material Reviewed/Consulted</b>            |   |
| OND Action Package for this cycle, including: |   |
| Medical Officer Review                        | Thomas Herndon, M.D./Albert Deisseroth, M.D., Ph.D.                               |
| Statistical Review                            | Qing Xu, Ph.D./Mark Rothmann, Ph.D.   |
| Pharmacology Toxicology Review                | Robeena Aziz, PhD./Haleh Saber, Ph.D. /John Leighton, Ph.D.                       |
| CMC Review/OBP Review                         | Jee Chung, Ph.D. /Dov Pluznik, Ph.D./Kathy Lee, M.S./Emanuela Lacan, Ph.D.        |
| Microbiology Review                           | Kalavati Suvarna, Ph.D. /Patricia Hughes Troost, Ph.D.                            |
| Clinical Pharmacology Review                  | Joseph Grillo, Ph.D./Julie Bullock, Pharm.D./Nam Atiqur Rahman, Ph.D.             |
| DDMAC   | James Dvorsky   |
| DSI   | Lauren Iacono-Connors, Ph.D./Susan Liebenhaut, M.D./Tejashari Purohit Sheth, M.D. |
| CDTL Reviews                                  | Albert Deisseroth, M.D., Ph.D.  |
| OSE/DMEPA                                     |   |
| OSE/Epidemiology                              |   |
| OSE/DRISK                                     |   |
| Other - statistical safety                    |   |
| Other – Pediatrics/<br>Maternal Health Team   | Jeanine Best, RNP./Hari C. Sachs, M.D./Lisa Mathis, M.D.                          |

# Signatory Authority Review Template

## 1. Introduction

On November 30, 2009, Teva filed a biologics licensing application (BLA) under section 351(a) of the Public Health Service (PHS) Act for XM-02. XM-02 is a biological protein. The FDA therapeutic class designation is a leukocyte growth factor. XM-02 can be referred to as a granulocyte colony stimulating factor (G-CSF). XM-02 is secreted by genetically-engineered bacteria (*E. coli*). The applicant has proposed the following indication: to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

The current submission is a response to the Agency's Complete Response letter issued September 29, 2010. The original submission had a number of issues precluding approval: concern about database being unlocked and whether vital data were altered, (b) (4), the device (pre-filled syringe), need for information on the potential for reproductive toxicity, and nomenclature, as well as the following other issues: characterization of the potential for binding and neutralizing anti-product antibodies, characterization of critical attributes and narrowing of specifications, information on pediatric use, and potential to prolong the QT interval. These issues were communicated in the Agency's Complete Response letter.

Teva submitted its application under section 351(a) of the PHS Act; therefore this application must contain all necessary nonclinical, clinical pharmacology, and clinical trial data necessary to support licensure. The applicant cannot rely on any proprietary data submitted to another BLA to support the safety and efficacy of XM-02.

The original submission contained one pivotal clinical trial comparing XM-02 to a non-US-approved filgrastim and to placebo. The key efficacy comparison for this application, and that upon which the demonstration of effectiveness relies, is the comparison of XM-02 to placebo.

The final product will be supplied in a pre-filled syringe with a container closure system ( (b) (4) ).

The PDUFA goal date for the current submission is August 29, 2012.

In 2008, Teva obtained market authorization in the EU under an EMA abbreviated pathway for biosimilar products.

## 2. Background

The following text is from the Complete Response letter issued September 29, 2010:  
1. Based on the FDA inspection of BioGeneriX AG (b) (4)

(b) (4) there is concern that the integrity of the database for Study XM02-02-INT, the single trial submitted to support the efficacy of your product, may have been compromised. Specifically, after the initial database lock on January 2, 2006, and subsequent data unblinding, the database was unlocked and the data were altered on at least two separate dates, i.e. January 17th and January 23rd, 2006. Describe the quality control and/or quality assurance activities at each stage of data handling, from initial entry into the database through the final database lock, that were undertaken to ensure the integrity of safety and efficacy data. In addition, provide documentation, including justification and the audit trail, for all changes made to the database after unblinding. Finally, provide a detailed analysis of the impact of all changes made to the database after initial lock and unblinding on the evaluation of safety and efficacy data.

(b) (4)

3. You have not provided adequate information concerning your device closure system. Based on our assessment, you appear to be relying solely on the fill weight as the definitive property to decide if the correct amount of therapy is being delivered through the syringe. There are physical aspects of syringes and needles such as dead space/volume, bond strength between the syringe/needle, and spacing of volumetric graduation markings that can impact the performance of the device. We are also aware that there have been several complaints from the medical community regarding (b) (4) and the ability for the user to manipulate these pre-filled syringes. Additionally, based on our review of DMF- (b) (4) (Drug Master File for (b) (4)) it appears that your syringes may not conform to current FDA consensus standards regarding syringes and needles.

Provide performance testing to demonstrate that your pre- filled glass syringe is safe and effective to deliver your drug product (DP) and that this syringe meets the specifications of the following guidance document and FDA Consensus Standards (most recent editions):

(b) (4)

(b) (4)

*In addition, there are aspects of other syringe standards that may still apply to your device. Specifically, the device constituent of this combination product consists of a (b) (4). In this capacity, all specifications of the current consensus standards such as (b) (4)*

*However, you must still consider the application of specific elements of these standards as they impact your device. (b) (4)*

(b) (4)

*Modify your testing procedures and pass/fail criteria to reflect the relevant portions of the standards that affect the performance of your device (such as bond strength).*

*4. The literature assessment of the potential reproductive toxicity of granulocyte colony stimulating factor(s) provided in support of BLA 125294 does not fulfill the regulatory requirements for nonclinical developmental and reproductive toxicity studies with Neutroval. Your BLA submitted under section 351(a) of the PHS Act may not rely on published literature describing studies of other biological products, including studies regarding a licensed biological product, to fulfill this requirement for approval.*

*To complete the application for BLA 125294 under the 351(a) pathway, provide the results of a nonclinical embryo-fetal toxicity study conducted with Neutroval in rabbits as a single, pharmacologically responsive species (refer to ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085389.pdf>)). We recommend that you submit a draft protocol for this study as an amendment to the BLA for review and comment by the nonclinical reviewers prior to initiation of this study.*

*5. We have determined that your proposed proper name (b) (4) " is not acceptable for this BLA submitted under section 351(a) of the PHS Act. (b) (4)*

(b) (4)

(b) (4)

The applicant's current submission addresses all deficiencies in the Complete Response Letter.

### 3. CMC/Device

The Office of Biotechnology Products (OBP) did not identify any issues that would have precluded approval during the first cycle. The reviews noted that the product is well-characterized and that the manufacturing processes are well-controlled and consistent. Facilities inspections (substance) performed during the first cycle also did not uncover any issues that would have precluded approval and there are no current issues involving the drug substance or drug product manufacture that would preclude approval.

OBP agreed with the applicant's request for a categorical exclusion. The OBP review states that the drug substance (b) (4) are stable when stored at (b) (4) for up to (b) (4) and the drug product is stable when stored at 2-8°C for up to 36 months.

CMC/OBP has asked Teva to perform additional testing for immunogenicity issues related to their antibody assay. CMC/OBP state in their review that the additional testing is not an approvability issue because immunogenicity-related issues such as extended neutropenia or loss of efficacy were not observed in the clinical trials. The requested additional testing will be part of the post marketing requirements.

(b) (4)

The applicant addressed other issues regarding how the pre-filled syringe (device) performs. These issues are considered by CDRH to have been adequately addressed.

I concur with the conclusions reached by the Office of Biotechnology Products and the Center for Device and Radiological Health reviewers regarding the acceptability of the

manufacturing of the drug product and drug substance. There are no outstanding issues which would preclude approval.

#### **4. Nonclinical Pharmacology/Toxicology**

The nonclinical safety of XM-02 was assessed in two GLP 26-week repeat dose toxicity studies with a 4 week recovery period in rats and monkeys. GLP safety pharmacology studies were also performed. Major toxicities identified were bone marrow hypercellularity, extramedullary hematopoiesis, increased alkaline phosphatase, painful joints (paws and limbs), and granulocyte infiltration. No effects were observed on the respiratory, cardiovascular or central nervous system.

Genotoxicity and carcinogenicity studies were not performed as these studies are not appropriate for large molecular weight proteins and the carcinogenicity study would not be necessary based on the indicated population.

During the first review cycle, there was only 1 issue identified which precluded approval: lack of an assessment of developmental and reproductive toxicity of XM02 in at least one relevant animal species. The relevant animal species identified and recommended was the rabbit.

The applicant submitted a nonclinical study addressing this issue. The following text is from the pharmacology/toxicology team leader's review:

*The current submission contains results of an embryofetal developmental toxicology study in rabbits, conducted with XM02. This study adequately addresses the nonclinical deficiency identified in 2010.*

*In brief, pregnant rabbits were treated with XM02 during the period of organogenesis. The adverse embryofetal effects are consistent with those reported for approved products (e.g. Neupogen) and those reported in published articles for other G-CSF products. Findings in rabbits include: spontaneous abortion, increased post-implantation loss, reduced fetal weight, reduced litter size, and malformations. Adverse findings are most evident at the high dose of 100 µg/kg/day. This dose resulted in significant increases in white blood cells (WBCs) and differentials.*

I concur with the conclusions reached by the pharmacology/toxicology reviewer, the supervisory pharmacologist and Dr. John Leighton, acting division director of DHOT, that there are no outstanding pharm/tox issues that preclude approval.

#### **5. Clinical Pharmacology/Biopharmaceutics**

The original review of this application did not identify any deficiencies which would preclude approval. The original package contained pharmacokinetic and bioavailability studies in healthy volunteers and XM-02's pharmacokinetics were assessed in subgroups of patients with cancer.

The following text is from Dr. Keegan's summary review of this application:

The median  $T_{max}$  was 6 hours and the median half-life ( $t_{1/2}$ ) was 8.9 hours for the 5 mcg/kg dose in healthy volunteers. Increasing the dose of XM02 from 5 to 10 mcg/kg resulted in an approximately 3-fold increase in both  $C_{max}$  and AUC 0-48h. In patients with cancer receiving chemotherapy, the median  $T_{max}$  of XM02 ranged from 4 to 6 hours and the median  $t_{1/2}$  ranged from 3.2 to 3.8 hours. Accumulation after repeated daily dosing was not observed. Based on this cross-study comparison, the pharmacology reviewer concluded that there were no interactions regarding dose adjustment based on the underlying cancer or chemotherapy regimen, across the limited numbers of cancer and chemotherapy regimens included in these studies.

No gender-related differences were observed in the pharmacokinetics of XM02 administered by the subcutaneous route of administration. Mild renal impairment (creatinine clearance 60–89 mL/min; N=11) had no clinically meaningful effect on XM02 pharmacokinetics. No dose adjustment is recommended for mild renal impairment. The pharmacokinetic profile in patients with moderate and severe renal impairment has not been assessed. However, based on the safety margin of XM02 and the lack of relationship between the incidence of the major adverse event (bone pain) and degree of renal impairment, an XM02 dosage adjustment would not be clinically warranted. The pharmacokinetic profile in patients with hepatic impairment has not been studied.

The review team recommended approval with a PMR for the QT study. The September 2010 Complete Response letter recommended that the applicant conduct a Thorough QT study.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

The TQT study comments will be communicated to the applicant. The lack of a completed TQT study does not preclude approval and can be addressed as a PMR.

## 6. Clinical Microbiology

During the first cycle review, product quality microbiology issues were identified that would preclude approval. The text below is from the review:

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) (4)
- 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 applicant responded to these deficiencies within this submission. The microbiology team reviewed the submission and recommended approval. The review team also recommended three post-marketing commitments which are verbatim from the microbiology review:

*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).

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

## 7. Clinical/Statistical-Efficacy

I have read the reviews based on the original submission. Only one pivotal trial was submitted for the indication. However, several additional trials were submitted which provided additional supportive safety data. There were two phase 1 trials in healthy volunteers and three phase 3 trials. The trial enrolling patients with breast cancer was

pivotal for the indication. The other phase 3 trials in lung cancer and non-Hodgkins Lymphoma were important for safety assessment.

XM02-02 was a large, international, multicenter, randomized controlled trial randomizing 350 patients with breast cancer (Stage II to IV) receiving initial chemotherapy to XM02, a non-US-approved filgrastim product, and placebo treatment. The primary efficacy endpoint was the duration of severe neutropenia. The trial had two planned comparisons: XM02 arm with placebo and XM02 with non-US-approved filgrastim product. The results after adjustment for “treatment”, “country” and “adjuvant vs. metastatic therapy” and baseline absolute neutrophil count revealed a statistically significant difference ( $P < 0.0001$ ,  $X^2$ ) in mean duration of severe neutropenia in cycle 1 between the XM02 arm (mean duration 1.1 days) and placebo arm (mean duration, 3.8 days).

The statistical review team performed several sensitivity analyses due to applicant’s method of data imputation for missing data to ensure the robustness of the applicant’s result for the primary comparison.

The utility of the comparison to the non-US-approved filgrastim product is uncertain. The applicant’s proposal for an equivalence or non-inferiority comparison was not discussed and agreed upon with the Agency prior to submission. A non-US-approved filgrastim product and US-licensed Neupogen are considered two separate products. No data has been submitted to compare them. The applicant did not provide justification for the one day margin. Therefore the comparison to the non-US-approved filgrastim product is not considered relevant for regulatory purposes to demonstrate the safety, potency, and purity of XM02. As noted above, the demonstration of effectiveness was based only on the data generated by the comparison of XM-02 to placebo.

I concur with the conclusions of the clinical and statistical review teams regarding the demonstration of efficacy for the single indication for which licensure was sought.

## **8. Safety**

The safety database was adequate. Approximately 750 patients and healthy volunteers received at least one dose of tbo-filgrastim. Approximately 680 patients were enrolled in the phase 3 trials. Of those 680 patients, 541 patients received tbo-filgrastim. The primary safety review concentrated on the 541 patients in the three clinical trials who received tbo-filgrastim.

During the first cycle review, Dr. Herndon reviewed all available sources of safety data and noted that one patient had an allergic reaction (after the tenth dose of XM02) and that bone pain was observed in 24% of patients receiving XM02 and 31% of patients receiving the non-US-approved filgrastim. The difficulty with adverse event attribution in the pivotal trial was the fact that patients were receiving chemotherapy as well therefore many of the serious adverse events noted were due to chemotherapy and not XM02.

### Immunogenicity

During the first cycle, the review teams determined that the immunogenicity testing using assays that were not validated was not considered reliable. However, these assays suggested that no patients enrolled in XM02-02 had binding antibodies or neutralizing antibodies during treatment. Review of the trial database did not reveal any patients treated with XM02 who had an unusually prolonged period of neutropenia which would suggest the development of antibodies. Therefore the review teams (clinical and OBP) decided that further study of the immunogenicity issue could be performed post-approval as a post-marketing requirement.

The review team and CDTL for the current and original submissions did not recommend a REMS program and Dr. Patricia Keegan who oversaw the review of the original submission did not. I concur.

I concur with the recommendations of the clinical team and the immunogenicity review team.

## 9. Advisory Committee Meeting

Since this is the fourth application for a product for the prevention of severe neutropenia and no unexpected clinical efficacy or safety issues were observed, no advisory committee meeting was held.

## 10. Pediatrics

During the first review cycle, the applicant had requested a partial waiver based on age (less than 1 month of age) and a deferral of pediatric studies as a post-marketing commitment. Both were granted.

Teva plans to assess tbo-filgrastim in pediatric patients as required under PREA by assessing the pharmacokinetic [systemic exposure (AUC<sub>0-t</sub>)] and pharmacodynamic [absolute neutrophil counts (ANC)] comparability of tbo-filgrastim in 50 pediatric patients between the ages of 1 month and 16 yrs 11 months, in three cohorts defined by age with at least 8-10 children per age cohort.

## 11. Other Relevant Regulatory Issues

The application complied with financial disclosure requirements.

During the first review cycle, the Office of Scientific Investigations (OSI) determined that there were multiple times where there was unlocking and unblinding of the database. After extensive investigation and multiple correspondence with the Applicant and contract research organization, (b) (4), OSI has concluded that the observations noted on field examination were not likely to impact data integrity and that the data submitted appear reliable.

There are no other unresolved relevant regulatory issues.

## 12. Labeling

The labeling was reviewed by all disciplines and consultant staff. A Proprietary name has not been established. The non-proprietary name is tbo-filgrastim.

## 13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Approval for the following indication: to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia

- Risk Benefit Assessment

The risk benefit assessment suggests that tbo-filgrastim is effective to reduce the duration of severe neutropenia when compared to placebo and is associated with few attributable adverse events (bone pain). Therefore a favorable risk-benefit profile exists.

- Recommendation for Post marketing Risk Management Activities

No need for a REMS program -- routine post-marketing surveillance

- Recommendation for other Post marketing Study Requirements (PMR)/ Commitments (PMC)

We have asked the applicant:

### **PREA requirements**

PMR-1: Phase 2 trial in 50 pediatric patients 1 month to 16 years of age to evaluate pharmacokinetic, pharmacodynamic, and safety data in patients with solid tumors without bone marrow involvement. Submit the protocol for Agency review and concurrence prior to beginning the trial and in advance of the "final protocol submission" date so that agreement on the essential trial elements can be reached.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

PMR-2 To develop validated screening and confirmatory assays to assess for the presence of anti-tbo-filgrastim antibodies. The validation of the assay should include the sensitivity and specificity for detection of anti-tbo-

filgrastim antibodies that are also cross-reactive with native human granulocyte colony stimulating factor (G-CSF).

- PMR-3 To develop a validated assay for identification of anti-product antibodies that neutralize the bioactivity of tbo-filgrastim. The validation of the assay should include the sensitivity and specificity for detection of anti-tbo-filgrastim antibodies that are also cross-reactive with and neutralize the bioactivity of native human granulocyte colony stimulating factor (G-CSF).
- PMR-4 To conduct an assessment for the presence of anti- tbo-filgrastim and anti-native human G-CSF binding antibodies using the validated assays developed under PMR 2 in at least 426 patients enrolled/to be enrolled in one or more clinical trials, as a substudy.
- PMR-5 To conduct an assessment for neutralizing antibodies using the validated assay developed under PMR 3 in all patients with binding antibodies to tbo-filgrastim or native G-CSF and in all patients with evidence of unexplained, persistent neutropenia. Sior should provide a listing of the clinical trials in which this assessment will be conducted.
- PMR-6 Conduct a clinical trial per ICH E14 to assess the potential for tbo-filgrastim to prolong the QT interval. Submit the protocol for review before starting the trial.

#### **POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

- PMC-7 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
- PMC-8 To submit winter shipment data from the shipping qualification study in a CBE-0 supplement
- PMC-9 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).

- PMC-10 To verify that the SE-HPLC method can accurately detect aggregates by using an orthogonal method conducted with stressed drug substance and drug product samples
- PMC-11 To characterize, using orthogonal methods, and monitor, throughout the dating period, sub-visible particulates (SVPs) in the range between <sup>(b) (4)</sup> μm and to propose an appropriate control strategy based on the risk to product quality, safety, and efficacy
- PMC-12 To conduct a validation study for a quantitative peptide map method for release and stability testing and set appropriate release and stability specifications for the quantitative peptide map based on the analytical capabilities, clinical trial experience, and manufacturing history.
- PMC-13 To conduct a quantitative (ppb and ppm) leachables study and risk assessment of leachates into the drug product and/or <sup>(b) (4)</sup> in the final container closure system using methods that are suitably validated for its intended purpose.
- PMC-14 To formulate drug product, at laboratory scale, using polysorbate 80 <sup>(b) (4)</sup> and evaluate the effects of the polysorbate 80 on product quality over time.

For final versions of the PMRs and PMC see the approval letter.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANN T FARRELL  
08/29/2012