CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125294Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # Product Name:	125294/tbo-filgrastim
PMC Description:	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 Schedule Milestones:	Study/Trial Completion:	03/2013
	Final Report Submission:	03/2013

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- X Theoretical concern
- ☐ Other

This is not an approvability issue because the SE-HPLC is able to detect aggregated species and Teva has validated the assay for its intended use, the detection of aggregates using drug substance and drug product samples.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The size exclusion chromatography method (SE-HPLC) was validated using unstressed (release) samples with an orthogonal method (analytical ultracentrifugation (AUC)). The unstressed samples have very low levels of aggregates. Therefore, the low amount of aggregates provides little sensitivity for determining whether the assay can accurately detect aggregate content. Because AUC may monitor species of aggregates that are not detected by SE-HPLC and that different aggregates can accumulate over time, it is important to understand whether SEC provides accurate information on aggregate content over the shelf-life of the product. As one possible approach to confirm the accuracy of SE-HPLC assay, we suggest the use of stress on the product under multiple conditions (such as temperature, agitation, and light) and determine if SEC provides an accurate assessment of aggregate contents as compared to AUC.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

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

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

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

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor has agreed to use multiple conditions (e.g. agitation, heat, and/or chemical) to produce stressed samples with different amounts of aggregates to confirm the accuracy of the SE-HPLC method for detecting aggregates using the AUC method as an orthogonal method.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

X Does the study/clinical trial meet criteria for PMRs or PMCs?
X Are the objectives clear from the description of the PMR/PMC?
X Has the applicant adequately justified the choice of schedule milestone dates?
X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

_____RCK_____
(signature line for BLAs)

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/s/

MONSURAT O AKINSANYA
08/29/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: STN125294/tbo-filgrastim

PMC Description: 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 tbo-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.

PMC Schedule Milestones:

Study Completion:	03/2011
Final Report Submission:	09/2012

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The drug substance manufacturer, Sicor Biotech UAB, is in the process of implementing revisions to the (b) (4) per FDA's recommendations. The requested data along with updated Module 3 will be submitted to the Agency in the 3Q, 2012. This is an improvement to the microbial controls in the manufacturing process.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Review issue: The current [redacted] (b) (4) does not includ [redacted] (b) (4) [redacted] Validation data after implementation of changes will be needed. This information will be requested as a post-marketing commitment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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 (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

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

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

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

__RCK_____
(signature line for BLAs)

Reviewer, DO YOU WANT TO REQUEST THE SPONSOR TO:

Submit a labeling supplement for this PMR trial with the final clinical study report and with complete raw datasets.-Not applicable

Submit the protocol for FDA review and concurrence before commencing the trial? No

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/s/

MONSURAT O AKINSANYA
08/29/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: STN125294/tbo-filgrastim

PMC Description: To submit winter shipment data from the shipping qualification study in a CBE-0 supplement

PMC Schedule Milestones:

Study Completion:	01/2013
Final Report Submission:	05/2013

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   The applicant provided shipping data for the maximum, minimum and routine load for summer shipment in the shipping qualification report. The winter shipment has not been completed. However, it is not an approvability issue as supporting shipping data is available. The data from the winter shipment from the shipping qualification study will be requested as a post-marketing commitment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Review issue: Shipping qualification study report for commercial shipper only included summer shipment profile. The winter shipment per shipping qualification study protocol is not complete. Data from the winter shipment is requested as a post-marketing commitment when available.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

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

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

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

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

____RCK_____
(signature line for BLAs)

Reviewer, DO YOU WANT TO REQUEST THE SPONSOR TO:

Submit a labeling supplement for this PMR trial with the final clinical study report and with complete raw datasets.-Not applicable

Submit the protocol for FDA review and concurrence before commencing the trial? No

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MONSURAT O AKINSANYA
08/29/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: STN125294/tbo-filgrastim

PMC Description: To 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) in a CBE-30 supplement.

PMC Schedule Milestones:

Study Completion:	12/2016
Final Report Submission:	03/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The applicant has set a [redacted] (b) (4) action limit of [redacted] (b) (4) based on limited commercial manufacturing experience. The bioburden limit will be re-evaluated after 30 commercial batches are manufactured and limits adjusted to reflect process capability. Therefore, this data is requested as a post-marketing commitment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Review issue: The bioburden limit is based on limited commercial manufacturing experience. Additional data from 30 commercial batches will be needed to understand process capability.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

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

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

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

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

To 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) should be submitted in a CBE-30 supplement by date (provided by applicant).

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

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

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

_RCK_____
(signature line for BLAs)

Reviewer, DO YOU WANT TO REQUEST THE SPONSOR TO:

Submit a labeling supplement for this PMR trial with the final clinical study report and with complete raw datasets. – Not applicable

Submit the protocol for FDA review and concurrence before commencing the trial? No

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MONSURAT O AKINSANYA
08/29/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

BLA # BLA 125294
Product Name: Tbo-filgrastim

PMR Description: Conduct a clinical trial per ICH E14 to assess the potential for Neutroval to prolong the QT interval.

PMR Schedule Milestones:

Final Protocol Submission:	02/2012
Trial Completion:	11/2013
Final Report Submission:	06/2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☒ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☒ Theoretical concern
   ☐ Other

   Per IRT review on 5/6/10, an assessment as a PMR is reasonable since we have some experience with the reference compound (Neupogen) and we do not expect QT liability to be high. In addition, no safety issues were identified during the review of the BLA submission that would jeopardize the safety of study participants.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Characterize the arrhythmic potential of Neutroval

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

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

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

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

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical trial evaluating the potential for Neutroval to prolong the QT interval

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☒ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

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

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

_RCK_____
(signature line for BLAs)

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MONSURAT O AKINSANYA
08/29/2012

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 125294/tbo-filgrastim

PMR Description: 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. Sicor should provide a listing of the clinical trials in which this assessment will be conducted.

PMR Schedule Milestones:

Final protocol Submission Date:	08/2013
Study Completion Date:	08/2014
Final Report Submission Date:	10/2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Immunogenicity related adverse events, such as extended neutropenia or loss of efficacy were not observed in the [INSERT NAME] trial. In the absence of safety or loss-of-efficacy signals that could be attributed to anti-drug antibodies it is acceptable to address the lack of immunogenicity data post-marketing. However it is critical that this data be obtained to more fully understand the safety profile of the drug. In addition these assays should be available in the post-marketing environment to allow for the rapid evaluation of serum samples from patients with adverse events that might be attributable to the presence of anti-drug antibodies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The Sponsor has banked samples for the [INSERT NAME] clinical trial. Once they have suitable assays they will analyzed patient serum samples for the presence of binding and neutralizing antibodies to [INSERT NAME] and assess the cross-reactivity of those antibodies to native human GCSF. These data will be published in the immunogenicity section of the product label to inform patients of the immunogenicity risk.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

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

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

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

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be laboratory analysis of existing samples.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☒ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☒ Other
Immunogenicity study as a marker of safety

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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/s/

MONSURAT O AKINSANYA
08/29/2012

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 125294/tbo-filgrastim

PMR Description: 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 PMR2 in at least 426 patients enrolled/to be enrolled in one or more clinical trials, as a substudy.

PMR Schedule Milestones:

Final protocol Submission Date:	08/2013
Study Completion Date:	08/2014
Final Report Submission Date:	10/2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Immunogenicity related adverse events, such as extended neutropenia or loss of efficacy were not observed in the [INSERT NAME] trial. In the absence of safety or loss-of-efficacy signals that could be attributed to anti-drug antibodies it is acceptable to address the lack of immunogenicity data post-marketing. However it is critical that this data be obtained to more fully understand the safety profile of the drug. In addition these assays should be available in the post-marketing environment to allow for the rapid evaluation of serum samples from patients with adverse events that might be attributable to the presence of anti-drug antibodies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The Sponsor has banked samples for the [INSERT NAME] clinical trial. Once they have suitable assays they will analyzed patient serum samples for the presence of binding and neutralizing antibodies to [INSERT NAME] and assess the cross-reactivity of those antibodies to native human GCSF. These data will be published in the immunogenicity section of the product label to inform patients of the immunogenicity risk.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

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

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

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

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be laboratory analysis of existing samples.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☒ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☒ Other
Immunogenicity study as a marker of safety

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

_____RCK_____
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/s/

MONSURAT O AKINSANYA
08/29/2012

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 125294/tbo-filgrastim

PMR Description: 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-Neutroval antibodies that are also cross-reactive with and neutralize the bioactivity of native human granulocyte colony stimulating factor (G-CSF).

PMR Schedule Milestones:

Final protocol Submission Date:	09/2012
Study Completion Date:	03/2013
Final Report Submission Date:	05/2013

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Immunogenicity related adverse events, such as extended neutropenia or loss of efficacy were not observed in the [INSERT NAME] trial. In the absence of safety or loss-of-efficacy signals that could be attributed to anti-drug antibodies it is acceptable to address the lack of immunogenicity data post-marketing. However it is critical that this data be obtained to more fully understand the safety profile of the drug. In addition these assays should be available in the post-marketing environment to allow for the rapid evaluation of serum samples from patients with adverse events that might be attributable to the presence of anti-drug antibodies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The Sponsor has banked samples from the [INSERT NAME] clinical trial. Once they have suitable assays they will analyzed patient serum samples for the presence of binding and neutralizing antibodies to [INSERT NAME] and assess the cross-reactivity of those antibodies to native human GCSF. These data will be published in the immunogenicity section of the product label to inform patients of the immunogenicity risk.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

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

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

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

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be laboratory analysis of existing samples.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☒ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☒ Other
Immunogenicity study as a marker of safety

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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MONSURAT O AKINSANYA
08/29/2012

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 125294/tbo-filgrastim

PMR Description: 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-Neutroval antibodies that are also cross-reactive with native human granulocyte colony stimulating factor (G-CSF).

PMR Schedule Milestones:

Final protocol Submission Date:	09/2012
Study Completion Date:	02/2013
Final Report Submission Date:	04/2013

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Immunogenicity related adverse events, such as extended neutropenia or loss of efficacy were not observed in the [INSERT NAME] trial. In the absence of safety or loss-of-efficacy signals that could be attributed to anti-drug antibodies it is acceptable to address the lack of immunogenicity data post-marketing. However it is critical that this data be obtained to more fully understand the safety profile of the drug. In addition these assays should be available in the post-marketing environment to allow for the rapid evaluation of serum samples from patients with adverse events that might be attributable to the presence of anti-drug antibodies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The Sponsor has banked samples for the [INSERT NAME] clinical trial. Once they have suitable assays they will analyzed patient serum samples for the presence of binding and neutralizing antibodies to [INSERT NAME] and assess the cross-reactivity of those antibodies to native human GCSF. These data will be published in the immunogenicity section of the product label to inform patients of the immunogenicity risk.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

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

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

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

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be laboratory analysis of existing samples.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☒ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☒ Other
Immunogenicity study as a marker of safety

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

___RCK_____
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MONSURAT O AKINSANYA
08/29/2012

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 125294/tbo-filgrastim

PMR Description: Conduct a trial to evaluate the safety and efficacy of tbo-filgrastim in pediatric patients of age 1 month to 16 years. The trial will include approximately 50 patients in an open-label program, including sparse pharmacokinetic sampling of tbo-filgrastim in solid tumors without bone marrow involvement.

Age groups to be included in the trial:

Infants 1-24 months,

Children 2-12 years,

Adolescents 12-16 years

PMR Schedule Milestones:

Draft protocol submission	02/2013
Final protocol Submission Date:	06/2013
Trial Completion Date:	06/2016
Final Report Submission Date:	12/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

To satisfy PREA requirements.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the study is to evaluate the safety of tbo-filgrastim in the pediatric population. There is a small risk that the safety profile may be different in this population. The new safety information will be in a pediatric population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

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

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

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

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A PK-PD and safety trial in 50 patients of age 1 month to 16 years.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
PREA

Agreed upon:

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

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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MONSURAT O AKINSANYA
08/29/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 125294 /tbo-filgrastim
Product Name:

PMC Description: To characterize, using orthogonal methods, and monitor, throughout the dating period, sub-visible particulates (SVPs) in the range between (b) (4) and to propose an appropriate control strategy based on the risk to product quality, safety, and efficacy.

PMC Schedule Milestones:		
	Study/Trial Completion:	03/2013
	Final Report Submission:	03/2013
	Other: Assay Development Findings	03/2013

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- X Theoretical concern
- ☐ Other

The sponsor committed to testing for the presence of subvisible particles in the drug product (DP) and they propose to set specifications after 12 batches of DP have been produced. However, the sponsor should perform a risk assessment on the necessity of continuing to monitor this potential product quality attribute. This is not an approvability issue because the sponsor has committed to testing for subvisible particles in the DP.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this PMC is for Teva to provide a risk assessment on the necessity for continuing to monitor subvisible particles in the range between (b) (4).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

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

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

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

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor has agreed to evaluate and provide a risk assessment on sub-visible particulates (SVPs) and their effects on the product safety, efficacy, and quality. Specifically, the sponsor will examine, orthogonal methods to study SVPs and to characterize the SVPs for the type and amount of aggregates, compare results obtained from the entire size range using the light obsuration method (i.e. the USP<788> test result together with the results obtained for the particulates between (b) (4) and an orthogonal technique. The sponsor may be able to use the USP <788> test in lieu of SVPs testing only if strong correlations could be made.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

X Does the study/clinical trial meet criteria for PMRs or PMCs?
X Are the objectives clear from the description of the PMR/PMC?
X Has the applicant adequately justified the choice of schedule milestone dates?
X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

_____RCK_____
(signature line for BLAs)

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/s/

MONSURAT O AKINSANYA
08/29/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	125294/tbo-filgrastim
Product Name:	
PMC Description:	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 Schedule Milestones:	Final Report Submission:	03/2013
	Other: Assay Specification	03/2013

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   X Theoretical concern
   ☐ Other

   The peptide mapping assay can be a quantitative assay which measures more than identity. This is not an approvability issue because Teva is currently using the peptide mapping assay as an identity test. The method has been validated for this purpose.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   The peptide map is currently used as an identity test. However, when appropriately analyzed, the peptide map data also provides a measure of the purity of the drug substance (DS) and drug product (DP). Therefore, the goal is to develop and validate the current peptide map method to be quantitative and to include quantitative acceptance criteria for peak areas, relative peak heights, and new peaks. We also recommend, when validating the assay for purity that the acceptance criteria should be based on more than one lot of DS and DP.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

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

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

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

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor agreed to validate the peptide map method as a quantitative assay for purity. The sponsor will set acceptance criteria for peak, areas, relative peak heights, and new peaks.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

X Does the study/clinical trial meet criteria for PMRs or PMCs?
X Are the objectives clear from the description of the PMR/PMC?
X Has the applicant adequately justified the choice of schedule milestone dates?
X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

_____RCK_____
(signature line for BLAs)

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/s/

MONSURAT O AKINSANYA
08/29/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 125294/tbo-filgrastim
Product Name:

PMC Description: To conduct a quantitative (ppb and ppm) leachables study and risk assessment of leachates into the drug product and/or (b) (4) in the final container closure system using methods that are suitably validated for its intended purpose.

PMC Schedule Milestones:		
	Final Protocol Submission:	10/2012
	Study Completion:	02/2013
	Final Report Submission:	06/2013

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- X Theoretical concern
- ☐ Other

The sponsor has performed extractable/leachable studies on the stopper alone. The syringe can also contribute to leachates into the final drug product over time. This is not an approvability issue because there is a low risk to product quality.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The sponsor provided only extractable/leachable data for the (b) (4) used in the container closure system of the drug product (DP). The sponsor did not provide extractable/leachable data on the (b) (4) in the presence of the DP or (b) (4). Because the presence of leachates in the DP may act as an adjuvant to product degradation, the sponsor should assess this risk to product quality. Therefore, the goal of this study is to obtain data on the types of leachables from the (b) (4) container closure system.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

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

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

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

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor has agreed to test for leachables for the DP in the final container closure system to the end-of-shelf-life, in the presence of the DP and [redacted] (b) (4) alone, and provide an evaluation of the risk to product quality.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

X Does the study/clinical trial meet criteria for PMRs or PMCs?
X Are the objectives clear from the description of the PMR/PMC?
X Has the applicant adequately justified the choice of schedule milestone dates?
X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

_____RCK_____
(signature line for BLAs)

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/s/

MONSURAT O AKINSANYA
08/29/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 125294/tbo-filgrastim
Product Name:

PMC Description: To formulate drug product, at laboratory scale, using polysorbate 80 (b) (4) and evaluate the effects of the polysorbate 80 on product quality over time.

PMC Schedule Milestones:		
	Final Protocol Submission:	12/2012
	Study/Trial Completion:	03/2016
	Final Report Submission:	05/2016
	Other: Assay Specification	05/2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- X Theoretical concern
- ☐ Other

The sponsor did not provide data to support the upper limit specification for polysorbate 80, which is a critical raw material,. This is not an approvability issue because the sponsor has been able to produce batches of the drug product (DP) which are within release specifications and within historical trends for G-CSF (b) (4) variants.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The sponsor revised the release and retest specification for the polysorbate 80 to (b) (4) However, long-term product quality data for the DP formulated with polysorbate 80 (b) (4) were not provided. Therefore, the goal of the study is to obtain data to support the use of polysorbate 80 at the current specification or to set new specification based on the data.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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

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

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

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

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

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

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor agreed to manufacture a laboratory scale product using polysorbate 80 (b) (4) and provide long-term product quality data.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

X Does the study/clinical trial meet criteria for PMRs or PMCs?
X Are the objectives clear from the description of the PMR/PMC?
X Has the applicant adequately justified the choice of schedule milestone dates?
X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

____RCK_____
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/s/

MONSURAT O AKINSANYA
08/29/2012

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Tel. 301-796-4242

FINAL LABEL AND LABELING REVIEW

Date: August 29, 2012

Reviewer: Kimberly Rains, Pharm.D.
Office of Biotechnology Products

Through: Jee Chung, Ph.D.
Division of Therapeutic Proteins

Amy Rosenberg, MD
Division Director
Division of Therapeutic Proteins

Application: BLA 125294

Product: Tbo-filgrastim

Applicant: Sicor Biotech UAB

Submission Date(s): November 30, 2009, June 28, 2012, August 9, 2012, August 27, 2012

EXECUTIVE SUMMARY

The carton and container labels for Tbo-filgratim were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57 and 21 CFR 200.100. USPC Official 8/1/12-11/30/12, USP 35/NF 30. Labeling deficiencies were identified, mitigated and resolved. Please see comments in the conclusions section. Each submission of labels has been evaluated. The labels submitted on August 27, 2012 (sequence 0045) are displayed in the review and are acceptable with the addition of the issued U.S. License No. 1803 in the final printed label submission requested in the approval letter.

Background:

STN 125294 is an original Biologic License Application (BLA). The product is a neutrophil growth factor indicated for the reduction in the duration of severe neutropenia with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated

with a clinically significant incidence of febrile neutropenia. The product is supplied as a solution in 300 mcg/0.5 mL and 480 mcg/0.8 mL in prefilled syringes. The application received a Complete Response on September 29, 2010. On June 28, 2012, August 9, 2012 and August 27, 2012, the applicant resubmitted revised carton and container labels to support the application. The agency will grant approval with a non-proprietary name (proper name) only.

Labels Reviewed:

<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea680c0768e> Sequences: 0000,0039,0044,0045

Tbo-filgrastim Container label

Syringe Label: 300 mcg/0.5 mL and 480 mcg/0.8 mL
Blister Label: 300 mcg/0.5 mL and 480 mcg/0.8 mL

Tbo-filgrastim Carton label (each strength has a single syringe, five count, and 10 count configuration).

Without Safety Device: 300 mcg/0.5 mL and 480 mcg/0.8 mL
Device included Carton: 300 mcg/0.5 mL and 480 mcg/0.8 mL

Tbo-filgrastim Prescribing Information

Review

Syringe Label
Final Submission
August 28, 2012

(b) (4)

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/s/

KIMBERLY M RAINS
08/29/2012

JEE Y CHUNG
08/29/2012

MARY K W LEE
08/29/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	August 08, 2012
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling (Patient Package Insert)
Drug Name (established name):	Neutroval (b) (4))
Dosage Form and Route:	Injection for subcutaneous use
Application Type/Number/Supplement:	BLA 125294
Applicant:	Sicor Biotech UAB, Lithuania c/o Teva Global Branded Pharmaceutical Industries, Ltd.

1 INTRODUCTION

On February 29, 2012 Teva Pharmaceuticals USA submitted a Complete Response (CR) in response to Complete Response (CR) letter issued by the Division of Hematology Products (DHP) on September 29, 2010, requesting additional information for the approval of a new Biologic License Application (BLA) 125294 for Neutroval (b) (4) Injection for subcutaneous use. The Applicant's proposed indication is for the reduction in 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.

On March 27, 2012, the Division of Hematology Products (DHP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for Neutroval (b) (4)) Injection for subcutaneous use. DHP notified DMPP on August 6, 2012 that the Applicant's name has changed to Sicor Biotech UAB, with Teva Global Branded Pharmaceutical Products R&D serving as the US Agent.

This review is written in response to a request by the Division of Hematology Products (DHP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for Neutroval (b) (4) Injection for subcutaneous use.

2 MATERIAL REVIEWED

- Draft Neutroval ((b) (4)) Injection for subcutaneous use Patient Package Insert (PPI) received on February 29, 2012 and received by DMPP on August, 2 2012.
- Draft Neutroval (b) (4) Injection for subcutaneous use received February 29, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on August 2, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the Package Insert (PI) to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

LATONIA M FORD
08/08/2012

SHARON R MILLS
08/08/2012

LASHAWN M GRIFFITHS
08/08/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 7, 2012

To: Lara Akinsanya, Regulatory Health Project Manager, DHP

From: Adora Ndu, Regulatory Review Officer, DCDP

Subject: BLA 125294
DCDP comments for Neutroval
Patient Information

On March 28, 2012, DCDP received a consult request from DHP to review the proposed Patient Information for Neutroval.

DCDP has reviewed the proposed labeling using the following version of the proposed label received from DHP on August 2, 2012:

- 125294_Neutroval Patient Information.doc

After review of the proposed labeling, DCDP offers the following comments. If you have any questions on the patient labeling, please contact Adora Ndu at 301-796-5114 or adora.ndu@fda.hhs.gov.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ADORA NDU
08/07/2012

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Therapeutic Proteins
Rockville, MD 20852
Tel. 301-827-1709

Memorandum

Date: 08/02/2012

To: File: BLA 125,294

From: Joao Pedras -Vasconcelos, Ph.D.
Susan L. Kirshner, Ph.D.
Associate Chief, Laboratory of Immunology
Division of Therapeutic Proteins
Office of Biotech Products
CDER/FDA

Through: Susan Kirshner, Acting Branch Chief, DTP

Through: Kathy Lee, Acting Branch Chief, DTP

Subject: Immunogenicity review for BLA 125,264

Indication: Treatment of severe neutropenia developed by cancer patients undergoing myelosuppressive chemotherapy.

Sponsor: Teva, validations carried out by (b) (4) except for the BIAcore assay, which was tested at the (b) (4)

Immunogenicity memo

In the original CR letter the sponsor was told to assess the induction of anti-GCSF antibodies in serum from treated patients using validated assays. However, for reasons described in the risk assessment below updated immunogenicity information was not required to be provided in response to the CR. The Sponsor was asked to:

a. establish validated screening, confirmatory and neutralizing assays to assess the immunogenicity of Tbo-filgrastim in patient samples.

b. establish validated assays to assess the ability of anti- Tbo-filgrastim antibodies to cross-react with native human GCSF.

d. analyze patient serum samples from the Neutroval phase 3 studies for the presence of anti-Tbo-filgrastim and anti-native human GCSF antibodies using validated screening, confirmatory and neutralizing assays.

In response to the immunogenicity requests the Sponsor committed to provide:

-Date of submission of the validation protocol: August 15th 2012

-Final report submission date: December 15th 2012

This was found acceptable based on the assessment described below, primarily because safety database for XM02 does not indicate that there were patients who lost efficacy or developed neutropenia during the course of the trial.

RISK ASSESSMENT:
The product, XM02, is a bacterial (*E. coli*) derived non-glycosylated 18.85 kDa human recombinant Granulocyte Colony Stimulating Factor (G-CSF) protein with an extra methionine residue at the N-terminus. Endogenous G-CSF is involved in the control of cell cycle, proliferation, survival and maturation of neutrophils. The role of these cells is critical during infections and bone marrow aplasia.

The proposed indication for XM02 is "reduction in the duration of severe neutropenia in patients with non-myeloid malignancies" undergoing myelosuppressive chemotherapy "associated with a clinically significant incidence of febrile neutropenia" (from the label). (b) (4)

Several factors can affect the immunogenicity of protein therapeutics: lack of glycosylation (Li H and d'Anjou M, Curr. Op. Biotech., 2009, 20:1-7), protein degradation variants (oxidized and deamidated forms) and protein aggregation (Rosenberg AS, AAPS J, 2006, 8: E501-507), therefore it is important to determine the presence of binding and neutralizing antibodies to a new recombinant protein through the development of sensitive assays.

The Sponsor has not validated a sensitive and specific screening assay for the evaluation of binding antibodies against XM02. Recalculation of the cut point value for the direct ELISA assay did not include a statistically significant sample number for the indicated patient populations, namely breast cancer, lung cancer and non-Hodging lymphoma. Therefore, the estimated percentage of patients positive for binding antibodies against the product is questionable. Similarly the Sponsor does not have adequate confirmatory and neutralizing assays.

The safety database for XM02 does not indicate that there were patients who lost efficacy or developed neutropenia during the course of the trial. Furthermore, preliminary immunogenicity data from the inadequate assays indicates a low immunogenicity rate, ~2.4%. The original assays would have detected robust anti-drug antibody responses, but it were not validated for the detection of low anti-drug antibody responses. Since the risk to safety and efficacy are low we find that it is acceptable to allow Teva to correct their

immunogenicity assays and then re-test banked serum samples as a post-marketing requirement.

Below are Immunogenicity CR comments from Aug 2010, along with sponsor response.

8. Please submit a description of your plan for development of a validated screening assay for the assessment of an anti-product antibody response to Tbo-filgrastim. The validation of the assay should include the sensitivity and specificity for detection of anti-Neutroval antibodies that are also cross-reactive with native human granulocyte colony stimulating factor (G-CSF). In your response, provide the protocol for the requested clinical trial. In addition, provide information on the following milestones:
Date of submission of the validation protocol
Final report submission date
If you require clarification on the deficiencies of the current assay, we recommend that you submit a request for a type C meeting with FDA.

Sponsor response
The Sponsor proposed to develop and validate screening assays. One option is to develop a bridging immunoassay using MesoScale Discovery (MSD) technology platform as a screening assay for assessing anti-Neutroval antibody responses. The assay consists of biotinylated Tbo-filgrastim as capture agent immobilized onto the streptavidin coated plate, and ruthenylated Tbo-filgrastim as detection agent. When anti- Tbo-filgrastim antibodies are present, an immune complex can be formed in the assay, which then can be detected by light emission. Alternatively, a homogeneous bridging ELISA will be developed for screening of anti- Tbo-filgrastim antibody responses. The method will be based on the formation of sandwich immune complex of anti- Tbo-filgrastim antibody with biotinylated Tbo-filgrastim and digoxigenin (DIG)- conjugated Tbo-filgrastim in solution phase. The complex then can be detected in an avidin-coated plate with labeled anti-DIG antibody. The assay development and validation will be conducted by following *FDA draft Guidance for Industry – Assay Development for Immunogenicity Testing of Therapeutic Proteins* (December 2009) and the Mire Sluis et al. white paper. The assay parameters will include sensitivity, precision, accuracy, interference and minimal required sample dilution, drug tolerance, specificity, robustness and sample stability.

- *Date of submission of the validation protocol will be August 15th 2012*
- *Final report submission date will be December 15th 2012*

Comment to the file:
In response to our request the Sponsor commits to providing validation protocol and final report by specific dates. This is acceptable for reasons noted above.

9. Please submit a description of your plan for development of a validated assay for confirmation of anti-product antibodies identified by the screening assay. The validation of the assay should include the sensitivity and specificity for detection of anti-Neutrova1 antibodies that are also cross-reactive with native human granulocyte colony

stimulating factor (G-CSF). In your response, provide the protocol for the requested clinical trial. In addition, provide information on the following milestones:
−Date of submission of the validation protocol
-Final report submission date
If you require clarification on the deficiencies of the current assay, we recommend that you submit a request for a type C meeting with FDA.

"In addition to the response above to Question 8, the validation of the confirmatory assay will include confirmatory cut point determination. The detection of anti- Tbo-filgrastim antibodies that are also cross-reactive with native human G-CSF will also be validated by measuring the competition capability from recombinant human G-CSF. A glycosylated human G-CSF protein produced from Chinese Hamster Ovarian cells (CHO cells) will be used as competitor.
The screened positive samples will be further analyzed in the confirmatory assay based on the competition with unlabeled drug:

-Neutroval as a competitor in the assay to confirm the antibody response specific to the product Neutroval;

-G-CSF protein as a competitor in the assay to confirm that anti-Neutroval antibodies are cross-reactive with G-CSF.
The confirmed positive samples will be measured in the titer assay and further characterized in the neutralizing antibody assay (please refer to response to Question 10 below)."
- *Date of submission of the validation protocol: August 15th 2012*
- *Final report submission date: December 15th 2012*

Comment to the file:
In response to our request the Sponsor commits to providing validation protocol and final report by specific dates. This is acceptable for reasons noted above.

10. Please submit a description of your plan for development of a validated assay for identification of anti-product antibodies that neutralize the bioactivity of Neutroval. The validation of the assay should include the sensitivity and specificity for detection of anti- Neutrova1 antibodies that are also cross-reactive with and neutralize the bioactivity of native human granulocyte colony stimulating factor (G-CSF). In your response, provide the protocol for the requested clinical trial. In addition, provide information on the following milestones:

-Date of submission of the validation protocol

-Final report submission date

If you require clarification on the deficiencies of the current assay, we recommend that you submit a request for a type C meeting with FDA.

Sponsor Response:
Teva proposes to develop and validate a cell-based assay for measuring neutralizing antibodies against Tbo-filgrastim using NFS-60 cell lines by following FDA draft *Guidance for Industry - Assay Development for Immunogenicity Testing of Therapeutic Proteins*

(December 2009). "The inhibition of NFS-60 cell proliferation is the read out. The assay parameters to be assessed include matrix interference, sensitivity, specificity, precision and accuracy." Teva will also determine whether anti- Tbo-filgrastim antibodies neutralize the bioactivity of G-CSF by performing the assay in the presence of glycosylated human G-CSF produced from CHO cells. "All confirmed antibody positive samples will be further characterized in the following cell-based neutralizing antibody assays in the presence of either Neutroval (Nab assay I) or G-CSF (Nab assay II):

-Nab-assay I: identification of neutralizing anti-Neutroval antibodies

-Nab-assay II: anti-Neutroval antibodies that are cross-reactive and neutralize the bioactivity of human G-CSF."

-Date of submission of the validation protocol will be on August 15th 2012

-Final report submission date: December 15th 2012

Comment to the file:
In response to our request the Sponsor commits to providing validation protocol and final report by specific dates. This is acceptable for reasons noted above.

11. Provide a plan for assessing for the presence, persistence, and effects of anti-Neutroval and anti-native human GCSF binding and neutralizing antibodies using validated assays in at least 500 patients enrolled or to be enrolled in one or more clinical trials. You should provide a listing of the clinical trials in which this assessment will be conducted. In your plan, you should provide information on the following milestones:

-Date of submission of the protocol for clinical immunogenicity assessment

-Date of completion of the study

-Final report submission date

Sponsor response:
Teva "conducted three clinical trials – XM-02-02-INT, XM02-03-INT and XM02-04-INT, from which there are a total of 426 enrolled patients making samples available for immunogenicity assessment. Serum samples collected from these subjects had been used for analysis using previous assays. However, second aliquots for each time point from these subjects' samples have been appropriately stored and are available for this analysis. Teva plans to analyze these samples for anti-Neutroval antibodies when the validated assays are available and agreeable by the FDA. These samples were collected during the clinical development program between December, 2004 and March, 2006. Detail on the studies and the storage conditions are provided in Table 1.
Justification to use these samples:
1. Selected patients in these studies were treated with XM02 (Tbo-filgrastim).
2. Serum aliquots have sufficient volume (>500 μl) to perform the planned new immunogenicity cascade mentioned below.

3. The serum sample aliquots are the back up samples. They were collected and stored for the purpose of additional analyses in response to questions if coming *a posteriori* from Health Authorities with respect to the assay.
4. Serum samples have been stored and consistently monitored at -80°C under GLP conditions, and have not undergone any freezing/thawing cycles."

Samples that screen and confirm positive will be titered and tested in the neutralizing antibody assays "to assess the neutralizing activities of the anti-product antibodies and their cross reactivity with and neutralization activities of the endogenous G-CSF."

Table 1: Listing of clinical trials to be re-analyzed by proposed immunogenicity cascade

Table 1: Listing of clinical trials to be re-analyzed by proposed immunogenicity cascade

Clinical Study	**XM02-02-INT**	**XM02-03-INT**	**XM02-04-INT**
Study date	Dec 2004 - Sep 2005	Dec 2004 - Dec 2005	Dec 2004 - March 2006
Patient Population	Breast Cancer	small cell or non-small cell lung cancer	Non-Hodgkin-Lymphoma
CTX	Doxorubicin (60mg/m^2) Docetaxel (75 mg/m^2)	Platinum-based chemotherapy	Cyclophosphamide-hydroxydaunomycin-oncovin-prednisolon (CHOP)

Clinical Study	**XM02-02-INT**	**XM02-03-INT**	**XM02-04-INT**
Sampling time points	Screen, C1D1, C2D1, C3D1, C4D1, D85, D180	Screen, C1D1, C2D1, C3D1, C4D1, C4D2, C5D1, C6D1, D127, D169, D180, D210	Screen, C1D1, C2D1, C3D1, C4D1, C5D1, C6D1, D127, D180
XM02 (Neutroval) treated patients (total)	**N=140**	**N=160**	**N=60**
all sampling time points available:	N=106	N=85	N=50
at least 2 sampling time points available:	N=31	N=74	N=9
Placebo/XM02 treated patients*	**N=72 total**	n.a.	n.a.
all sampling time points available:	N=53	n.a.	n.a.
at least 2 sampling time points available:	N=18	n.a.	n.a.
Serum volume/aliquot	>500µl	>500µl	>500µl
Sample storage conditions	GLP-storage at -80°C	GLP-storage at -80°C	GLP-storage at -80°C
Freeze and thaw cycle	0	0	0
*Placebo treated in the first CTX-cycle and XM02 in the following CTX-cycles			

i. Date of submission of the protocol for clinical immunogenicity assessment will be December 15th 2012
ii. Date of completion of the study will be June 01st 2013
iii. Final report submission date September 15th 2013

Comment to the file:
The Sponsor provided an update on the samples available for retesting. Based on the initial immunogenicity data from the clinical trial the incidence is expected to be at least 2.4%. Therefore data from 426 patients should be adequate to assess immunogenicity. This is acceptable for reasons noted above.

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/s/

JOAO A PEDRAS VASCONCEL
08/15/2012

EMANUELA LACANA on behalf of SUSAN L KIRSHNER
08/17/2012

MARY K W LEE
08/17/2012

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:
The review team should email this form to the email account "CDER-TB-EER" to submit:

1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing[1] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: August 30, 2012

Applicant Name: SICOR Biotech UAB
U.S. License #: 1803
STN(s): 125294/0/32
Product(s): NEUTROVAL™ ([redacted (b) (4)])

Short summary of application: BLA resubmission – Final TB-EER request

FACILITY INFORMATION

Manufacturing Location:
Firm Name: SICOR Biotech UAB
Address: Moletu, Pl.5, Vilinus, Lithuania.
FEI: 3008110727
Short summary of manufacturing activities performed: Drug substance manufacturing.

Inspected by CDER-DMPQ from 5/31/10-6/4/10 and classified NAI. This inspection was a comprehensive PLI and CGMP inspection for [redacted (b) (4)] operations. This site was found acceptable for these operations.

Manufacturing Location:
Firm Name: TEVA Pharmaceutical Industries, Ltd,
Address: 64 Hashikma St., Industrial Zone, Kfar Saba, Israel 44102

[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

FEI: 3002721084
Short summary of manufacturing activities performed: Drug product manufacturing

Inspected by IOG from 8/23/10-8/26/10 and classified VAI. This CGMP inspection covered sterile manufacturing operations and found the SVS profile updated and acceptable.

OVERALL RECOMMENDATION:

There are no pending or ongoing compliance actions that prevent approval of this BLA.

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/s/

MAHESH R RAMANADHAM
07/25/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	July 23, 2012
Reviewer:	Sarah K. Vee, PharmD, Safety Evaluator **Division of Medication Prevention and Analysis**
Team Leader	Yelena Maslov, PharmD, Acting Team Leader **Division of Medication Prevention and Analysis**
Division Director	Carol A. Holquist, RPh **Division of Medication Prevention and Analysis**
Drug Name and Strengths:	Neutroval (XM-02) Injection 300 mcg/0.5 mL, 480 mcg/0.8 mL prefilled syringes
Application Type/Number:	BLA 125294
Applicant/sponsor:	Teva
OSE RCM #:	2012-917

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton, blister, and insert labeling for Neutroval, BLA 125294, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Neutroval label and labeling was reviewed under OSE Review #2009-2469, dated August 16, 2010. The application received a Complete Response (CR) on September 29, 2010. On April 17, 2012, the Applicant resubmitted Neutroval for review and stated that the product characteristics have not changed from the original BLA submission. [redacted (b) (4)]. The recommendations from the previous review were communicated to the Applicant on June 13, 2012. On July 2, 2012, the Applicant submitted the revised label and labeling for review.

The proper name for this product is pending at this time. The discussion regarding the proper name nomenclature is still ongoing, and thus the active ingredient will be referenced as XM-02 throughout this review.

1.2 PRODUCT INFORMATION

The following product information is provided in the package insert submitted on July 2, 2012.

- Active Ingredient: XM-02
- Indication of Use: reduction in 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
- Route of Administration: subcutaneous injection
- Dosage Form: Solution for injection
- Strength: 300 mcg/0.5 mL, 480 mcg/0.8 mL
- Dose and Frequency: 5 mcg/kg/day 1st dose should be administered no earlier than 24 hours following myelosuppressive chemotherapy [redacted (b) (4)] Daily dosing should continue [redacted (b) (4)] until neutrophil count has recovered to the normal range.
- How Supplied: 300 mcg/0.5 mL, 480 mcg/0.8 mL single use prefilled syringe
  - Packs of 1, 5, and 10 without a safety needle guard
  - Packs of 1, 5, and 10 with a safety needle guard in trays
  - Packs of 1, 5, and 10 with a safety needle guard in blisters
- Storage: Refrigerated at 36° to 46°F (2° to 8°C), may be stored at room temperature [redacted (b) (4)]

- Container and Closure Systems: Primary: Type I glass syringe barrel, (b) (4) rubber stopper, steel needle. Secondary: cardboard cartons (1, 5, or 10 syringes)

2 METHODS AND MATERIALS REVIEWED

We reviewed the Neutroval labels, carton, blister, and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted July 2, 2012 (Appendix A)
- Carton Labeling submitted July 2, 2012 (Appendix B)
- Blister Pack Labeling submitted July 2, 2012 (Appendix C)
- Insert Labeling submitted July 2, 2012 (No image)

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the label and labeling in OSE Review# 2009-2469. The comments were sent the Applicant on June 13, 2012.

3 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the labels and labeling to promote the safe use of the product.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA:

A. All Syringe Labels, Carton Labeling, Blister Pack Labeling:

1. The grey color font used for the 480 mcg strength is too similar to the background information printed in black font surrounding the strength thereby giving the strength statement a less prominent appearance on the label. We recommend that you change the color of the strength for the 480 mcg, so that the strength stands out among the text and does not overlap with other colors on the syringe label, carton labeling, and blister pack labeling.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

B. Carton Labeling (300 mcg/0.5 mL and 480 mcg/0.8 mL)

1. The boxed strength statement on the 480 mcg 5 pack pre-filled syringes with safety needle guard reads (b) (4) Please correct this statement so that it reads 480 mcg.
2. Add the word "only" to the statement "For subcutaneous use" and increase the font size of the statement so that it stands out among the surrounding text. Thus, the route of administration should read:

   "For Subcutaneous Use Only"
3. Revise the boxed strength statement to include the volume since this is a solution, thus the strength should be expressed as mcg/mL (i.e. 300 mcg/0.5 mL and 480 mcg/0.8 mL)
4. Relocate the statement "Discard Unused Portion" to appear immediately below the "Single-use pre-filled syringe" statement.
5. Decrease the font size of the net quantity so that it appears less prominent than the statement of strength to help prevent confusion between the numeric value of the net quantity and the strength.

C. Blister Pack Labeling (300 mcg/0.5 mL and 480 mcg/0.8 mL)

1. See comments B. 2 through B.4 and revise the blister pack labeling accordingly

D. Insert Labeling

1. Section 2.3 Instructions for Use of the Safety Needle Guard Device: We recommend that you provide detailed, color illustration for each step of the instructions for use to ensure safe and proper use of the device.

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SARAH K VEE
07/24/2012

YELENA L MASLOV
07/24/2012

KELLIE A TAYLOR
07/24/2012

CAROL A HOLQUIST
07/24/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: July 18, 2012

From: LCDR Alan Stevens, Infusion Pump Team Leader, WO66, RM 2561
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Lara Akinsanya, Regulatory Project Manager, WO 22 RM2313
Division of Hematology Products, OHOP, CDER

Subject: CDRH Consult,GEN1200494, BAL 125294, (b) (4)

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding BLA 125294. The device constituent of this combination product consists of a (b) (4) .

This memo is limited to providing a review of the sponsor's additional information submitted in response to Mr. William Burdick's prior review.

2. Documents Reviewed

BLA 125294, Sequence #0036, Dated June 21, 2012

3. CDRH Review and Comments

Prior Deficiency

Please re-test for dose accuracy determination performed on filled syringes to ensure that the appropriate volume of the drug is expelled at every graduation mark. Please test according to (b) (4) *This test specifies both high and low tolerances for each graduation mark on the syringe.*

Response, June 21, 2012

The sponsor provided additional analysis to support the use of the +/-10% accuracy specification. The sponsor also provided additional testing using the clinical practice as the test method.

The results were compared to the (b) (4) syringe specification and the (b) (4) specification.

The test results met both sets of criteria.

Table 3: Neutroval dose accuracy retest results in %

Graduation:	0.8mL	0.6mL	0.4mL	0.3mL
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
Average				
Highest				
Lowest				
RSD				

These results are acceptable.

4. CDRH Recommendation

Based on our review, CDRH does not have any concerns regarding the device constituent of this Combination Product.

If you have any questions, please contact LCDR Alan Stevens at 301-796-6294.

Sincerely,

_____
LCDR Alan M. Stevens
Infusion Pump Team Leader

Concurred By:

_____
Dr. Jacqueline Ryan
Combination Products Team Leader

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/s/

MONSURAT O AKINSANYA
07/23/2012

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 125294

Application Type: New BLA – Resubmission to CR

Name of Drug: Neutroval (b) (4) Injection

Applicant: Teva Pharmaceuticals USA

Submission Date: February 29, 2012

Receipt Date: February 29, 2012

1.0 Regulatory History and Applicant's Main Proposals

This submission contains a response to the complete response (CR) letter that was issued on September 29, 2010. In this submission, Teva Pharmaceuticals is addressing all deficiencies and information requests identified by the Agency in the Complete Response letter. PDUFA Goal Date is **August 30, 2012**.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by June 22, 2012. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. HL is one-half page or less than one-half page (the HL Boxed Warning does not count against the one-half page requirement). If longer than one-half page:

- Filing Period (Regulatory Project Manager Physicians' Labeling Rule (PLR) Format Review): RPM has notified the Cross-Discipline Team Leader (CDTL).
- End-of Cycle Period: A waiver has been or will be granted by the review division.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")

• **Warnings and Precautions**	Not required by regulation, but should be present**
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* See Recent Major Changes section below.
** Virtually all product labeling should include at least one Warning and Precaution.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).
Comment:

HIGHLIGHT DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.
Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."
Comment:

Product Title

YES 10. Product title in HL must be **bolded.**
Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.
Comment:

Boxed Warning

N/A 12. All text must be **bolded**.
Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").
Comment:

N/A

14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Should use sentence case for summary (combination of uppercase and lowercase letters typical in a sentence).

Comment:

Recent Major Changes (RMC)

NO 17. Other than these five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions, there are no other sections noted in RMC.

Comment: *This Section Only Applies To Changes Being Made To An Already Approved Pi.*

N/A 18. Must be listed in same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and if appropriate subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A

24. Each contraindication is bulleted when there is more than one contraindication.
Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**". Only includes a U.S. phone number.

Comment: *FDA website should not be in italics.*

YES **Patient Counseling Information Statement**

26. Must include one of the following **bolded** verbatim statements:

Product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

Product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *Revision Date is not In MM/YYYY Format.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *Subheading For 6.1 Does Not Match Subheading In FPI.*

Subheading For 6.3 Should Be Removed - not present in FPI.

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics

12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI at approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.1)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Should use sentence case (combination of uppercase and lowercase letters typical in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *The Type Of Patient Labeling (Patient Information) Was Not Included.*

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/s/

MONSURAT O AKINSANYA
06/05/2012

JANET K JAMISON
06/05/2012

Interdisciplinary Review Team for QT Studies Consultation: Protocol Review

BLA	125294
Generic Name	XM02
Sponsor	Teva Pharmaceuticals, Inc.
Indication	Reduction in 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.
Dosage Form	Subcutaneous (b) (4) administration
Drug Class	Device-biologic combination Recombinant methionyl human granulocyte colony stimulating factor
Therapeutic Dose	5 (b) (4) µg/kg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	NA
Application Submission Date	February 29, 2012
Review Classification	TQT study protocol
Date Consult Received	March 23 2012
Clinical Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

(b) (4)

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Pediatric and Maternal Health Staff Labeling Review

Date: May 14, 2012 **Date Consulted:** March 23, 2012

From: Jeanine Best, MSN, RN, PNP
Senior Clinical Analyst, Pediatric and Maternal Health Staff (PMHS)

Through: Hari, Cheryl Sachs, M.D.
Medical Team Leader, Pediatric Team

Lisa Mathis, MD
OND Associate Director, Pediatric and Maternal Health Staff (PMHS)

To: Division of Hematology Products

Drug: Neutroval (b) (4) injection for subcutaneous (b) (4) use, BLA 125294

Subject: Pediatric Use Labeling

Materials Reviewed:

- Sponsor proposed labeling
- PeRC Minutes

Consult Question: DBOP requests that The Pediatric and Maternal Health Staff (PMHS) – Pediatrics review and comment on the proposed Pregnancy Use labeling for Neutroval (b) (4)) injection for subcutaneous (b) (4) use.

INTRODUCTION

On February 29, 2012, TEVA Pharmaceuticals submitted a Complete Response Submission for Neutroval (b) (4)) injection for subcutaneous (b) (4) use, BLA 125294, addressing deficiencies and information requests outlined in the Agency's September 10, 2010, Complete Response Letter. The original Neutroval BLA was submitted November 30, 2009. Neutroval is proposed for the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer.

On March 23, 2012, the Division of Hematology Products (DHP) consulted the PMHS-Pediatrics to review the Pediatric Use subsection of the proposed Neutroval labeling.

BACKGROUND

Neutroval (b) (4)) injection for subcutaneous (b) (4) use

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. Colony-stimulating factors are proteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation. Neutroval was developed as a similar biological medicinal product to the innovator Neupogen; however, the biologic product was submitted under section 351(a) of the PHS Act; therefore, the Sponsor cannot rely on existing data from the Neupogen application. Of note, the same application has been submitted in Europe as a biosimilar to the European Medicine Agency's (EMA) approved filgrastim product

The Pediatric Research Equity Act (PREA) was triggered by this application because the Neutroval BLA was submitted under section 351(a) of the PHS Act as a new active ingredient, and not as a biosimilar to Neupogen. Pediatric studies have been conducted with Neupogen (filgrastim) and that product is labeled with data from the pediatric studies.[1]

TEVA Pharmaceuticals submitted a Partial Waiver, Deferral, and Pediatric Plan for Neutroval with their original BLA submission on November 30, 2009. The Partial Waiver/Deferral/Pediatric Plan for Neutroval was discussed at a Pediatric Review Committee Meeting (PeRC) on August 11, 2010 (see Appendix A for the PeRC August 11, 2010 minutes).

PROPOSED PEDIATRIC USE LABELING (dated February 29, 2012)

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- The safety and effectiveness of Neutroval have not been established in patients under 18 years of age (8.4)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of Neutroval in pediatric patients have not been established.

[1] See Current Approved Neupogen labeling, March 2, 2010

DISCUSSION and CONCLUSIONS

Pediatric Use Labeling

The Pediatric Use subsection should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted.

A pediatric use statement is not required in the Highlights of Prescribing Information section of Neutroval labeling as there is no specific pediatric use information to convey; studies have not been conducted in pediatric patients and no safety concerns exist regarding use of Neutroval in children. The Sponsor's proposed pediatric use statement in subsection 8.4 Pediatric Use is the appropriate regulatory statement (per 21 CFR 201.57 (c) (9) (iv) (F)) to use in Neutroval labeling as pediatric studies have not been conducted with this biological product.

PeRC

DHP does not have to return to PeRC to discuss the submitted Partial Waiver/Deferral/ Pediatric plan for Neutroval unless the Division's scientific thinking regarding pediatric studies with this biological product have changed since August 11, 2010.

PMHS PEDIATRIC USE LABELING RECOMMENDATIONS

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- Pediatric Use: Safety and effectiveness not established (8.4).

Reviewer Comment: This information is optional as there is no specific pediatric use information to convey in the Highlights of Prescribing section of labeling.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of Neutroval in pediatric patients have not been established.

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/s/

JEANINE A BEST
05/14/2012

HARI C SACHS
05/14/2012
I agree with these recommendations.

LISA L MATHIS
05/17/2012

C O N S U L T R E V I E W

Date: March 26, 2012

From: William M. Burdick, Biomedical Engineer/Physicist
ODE/DAGID, General Hospital Device Branch

To: Albert Deisseroth, MD, CDER/Div. of Hematology Products
WO22, RM2234

Subject: GEN 1200222: BLA 125294-Neotroval delivery system, sponsored by Teva Pharmaceuticals USA

Purpose

Cycle 2 review of documents contained in subject submission and advise whether if the sponsor has adequately addressed the CDRH issues listed in the CR letter issued September 29, 2010.

Assessment of Response to CDRH Deficiencies

The CDRH deficiencies conveyed to the sponsor in the September 29, 2010 Complete Response letter from the former Division of Biologic Oncology Products, CDER is provided below in bold typeface. The responses from Teva Pharmaceuticals USA (Teva) is shown in regular typeface, and the CDRH assessment of the responses is provided in bold italics.

(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 the (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 the syringe meets the specifications of the following guidance document and FDA Consensus Standards (most recent editions):

- (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) glass syringe with the needle pre-attached. 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. For example, (b) (4) However, your test protocols and results do not demonstrate that the bond strength between the syringe and needle has been assessed. Bonding of the needle to the syringe is a critical

mechanical property of your device. 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).

Teva cited the January 12, 2011 industry meeting in which Teva, CDER, and CDRH representatives were present. Teva also stated that they have been in close communication with (b) (4) and have been assured that all deficiencies have been addressed in the DMF Amendment submitted to FDA on September 12, 2011.

As a manufacturer of the combination product, Teva also stated that they have performed the required performance testing on the pre-filled syringes containing Neutroval drug product. Test results from the following analyses were presented in Module 3.2.P.2.4 Container Closure System, Appendix 11:

- Dead space test performed on filled syringes
- Needle bond strength test performed on empty syringes
- Needle bond tightness test performed on filled syringes to evaluate integrity of the bond is maintained while force is applied to expel the drug component
- Dose accuracy determination performed on filled syringes to ensure that appropriate volume of the drug is expelled at every graduation mark

CDRH Assessment of Response

The results were acceptable for three of the four analyses (Appendix 11) cited above:

- ***Dead space test performed on filled syringes***
- ***Needle bond strength test performed on empty syringes***
- ***Needle bond tightness test performed on filled syringes to evaluate integrity of the bond is maintained while force is applied to expel the drug component***

In determining dose accuracy at every graduation mark, Teva chose testing requirements from the USP standard. That test only specified that the minimum amount of fluid for each graduation mark must be satisfied. The actual test as outlined in Section 9 (Tolerance on graduated capacity) of FDA Consensus Standard ISO 7886-1, Sterile hypodermic needles for single use – Part 1: Syringes for manual use, specifies both high and low tolerances for each graduation mark. According to the results for the USP test, the results was acceptable for only one graduation mark (0.7 ml).

RECOMMENDATION

Teva should be requested to re-test for dose accuracy determination performed on filled syringes to ensure that the appropriate volume of the drug is expelled at every graduation mark. The deficiency can be stated as following:

Please re-test for dose accuracy determination performed on filled syringes to ensure that the appropriate volume of the drug is expelled at every graduation mark. Please test according to Section 9 (Tolerance on graduated capacity) of FDA Consensus Standard ISO 7886-1, Sterile hypodermic needles for single use – Part 1: Syringes for manual use; 1993/Corrigendum 1:1995 (2007 edition). This test specifies both high and low tolerances for each graduation mark on the syringe.

Sincerely,

Bill

William M. Burdick

Biomedical Engineer/Physicist
FDA/CDRH/ODE/DAGID/General Hospital
HFZ-480, Rm 340U
9200 Corporate Blvd.
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/s/

MONSURAT O AKINSANYA
05/31/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY ADDENDUM

DATE: September 15, 2010

TO: Danyal Chaudhry, Regulatory Project Manager
Robert Thomas Herndon, Medical Officer
Division of Biologic Oncology Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

BLA: 125294/0

APPLICANT: Teva Pharmaceuticals

DRUG: Neutroval (XM02)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: The reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer.

CONSULTATION REQUEST DATE: 2/3/2010

DIVISION ACTION GOAL DATE: 07/31/2010

PDUFA DATE: 09/30/2010

ADDENDUM To CIS:

This is an addendum to the finalized Clinical Inspection Summary for BLA 125294, dated August 23, 2010. The basis for this addendum is to provide an update to DSI's plan to review additional information provided by the applicant in response to an August 17, 2010 Information Request.

Background: Briefly, DSI informed DBOP of the inspectional findings and subsequent concerns related to lack of verification of the validity of the clinical database [Study XM02-02-INT] on several occasions since the completion of the sponsor, BioGenerix AG, inspection on (b) (4) During a telecon held on August 16, 2010 between DSI and DBOP representatives, it was agreed that DSI would develop and forward an Information Request directed to the applicant, Teva, to request that they address the deficiencies noted in relation to the integrity of the database during the present inspection of the study sponsor, BioGenerix AG (b) (4) The Information Request was provided to DBOP on August 17, 2010. DSI recommended in the CIS, dated August 23, 2010, that once the response to the Information Request has been submitted to BLA 125294 that both DSI and DBOP may assess the response to determine if database integrity can be confirmed. DSI also indicated that conduct of an inspection of (b) (4) may be warranted.

Update: The applicant's response to the IR was received on September 2, 2010. A telecon was held between DSI and DBOP on September 8, 2010, where it was decided that due to the complexity and magnitude of the response it would not be reviewed for the current action, PDUFA date September 30, 2010. It was also decided that language to this effect would be included in the Complete Response (CR) Letter. Finally, it was agreed that the CR letter would also request that the applicant, Teva, 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.

Therefore, DSI will not review the response to the IR in support of this action. Instead, DSI and DBOP plan to review information provided by the applicant in response to the CR letter upon submission to BLA 125294.

/Lauren Iacono-Connors, Ph.D./
Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

/Tejashri Purohit-Sheth, M.D./
Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Attachment

Clinical Inspection Summary, dated August 23, 2010

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 23, 2010

TO: Danyal Chaudhry, Regulatory Project Manager
Robert Thomas Herndon, Medical Officer
Division of Biologic Oncology Products

FROM: Lauren Iacono-Connors, Ph.D. 8/24/10
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D. 8/23/2010
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

BLA: 125294/0

APPLICANT: Teva Pharmaceuticals

DRUG: Neutroval (XM02)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: The reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer.

CONSULTATION REQUEST DATE: 2/3/2010

DIVISION ACTION GOAL DATE: 07/31/2010

PDUFA DATE: 09/30/2010

I. BACKGROUND:

Teva Pharmaceuticals USA seeks approval of Neutroval (XM02), a bacterially synthesized non-glycosylated recombinant methionyl form of human granulocyte colony-stimulating factor (G-CSF), 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 natural human G-CSF is a glycoprotein composed of a single polypeptide chain of 174 or (b) (4). The bacterially synthesized non-glycosylated recombinant methionyl form of human G-CSF (r-metHuG -CSF) has been approved by the FDA in 1991 under the generic name Filgrastim (Neupogen™). It is used for reducing the duration of neutropenia and the incidence of febrile neutropenia (FN) in patients undergoing myelosuppressive chemotherapy (CTX) malignant diseases and for reducing the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation and who are at risk of prolonged severe neutropenia.

BioGenerix AG has developed XM02, a non-glycosylated r-metHuG-CSF expressed in Escherichia coli for subcutaneous administration in the treatment for CTX-induced neutropenia. XM02 was principally developed as a similar biological medicinal product to the innovator Neupogen®. Non-clinical and clinical development of XM02 formulation was conducted by BioGeneriX AG. (b) (4) Under a license agreement between BioGeneriX AG and Sicor Biotech UAB in Lithuania, XM02 was brought to market in the European Union as a biosimilar product (reference to Neupogen®) and approved in September 2008. Sicor Biotech UAB is an indirect wholly-owned subsidiary of Teva Pharmaceuticals USA, Inc. Identical formulations of parenteral XM02 are registered under the following tradenames: Biograstim®, Filgrastim-Mepha, Filgrastim ratiopharm, Ratiograstim®, and TEVAGRASTIM® and are marketed in Europe by BioGenerix AG, RatioPharm, or Teva.

The application is supported primarily by data from the pivotal study, Study XM02-02-INT entitled, "Efficacy and Safety of XM02 compared to Filgrastim in patients with breast cancer receiving chemotherapy. A multinational, multicentre, randomized, controlled study." This pivotal study, conducted entirely outside the U.S., was targeted for inspection. The study planned for 350 subjects enrolled and the study actually enrolled 378. The study was conducted in 52 study centers in 10 countries (Belarus, Slovenia, South Africa, Brazil, Chile, Russia, Hungary, Lithuania, Romania, and Poland).

Two clinical sites were inspected in accordance with the CDER Clinical Investigator Data Validation Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811). In addition, the Study XM02-02-INT Sponsor, BioGenerix AG, (b) (4) (b) (4) were inspected in accordance with the CDER Sponsor/Monitor/CRO Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.810).

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor & Location	Protocol # and # of Subjects	Inspection Date	Final Classification
CI 1: Site #2513 (Russia) Irina Zbarskaya (Former CI: Maria Konstantinova) Leningrad Regional Oncology Dispensary 1-2, Zaozemaya str. p. Kuzmolovsky St. Petersburg 188663 Russia	Protocol: XM02-02-INT Site Number: 2513 Number of Subjects: 26	June 6-11, 2010	Pending Interim classification: VAI
CI 2: Site #2519 (Russia) Anatoli Makhson Moscow City Oncology Clinical Hospital #62 p/o Stepanovskoe Kranogorsky Region Moscow Area, Moscow 143423 Russia	Protocol: XM02-02-INT Site Number: 2519 Number of Subjects: 21	June 15-17, 2010	Pending Interim classification: NAI
Sponsor (BioGenerix AG) (b) (4)	Protocol: XM02-02-INT Sites: #2513 #2519	(b) (4)	Pending Interim Classification: VAI
(b) (4)	Protocol: XM02-02-INT Sites: #2513 #2519	(b) (4)	Pending Interim Classification: NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. CI#1: Dr. Irina Zbarskaya

(Site Number 2513)
Leningrad Regional Oncology Dispensary
1-2, Zaozemaya str.
p. Kuzmolovsky
St. Petersburg 188663
Russia

a. What was inspected: The study records of 9 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to

inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. General observations/commentary: Generally, the investigator's execution of the XM02-02-INT protocol was found to be adequate. The study was found to be well controlled and well documented. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in BLA 125294. An issue of record keeping on laboratory equipment maintenance was found related to 1 of 2 hospital laboratory analyzers used during the study. Briefly, the ABX Hematology analyzer printout of subject test results, found in source records, at times, indicated that the instrument reagents may have been out of date. The site, Laboratory Director, stated that they ensured that the piece of laboratory equipment in question was maintained in working order but could not prove this with supporting documentation.

A Form FDA 483 was issued to the clinical investigator citing 1 inspectional observation.

Observation 1: *The study used both of these two these two hospital laboratory hematology analyzers, a Sysmex KX21 Hematology analyzer and an ABX MICROSOT RAB 025 (ABX) hematology analyzer to routinely analyze blood samples for study patients to determine screen and specific study inclusion/exclusion criteria blood values (White Blood Cell counts, Red Blood Cell Counts, ect) for study patients. Both hematology analyzer units were used throughout the study.*

Noted during the review of Case Report Forms on study patients in the study were laboratory reports from both units used interchangeably throughout the study. Noted on review of numerous printout strips included in the CRFs of study patients of laboratory results from the ABX Hematology analyzer is the statement "STARTUP FAILED-Check REAGENTS" (Several examples of this statement can be seen in the following examples of CRFs: Study Patient #26: 6/16/05-6/26/05, Patient #17: 6/5,7,9,14,15/05, and Study Patient #12: 5/31/05, 6/4,7,9/05 ect.)

The service manual for the ABX Hematology manual states in section "P- STARTUP FAILED, CHECK REAGENTS," on page 9/18, "is displayed when the instrument gives

out of range blank values after 3 consecutive startup cycles (see section 6.3) check the expiration dates, replace the reagents if necessary or perform a concentrated cleaning according to the procedure described in section 9.1.3.4." There is no documentation either of these quality control functions was performed or that the laboratory performed any corrective action. There is no documentation the laboratory contacted the manufacturer or servicing agent for the analyzer to have the unit serviced or that the unit was working correctly within operating parameter described by the manufacturer.

DSI Reviewer's Note: The FDA field investigator, Ed Janik, provided additional insights, via personal communication, into this observation and its' impact on the data integrity for this site. Briefly, he stated that there were no missed assessments at the site, whatsoever, nor did he believe that any data was compromised. No data was missing from the source records and all of the required lab values were recorded in lab sheets, reviewed and entered into the patient records.

The actual observation made was that the printout stated "STARTUP FAILED CHECK REAGENTS" indicting the reagents may have been beyond their expiration date, and that the site Laboratory Director could not produce the documentation that showed they had actually contacted the manufacturer of the test equipment to have the test equipment serviced. The Laboratory Director informed Mr. Janik during the inspection that she had contacted the manufacturer of the test equipment to have the test equipment serviced during the study. The inspectional observation appears to be one of record keeping regarding quality control of laboratory equipment used to conduct study-specified hematology assessments. The site stated that they ensured that the piece of laboratory equipment in question, was maintained in working order, but could not prove this with supporting documentation.

c. **Assessment of data integrity:** The data for Dr. Irina Zbarskaya's site, associated with Study XM02-02-INT submitted to the Agency in support of BLA 125294, appear reliable based on available information. The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

2. **CI#2: Dr. Anatoli Makhson**
(Site Number 2519)
Moscow City Oncology Clinical Hospital #62
p/o Stepanovskoe
Kranogorsky Region
Moscow Area, Moscow 143423
Russia

a. **What was inspected**: The study records of 14 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to

inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.

b. **General observations/commentary**: Generally, the investigator's execution of the XM02-02-INT protocol was found to be adequate. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in BLA 125294. A Form FDA 483 was issued to the clinical investigator citing 1 inspectional observation.

Observation 1: *The study used the hospital laboratory hematology analyzer, a Sysmex KX-21 Hematology analyzer to analyze blood samples for study patients to determine screen and specific study inclusion/exclusion criteria blood values (White Blood Cell Counts, Red Blood), to determine study required blood values for study patients.*

There is no documentation of the quality control testing for the time period 2004 and 2005 required in the Sysmex KX-21 manual, section 4.3 to demonstrate the validity of the data.

DSI Reviewer's Note: The FDA field investigator, Ed Janik, informed in an email dated, July 21, 2010, that the Form FDA 483 inspection observation for this site is no longer valid. According to Mr. Janik, the site was able to locate the missing documentation noted in the inspectional observation after the completion of the inspection, and has since provided the documentation to Mr. Janik.

c. **Assessment of data integrity:** The data for Dr. Makhson's site, associated with Study XM02-02-INT submitted to the Agency in support of BLA 125294, appear reliable based on available information. The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

3. **Sponsor: BioGenerix AG**

(b) (4)

a. **What was inspected**: The sponsor was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The study

was conducted at 52 clinical sites in 10 Countries. During the inspection, the FDA investigator assessed records/files from 19 clinical sites. Specifically, the inspection covered the operations of the study sponsor, BioGenerix AG, and their retained roles and responsibilities, and identification of critical CRO's who were delegated sponsor-specific tasks in the conduct of the clinical study. Assessment of the firm included SOPs, clinical site files, including investigator statements, agreements, and training, case report forms, the SAE database and monitoring activities. In addition, all primary and secondary endpoint data were assessed.

DSI Reviewer's Note: This inspection was performed at the (b) (4) (b) (4)

During this inspection the FDA field investigator assessed the overall operations of the study sponsor, BioGenerix, and the operations of one CRO, (b) (4) (summary of inspectional findings for (b) (4) is provided below under item 4 of this Clinical Inspection Summary).

The FDA field investigator also assessed a portion of the operations of a key CRO, (b) (4) (responsible for study data management, including management and maintenance of the clinical database for Study XM02-02-INT). A (b) (4) representative was present during this inspection; however, (b) (4) was not audited during this inspection. (b) (4) pertinent operations related to the clinical database were not able to be covered at the sponsor site where this inspection took place. The clinical database for the study was not on site during this inspection. Allegedly, per agreement, the clinical database was maintained by (b) (4) at their (b) (4) facility during the study, and per agreement, was never turned over to the sponsor, BioGenerix AG, after the study was concluded.

During this inspection the clinical database for the XM02-02-INT study was reportedly retrieved from archive by (b) (4) and was returned to the (b) (4) facility in (b) (4) (b) (4)

b. **General observations/commentary**: Records and procedures were clear, and generally well organized. There was nothing to indicate under-reporting of AEs/SAEs. Overall, site monitoring appeared adequate. The primary efficacy endpoint data were verifiable at the sponsor site. However, during the inspection the FDA field investigator was not able to verify the integrity of the clinical database maintained by CRO (b) (4)

For the XM02-02-INT study, the primary CRO utilized by BioGenerix was (b) (4) (b) (4) was contracted for writing the protocol, data collection and data management, site monitoring, reporting to ethics committees, maintaining the clinical database, SAE processing and reporting to regulatory authorities, biostatistics and writing the clinical study report. A copy of the contract between BioGenerix and (b) (4) was obtained during the inspection. CRO (b) (4) (b) (4) was responsible for supervising all SAE reports (medical review, narrative writing) and interacting with (b) (4) Medical Regulatory Specialist, and maintenance of the safety database.

Regarding the clinical database, the contract specifies in part (b) (4) (b) (4)

During the inspection the FDA field investigator questioned those present, including the (b) (4) representative, regarding whether the clinical database had been unlocked for any reason after the initial locking and unblinding. The FDA field investigator was initially told by the (b) (4) representative that to her knowledge there had been "no unlocking of the clinical database after it was initially locked". No one else present questioned or disagreed with her statement. Subsequent, the FDA investigation revealed evidence that the database was locked on January 2, 2006 and unblinded on the same date. The Trial Master File included a chronology of database-related events that confirmed the database locking/unblinding for January 2, 2006, and then subsequent multiple unlocking/relocking of the clinical database as follows:

- 2 January 2006: initial **locking** and **unblinding**
- 17 January 2006: **unlocking** of the unblinded database
- 17 January–23 January 2006: unblinded database **remains unlocked**
- 23 January 2006: initial **relocking** of the database
- Between 23 January and 27 February – **on an undetermined date**, the unblinded database was **unlocked a second time**, and remained open until relocking;
- 27 February 2006 – **final database lock**

The sponsor did not have adequate documentation that demonstrated sponsor-authorized/justified database manipulations, nor could they provide documentation that described exactly what was altered in the clinical database. Briefly, the "Tasks and Responsibilities" plan for the covered study assigned quality control of the clinical database to the CRO (b) (4) The approved "Archiving" plan for the covered study required that specific database quality control documents be sent to the sponsor. Section 21.1 of the archiving plan requires that "Critical Item Quality Control" documents be sent to the sponsor, and section 21.2 requires that "Final Database Quality Control" documents be sent to the sponsor. However, the FDA field investigator's review of the Trial Master File during the inspection revealed that the clinical database quality control

documents, including "Critical Item Quality Control" documents and "Final Database Quality Control" documents, are not included in the Trial Master File and could not be found by the sponsor during the inspection.

Therefore, with respect to the pivotal study XM02-02-INT, the inspectional findings at the sponsor site called into question the integrity of the clinical database. Specifically, the validity of the database could not be verified. A Form FDA 483 was issued to the Sponsor citing 1 inspectional observation.

Observation 1: *Failure to ensure the investigation was conducted in accordance with the general investigational plan and protocol, as follows:*

(A) The clinical database maintained by CRO (b) (4) was locked AND UNBLINDED on 2 January 2006. It was subsequently unlocked on 17 January 2006, and remained in unlocked status until it was relocked on 23 January 2006. It was subsequently unlocked again and appears to have remained in an unlocked status until a second relocking on 27 February 2006. Records at this site document that during the unlocked period between 17 and 23 Jan 2006, and the second unlock period that occurred sometime between 23 Jan 2006 and 27 Feb 2006, data was added and/or revised in the clinical database. The following was noted regarding the lock/unblind/relock events:

(1) Study records fail to include detailed written justifications for unlocking the database after it was unblinded;

(2) Failure to follow the SOP ((b) (4) SOP WSOP 1211-03) for database unlocking/relocking events, including:

(a) Section 3.2 of the SOP states "Obtain sponsor approval to unlock the database (signature is required)". There is no record of sponsor approval via signature for the unlocking events. The sponsor was not advised of the first unlocking event until the day after it occurred;

(b) Section 3.1 of the SOP requires approval of several individuals for a database unlock, including the Data Mgr. Functional Lead, who for this study was a (b) (4) official (b) (4) However, the unlock approval section of the "Locked Database Change Request" form for the first event fails to include his signature.

(c) There is no "Locked Database Change Request Form" at the site for the unlocking event that appears to have occurred sometime after 23 January;

(d) The SOP-required signature of the (b) (4) Project Manager (b) (4) (b) (4) on the unlock approval section of the form was added retrospectively, after the database had already been unlocked and relocked. That signature was added sometime after 23 January 2006,

but was backdated to the unlock date of 17 January 2006, with no explanatory annotation on the form.

(B) Database quality control documents for the clinical database, as required by WSOP 1210-03, were not retained by the sponsor in accordance with the approved archiving plan. Required documentation not found on site includes "Critical Item Quality Control" documents specified in Section 4 of WSOP 1210-03, and "Final Database Quality Control" documents specified in Section 5 of WSOP 1210-03. Section 4.9 of the SOP states in part "Retain all the documentation relating to this activity in the project files", and the study archiving plan requires the documents to be retained by the sponsor.

(1) For "Critical Item Quality Control", missing documentation includes the listing of critical items to be checked, documentation of the comparison of the QC items to the CRFs and/or any other documentation, documentation of updates made to the database as part of the QC process, and documentation of the review of the updates for accuracy.

(2) For "Final Database Quality Control", documentation found to be missing includes documentation of the randomization criteria and how the sample size was determined for final QC, project-specific QC guidelines that were generated, QC listing for patients, documentation of differences between corrected CRFs and the listing, the annotated listing, documentation of database updates, and other associated documentation.

An inspection close-out discussion with management was held at the conclusion of the inspection on (b) (4). At that time, The Form FDA-483 Inspectional Observations was issued directly to (b) (4) (b) (4) (b) (4) stated that a prompt written response to the Form FDA 483 inspectional observations would be forthcoming.

DSI reviewer's Notes: DSI has had extensive correspondence with the FDA field investigator both during and subsequent to the above inspection. The inspection of the sponsor revealed that the clinical database, developed and maintained by a CRO, (b) (4) had been altered after the database had been locked and unblinded. Unfortunately, the sponsor site was unable to produce adequate documentation of these events while the inspection was ongoing. Therefore, the sponsor's inadequate study-specific recordkeeping compliance as it pertains to the study XM02-02-INT database has called into question the validity of the clinical database in its entirety. However, no specific evidence has been collected to date, which indicates that the database is corrupt. The inspectional observations support the present conclusion, that the database validity could not be verified during the inspection. DSI informed the review division (DBOP) project manager and Medical Officers, among others, of these concerns on several occasions since the completion of the inspection.

During a telecom held on August 16, 2010, between DSI and DBOP representatives it was agreed that DSI would develop and forward an Information Request directed to the sponsor to address the deficiencies noted on the integrity of the database during the inspection. The Information Request (IR) was provided to DBOP on August 17, 2010.

DSI recommends that once the response to the Information Request has been submitted to BLA 125294 that both DSI and DBOP review the response to determine if database integrity can be confirmed. To that end, DSI may also conduct an inspection of (b) (4) (b) (4) if warranted and feasible.

c. **Assessment of data integrity:** Based on a preliminary review of the inspectional findings, and the Form FDA 483 inspectional observations, the study appears to have been conducted adequately, however, the reliability of clinical data, stored in a clinical study database maintained by CRO (b) (4) could not be verified during the inspection. It is unclear, based on available inspectional findings, whether the clinical database is corrupt. The current findings call into question data integrity for the XM02-02-INT Study submitted to the Agency in support of BLA 125294. The clinical data reliability will be further assessed when the applicant responds to the IR related to this issue, and if warranted, an inspection of CRO (b) (4)

4. (b) (4)

a. **What was inspected:** The CRO was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The CRO (b) (4) was responsible for supervision of all SAE reports, medical review of SAE reports, writing the SAE narratives, maintaining an SAE database for reporting to regulatory authorities, and reconciling their SAE database with the clinical database maintained by (b) (4) The FDA field investigator reviewed the SAE database maintained by (b) (4) assessed database reconciliation documentation, and assessed the integrity of the SAE database.

Note: The EIR was not available at the time this CIS was written. The EIR for the CRO is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary:** Assessment of the safety database, pharmacovigilance plan, and related activities, found no deficiencies related to the activities of (b) (4) in their CRO capacity. The FDA field investigator was also able to validate the integrity of the safety database. The safety database

and related records were available on site and no recordkeeping deficiencies were noted. The safety database was available during the inspection and the FDA field investigator was able to challenge it and verify the integrity of the safety data for this study. Briefly, SAEs reported in the site files were compared to SAEs included in the safety database and no discrepancies were found. All SAEs that were included in CRO's database were compared to the SAE data reported in the clinical study report, no discrepancies were noted. Of note, training of the 3 individuals responsible for reviewing and evaluating the SAEs revealed that none possessed an M.D. degree, but instead were veterinarians or were pharmacists.

c. **Assessment of data integrity:** The data generated at this site, as it pertains to Study XM02-02-INT were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this CRO submitted to the agency as part and in support of BLA 125294 appear reliable. The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Zbarskaya, and Dr. Makhson, and study CRO (b) (4) the study data collected appear reliable.

A Form FDA 483 was issued to Dr. Zbarskaya for essentially, failure to maintain records related to laboratory instrumentation maintenance. Briefly, the ABX Hematology analyzer printout of subject test results, found in source records, at times, indicated that the instrument reagents may have been "out of date". The site, Laboratory Director, stated that they ensured that the piece of laboratory equipment in question was maintained in working order but could not prove this with supporting documentation.

A Form FDA 483 was issued to Dr. Makhson for a similar observation, lack of documentation for quality control testing for a hematology analyzer used during the study. However, according to the FDA field investigator, the site was able to locate the missing documentation noted in the inspectional observation after the completion of the inspection, and has since provided the documentation to the FDA field investigator.

The FDA field investigator reported that inspection of CRO, (b) (4) covered the safety database, pharmacovigilance plan, and related activities. No deficiencies related to the activities of (b) (4) in their CRO capacity were noted.

Based on a preliminary review of the inspectional observations of the Study XM02-02-INT sponsor, BioGenerix AG, the validity of clinical data from the study database, maintained by CRO (b) (4) could not be verified and a Form FDA 483 was issued to BioGenerix AG for failure to ensure the investigation was conducted in accordance with

the general investigational plan and protocol. During the inspection of the sponsor, BioGenerix AG, the FDA investigator found deficiencies in record keeping and procedures related to the management and integrity of the clinical database for Study XM02-02-INT. The inspection of the sponsor revealed that the clinical database, developed and maintained by a CRO, (b) (4) had been altered after the database had been locked and unblinded. Unfortunately, the sponsor site was unable to produce adequate documentation of these events while the inspection was ongoing. Therefore, the sponsor's inadequate recordkeeping and study compliance as it pertains to the study XM02-02-INT database has called into question the validity of the clinical database in its entirety. It should be noted that no specific evidence has been collected to date that indicates that the database is corrupt. The inspectional observations support the present conclusion, that the database validity could not be verified during the inspection. DSI recommends that the clinical data not be used in support of the application unless the database integrity can be verified.

DSI informed DBOP of the concerns related to lack of verification of the validity of the clinical database on several occasions since the completion of the inspection. During a telecom held on August 16, 2010, between DSI and DBOP representatives it was agreed that DSI would develop and forward an Information Request directed to the applicant, Teva, to request that they address the deficiencies noted in relation to the integrity of the database during the present inspection of the study sponsor. The Information Request was provided to DBOP on August 17, 2010. DSI recommends that once the response to the Information Request has been submitted to BLA 125294 that both DSI and DBOP assess the response to determine if database integrity can be confirmed. To that end, DSI may also conduct an inspection of (b) (4) if warranted and feasible.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

Follow-Up Actions:

1. DSI will generate an inspection summary addendum if the conclusions change significantly upon final review of the EIRs and supporting inspection evidence and exhibits.

2. DSI forwarded an Information Request to DBOP for the BLA 125294, Teva, requesting clarification and supporting documentation addressing the study database quality control and integrity concerns revealed during the current inspections. DSI will review the response concordantly with DBOP to determine if database integrity can be confirmed.

3. If the study database integrity cannot be confirmed after review of Teva's complete response to the Information Request DSI may conduct an inspection of (b) (4) (b) (4) if warranted and feasible, with DBOP concurrence.

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Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
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Memorandum

Label Review

Application Number:	STN 125294/0
Name of Drug:	Neutroval® (proper name)
Sponsor:	Teva Pharmaceuticals USA
Material Reviewed:	Neutroval®(proper name) Carton and Container Labels
Submission Date:	November 30, 2009

EXECUTIVE SUMMARY

The carton and container labels for Neutroval® (proper name) were reviewed and found to comply with the following regulations : 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57 and 21 CFR 200.100. USPC Official 12/1/09-10/1/10, USP 32/NF27. Labeling deficiencies were identified and will be communicated to the applicant. Please see comments in the conclusions section.

Background:

STN 125294 is an original Biologic License Application (BLA) and is not considered a biosimilar. The product is a neutrophil growth factor indicated for the reduction in the duration of severe neutropenia with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The product is supplied as 300 mcg/0.5 mL and 480 mcg [redacted] in prefilled syringes.

Labels Reviewed:

Neutroval®(proper name) Container label
- Syringe Label: 300 mcg/0.5 mL and 480 mcg/[redacted]
- Blister Label: 300 mcg/0.5 mL and 480 mcg/[redacted]

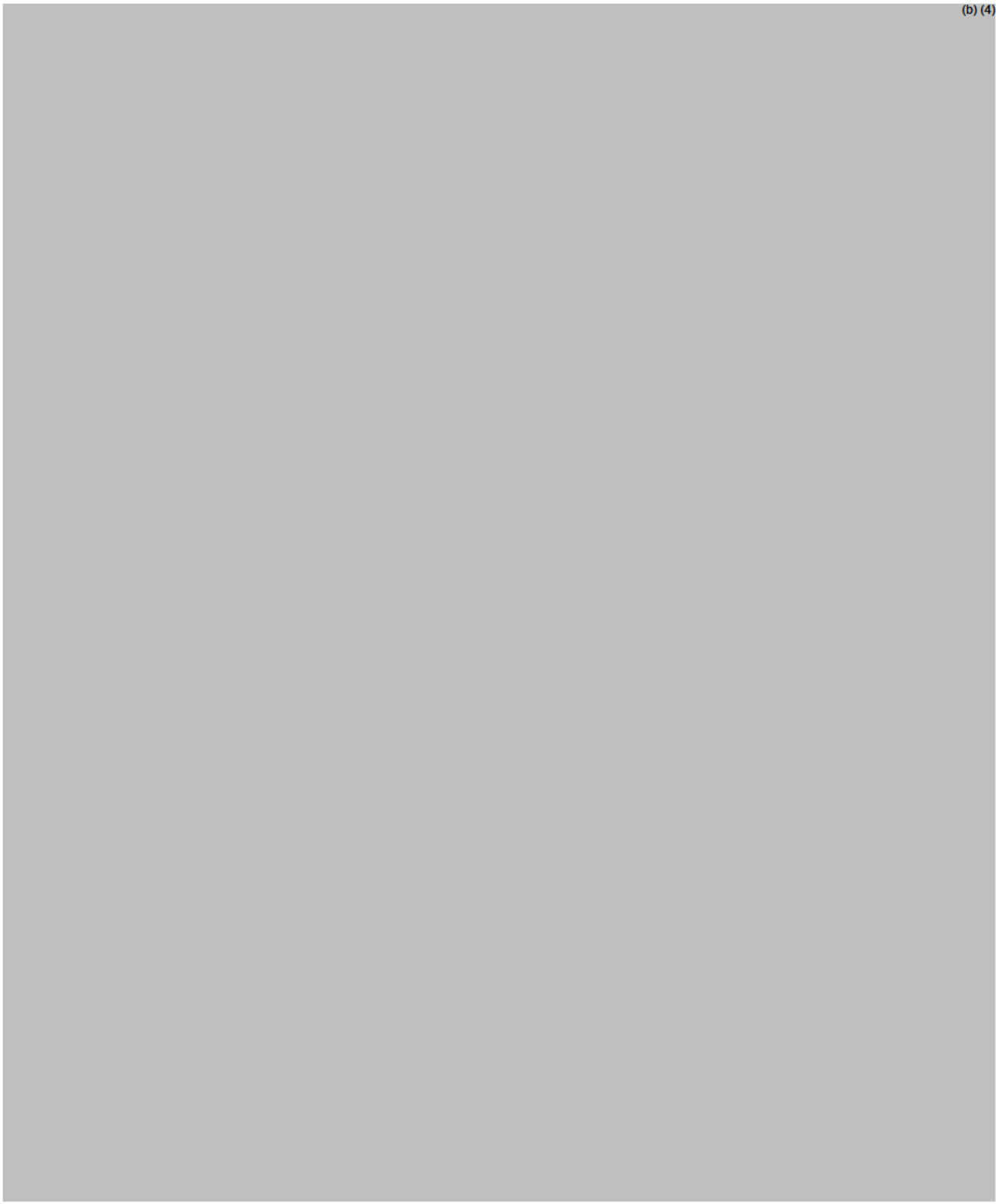
Neutroval™ (proper name) Carton label
- No device Carton: 300 mcg/0.5 mL and 480 mcg/[redacted]
- Device included Carton: 300 mcg/0.5 mL and 480 mcg/[redacted]

Neutroval® (proper name) Prescribing Information

Review

Syringe Label

(b) (4)



I. Container

A. 21 CFR 610.60 Container Label-Syringe Label

1. Partial label. The following items shall appear on the label affixed to each container of a product capable of bearing a partial label:

   a. (b) (4) [redacted]

   b. The name of the manufacturer – The manufacturer is listed as Teva Pharmaceuticals USA. This conforms to the regulation.

   c. The lot number or other lot identification – The lot number is located on the syringe label. This conforms to the regulation.

2. Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – This conforms to the regulation.

B. 21 CFR 610.60 Container-Blister label

1. Full Label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label.

   a. (b) (4) [redacted]

   b. The name, address, and license number of manufacturer-The name, address, or license number does not appear. This does not conform to the regulation.

   c. The lot number or other lot identification-The lot number appears on the label. This conforms to the regulation.

   d. The expiration date-The expiration date appears under the lot number. This conforms to the regulation.

e. The recommended individual dose for multiple dose containers-This is a single-use prefilled syringe configuration. This regulation does not apply.

f. Medication guide statement-A medication guide is not required. This regulation does not apply.

g. Package label information-The container is enclosed in a carton. This regulation does not apply.

h. Partial label- The container is capable of bearing the full label. This regulation does not apply.

C. 21 CFR 201.2 Drugs and devices; National Drug Code (NDC) numbers if present shall comply with 21 CFR 207.35 –An NDC appears on the blister label and does not conform to a 4-2 product –package code configuration. This does not conform to the regulation. Configuration should match previously approved products from this manufacturer.

D. 21 CFR 201.5 Drugs; adequate directions for use – This is not needed for the syringe label as the minimum requirements are listed in 21 CFR 610.60 under partial label requirements. The blister label does not comply with all requirements, however the carton does. This conforms to the regulation.

E. 21 CFR 201.6 Drugs; misleading statements – The only names that appear on the label are the trade name and proper name. This conforms to the regulation.

F. 21 CFR 201.10 Drugs; statement of ingredients – [redacted] (b) (4) (b) (4)

G. 21 CFR 201.15 Drugs; prominence of required label statements – The required label statements, "Do not Shake or Freeze" and "Protect from light" do not appear on the blister label. The syringe label is exempt because it is a partial label. This does not conform to the regulation for the blister label.

H. 21 CFR 201.17 Drugs; location of expiration date – The expiration date is listed on the label. This conforms to the regulation.

I. 21 CFR 201.25 Bar code label requirements – Bar code appears on the label. This conforms to the regulation.

J. 21 CFR 201.50 Statement of identity – The proper name, (proper name) is stated on the label. The proper name and trade name conform to 21 CFR 201.10. This conforms to the regulation.

K. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity of contents (300 mcg/0.5 ml or 480 mcg/0.8 ml) is declared on the syringe label. This conforms to the regulation.

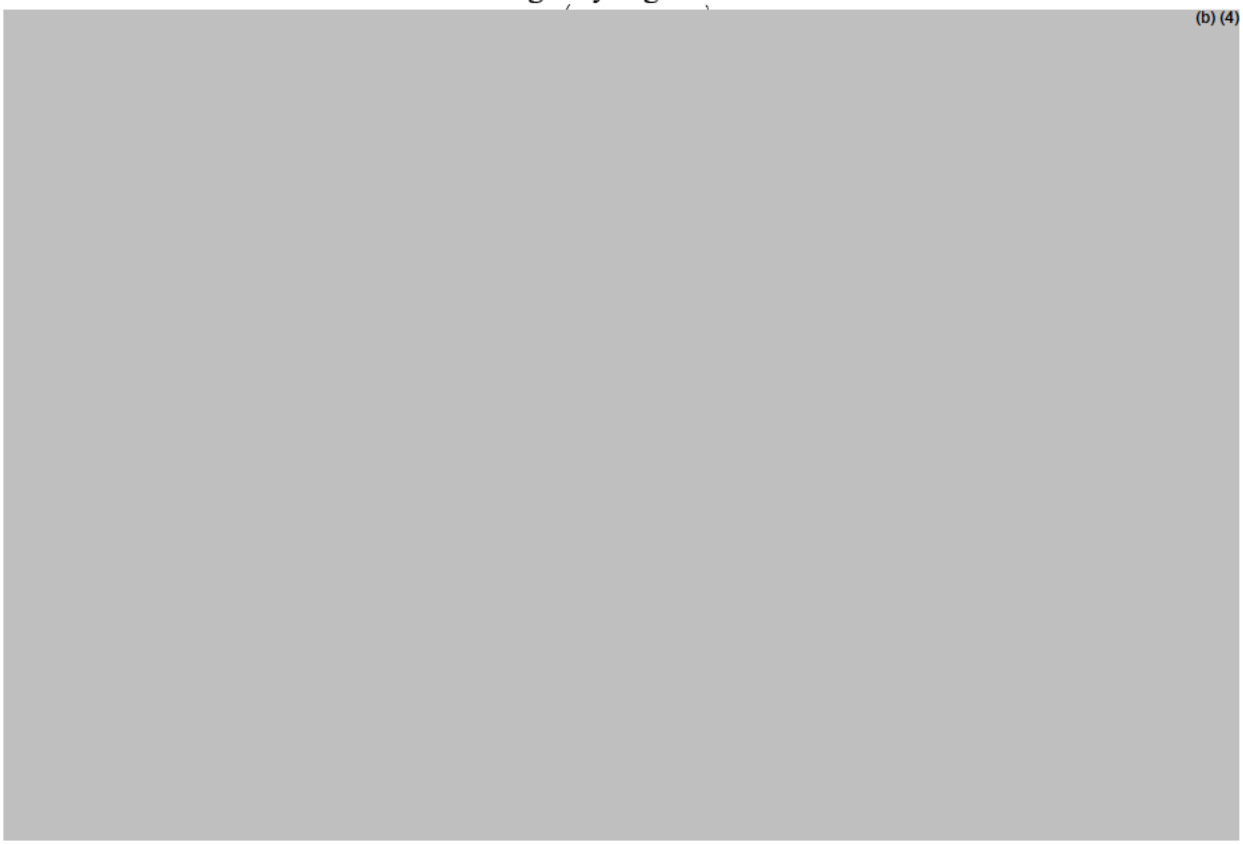
L. 21 CFR 201.55 Statement of dosage –Sufficient space for a dosage statement is not available. A statement does appear on the carton. This conforms to the regulation.

M. 21 CFR 201.100 Prescription drugs for human use – The syringe label bears statements required for a partial label including lot number and expiration date. The blister label does not contain required statements. This does not conform to the regulation.

Carton Labels

Single Syringe without a Device

(b) (4)



5 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[redacted] (b) (4)

II. Carton

A. 21 CFR 610.61 Carton/Package Label –

a. [redacted] (b) (4)

b. The name addresses, and license number of the manufacturer. The presentation of the manufacturer is incorrect. This does not conform to the regulation.

c. The lot number or other lot identification – The lot number is located on the end panel of the carton. This conforms to the regulation.

d. The expiration date – The expiration date is listed below the lot number on the end panel of the carton. This conforms to the regulation.

e. The preservative used and its concentration, if no preservative is used and the absence of a preservative is a

safety factor, the words "no preservative" –The statement (b) (4) contains no preservative" is displayed on the carton. This conforms to the regulation.

f. The number of containers, if more than one – There are multiple package configurations and each package lists the number of containers. This conforms to the regulation.

g. The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable – The amount of product is expressed as a concentration. This conforms to the regulation.

h. The recommended storage temperature – The statement "Storage conditions: Keep refrigerated (36 -46°F/ 2-8°C)." is displayed on the back panel of the carton. This conforms to the regulation. Recommend changing format to 2-8°C (36 -46°F).

i. The words "Shake Well", "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product – "Store in carton to protect from light" and "Do not shake." should be added to the carton. This does not conform to the regulation.

j. The recommended individual dose if the enclosed container(s) is a multiple-dose container –Single-use syringe configurations. Therefore, this does not apply.

k. The route of administration recommended, or reference to such directions in and enclosed circular – The statement "For subcutaneous or intravenous use only" is located on the front panel of the carton. Approval will be for subcutaneous use, remove intravenous.

l. Known sensitizing substances, or reference to an enclosed circular containing appropriate information –This does not apply.

m. The type and calculated amount of antibiotics added during manufacture – This does not apply.

n. The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information – Ingredients are listed on the carton. This conforms to the regulation.

o. The adjuvant, if present – This does not apply.

p. The source of the product when a factor in safe administration – This conforms to the regulation.

q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information. – The statement, "A recombinant Granulocyte Colony Stimulating factor (rG-CSF) derived from *E Coli"*. This conforms to the regulation. Recommend removing the statement and stating "Derived from E Coli" near ingredient information on the side panel.

r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency" – "No U.S. Standard of Potency" is not displayed on the label. This does not conform to the regulation.

s. The statement "Rx only" for prescription biologicals – The statement "Rx Only" is located on the front and back of the carton. This conforms to the regulation.

t. If a Medication Guide is required under part 208 of this chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – A medication guide statement is not required. This regulation does not apply.

B. 21 CFR 610.62 Proper name; package label; legible type *[Note: Per 21 CFR 601.2©(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]* – This is an exempted (monoclonal antibody products for in vivo use). Therefore the label does not need to conform to this regulation.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown – [redacted] (b) (4) is the only manufacturer listed on the label. This conforms to the regulation.

D. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or 'Marketed by _____". The qualifying phrases may be abbreviated. –A distributor is not listed. This regulation does not apply.

E. 21 CFR 610.65 Products for export – This is for US use only. Therefore, this regulation does not apply.

F. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter. – Bar code appears on the carton label. This conforms to the regulation.

G. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on the carton. The NDC number does not conform to 21 CFR 207.35 as a 4-2, Product-Package Code configuration. This conforms to the regulation. Configuration should match previously approved products from this manufacturer.

H. 21 CFR 201.5 Drugs; adequate directions for use – The label states "Information for use and dosage-See Package Insert." This conforms to the regulation.

I. 21 CFR 201.6 Drugs; misleading statements – The names shown on the carton label are [redacted] (b) (4) and (proper name). Therefore, this cannot be confused with other drug, device, food, or cosmetic. This conforms to the regulation.

J. 21 CFR 201.10 Drugs; statement of ingredients –This conforms to the regulation.

K. 21 CFR 201.15 Drugs; prominence of required label statements – The required statements "Do not shake or freeze" and "Store in carton to protect from light." are not listed on the carton. This does not conform to the regulation.

L. 21 CFR 201.17 Drugs; location of expiration date – The expiration date appears under the lot identification number on the end panel of the carton label. This conforms to 21 CFR 610.60 and 21 CFR 201.17.

M. 21 CFR 201.25 Bar code label requirements – Bar code appears on the carton label. This conforms to the regulation.

N. 21 CFR 201.50 Statement of identity – The established name (proper name), proper name and proprietary name, (trade name) conform to 21 CFR 201.10. This conforms to the regulation.

O. 21 CFR 201.51 Declaration of net quantity of contents – Net quantity of contents is declared on the carton label. This conforms to the regulation.

P. 21 CFR 201.55 Statement of dosage – The label states "Information for use and dosage-See Package Insert". This conforms to the regulation.

Q. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of "Rx Only", an identifying lot number, storage conditions, and reference to the package insert. The statements "Do not shake or freeze" and "Store in carton to protect from light." do not appear on the carton. This does not conform to the regulation.

III. Conclusions and Recommendation

A. Carton and Container (blister)

1. As defined in 21 CFR 600.3(t), manufacturer is the "applicant." The manufacturer, name, address and license number must be listed on the container (blister) and the carton per 21 CFR 610.60(a)(2) and 21 CFR 610.61(b). Please revise the statement, [redacted] (b) (4) to "[redacted] (b) (4) on the carton to conform to the regulation. Please add the manufacturing information to the blister label to conform to the regulation. The license number must follow the manufacture's address.

2. Please revise the temperature statement listed as, "(36-46°F/2-8°C)" to "2-8°C (36-46°F) on the container (blister) and carton label.

3. Please add the statements, "Do not Shake or Freeze." and "Store in carton to protect from light," to the container (blister) and carton labels per 21 CFR 201.15 and 21 CFR 610.61(i).

4. Per USPC Official 12/1/09-10/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients and 21. CFR 201.100(b)(5)(iii),

please list the names of all inactive ingredients in alphabetical order on the carton with corresponding amounts, except ingredients added to adjust the pH or to make the product isotonic may be declared by name and effect.

5. The statement, "[redacted] (b) (4) separates the proprietary name and proper name from the statement of strength. Remove the statement from the blister pack and carton labels altogether. *E. Coli* should be listed on the carton per 610.61(q) and should be listed away from the primary panel.

6. Please consider revising the presentation of the dosage form, route of administration, single-use statement (Discard unused portion) to the following presentation:

[redacted] (b) (4)

The agency is working toward standardizing the presentation of the trademark, proper name or established name, dosage form, and route of administration for Therapeutic Biologics.

6. Please remove the [redacted] (b) (4) [redacted] (b) (4) from all carton and container labeling.

7. The NDC product-package code configuration presented on the labels is not consistent with previously approved products per 21 CFR 207.35(b)(2)(ii). Please revise configuration to a 4-2 configuration.

B. Blister Pack Labeling

1. An inactive ingredient list is not required to comply with container labeling regulations. This information may be removed to provide adequate space for requested changes to the blister label.

2. Relocate the proper name to the line immediately below the proprietary name. See format above in A. 5.

C. Carton

1. Please add the statement, "No U.S. standard of potency" to the carton per 21 CFR 610.61(r).

D. Package Insert

1. Please revise the title line of the Package Insert to the following presentation to comply with 21 CFR 201.57(a)(2) and SPL formatting requirements:

(b) (4)

2. Per USPC Official 12/1/09-10/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients and 21. CFR 201.100(b)(5)(iii), please list the names of all inactive ingredients in alphabetical order with corresponding amounts, except ingredients added to adjust the pH or to make the product isotonic may be declared by name and effect.

3. Please add the route of administration to the "DESCRIPION" section per 21 CFR 201.57(c)(12).

9/22/10

Kimberly Rains, Pharm. D.
Regulatory Project Manager
CDER/OBP/IO

Concurrence/Comments:

9/22/10

Dov Pluznik, Ph.D.
Product Reviewer
CDER/OPS/OBP/DTP

9-22-10

Barry Cherney, Ph.D.
Deputy Director
CDER/OPS/OBP/DTP

SEALD LABELING REVIEW

This review identifies aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	BLA 125294
APPLICANT	Teva
DRUG NAME	Neutroval, (b) (4)
SUBMISSION DATE	June 6-28-2010
PDUFA DATE	
SEALD REVIEW DATE	July 8 2007
SEALD LABELING REVIEWER	Elisabeth Piault-Louis 8/18/10

G:\SEALD\Labeling Development\Labelin

Laurie Burke 8/18/10
Dir, SEALD

Outlined below are the following outstanding labeling requirements that must be corrected before the final draft labeling is approved. Issues are listed in the order mandated by the regulations or guidance.

If there are no issues for a particular heading in highlights (HL) or for sections in the full prescribing information (FPI), "none" is stated. If clearly inapplicable sections are omitted from the FPI, "not applicable" is stated. In addition, "not applicable" is stated if optional headings (i.e., Drug Interactions or Use in Specific Populations) are omitted from HL.

Highlights (HL):

- **Highlights Limitation Statement:** None
- **Product Title Line:** None
- **Initial U.S. Approval:** The review division must enter the initial approval year of the NME. Do not leave blank.
- **Boxed Warning:** Not applicable
- **Recent Major Changes:** Not applicable
- **Indications and Usage:** Remove "r" after Neutropenia
- **Dosage and Administration:** Spell out CTX

- **Dosage Forms and Strengths:** Indicate that Neutroval is sterile
- **Contraindications:** None
- **Warnings and Precautions:** None
- **Adverse Reactions:** None
- **Drug Interactions:** None
- **Use in Specific Populations: None**
- **Patient Counseling Information Statement:** None
- **Revision Date:** Revision date is the month/year that the supplement is approved. The review division enters this information upon approval. Do not leave blank.

Table of Contents (TOC):
Ensure that the TOC reflects the FPI, for instance:

- In section 5.3, the subheading is "Allergic Reactions" in the TOC, while (b) (4) (b) (4) in the FPI;
- Section 6.3: Post-Marketing Experience is listed in the TOC but not in the FPI

Full Prescribing Information:

Boxed Warning: Not applicable

1 Indications and Usage: No need for space between header and text; this comment applies to all the other sections.

2 Dosage and Administration: None

3 Dosage Forms and Strengths:

- Add description of identifying characteristics of the dosage forms as applicable, such as color.

4 Contraindications: None

5 Warnings and Precautions:

- Under subsection "Use in Patients with Sickle Cell Disorders" describe steps to take if this occurs.

6 Adverse Reactions:

- Clinical Trials Experience: This section refers to three studies, however, only one adverse reaction (bone pain) that was observed in study one is listed. Is there any information that might have been forgotten or inadvertently deleted? List adverse reactions (in table format) identified in clinical trials that occurred at or above a specified rate appropriate to the safety database (Include event, number of patients, incidence, and comparators, if appropriate.)

7 Drug Interactions: None

8 Use in Specific Populations: None

9 Drug Abuse and Dependence: Not applicable

10 Overdosage: None

11 Description: None

12 Clinical Pharmacology: None

13 Nonclinical Toxicology:
Consider revising the term (b) (4) that is not specific in the following sentence: (b) (4)

(b) (4)

14 Clinical Studies:
Please double check the following sentence for accuracy: (b) (4)

(b) (4)

15 References: Not applicable

16 How Supplied/Storage and Handling: None

17 Patient Counseling Information: None

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

MEMORANDUM – Maternal Health Team

Date: August 17, 2010 **Date Consulted:** January 19, 2010

From: Jeanine Best, MSN, RN, PNP
Senior Clinical Analyst, Pediatric and Maternal Health Staff (PMHS)

Through: Karen B. Feibus, M.D. LBM for Karen Feibus 8/17/2010
Medical Team Leader, Maternal Health Team (MHT)

Lisa Mathis, MD LBM 8/17/2010
OND Associate Director, Pediatric and Maternal Health Staff (PMHS)

To: Division of Biologic Oncology Products (DBOP)

Drug: Neutroval (b) (4) injection for subcutaneous (b) (4) use, BLA 125294

Subject: Pregnancy and Nursing Mothers Labeling

Materials Reviewed:

- Sponsor BLA submission dated November 30, 2009
- Sponsor Assessment of the Potential Reproduction Toxicity of Neutroval, June 15, 2010 (submitted in response to FDA Information Request Letter, May 24, 2010)
- Discussion Points and Action Items: Teva's Neutroval (XM02) Application, June 26, 2010 (OCC and ORP discussion)

Consult Question: DBOP requests that the Maternal Health Team (MHT) review and comment on the proposed Pregnancy and Nursing Mothers labeling for Neutroval (b) (4) injection for subcutaneous (b) (4) use.

SUMMARY

On January 19, 2010, the Division of Biologic Oncology Products (DBOP) consulted the Maternal Health Team (MHT) to review and comment on the proposed pregnancy and nursing mothers sections of labeling for Teva Pharmaceutical's Neutroval (b) (4) injection for subcutaneous (b) (4) original Biologic License Application, BLA 125294, submitted on November 30, 2009. BLA 125294 was submitted under the 351(a) BLA regulatory pathway; however, required product-specific developmental and reproductive toxicity studies were not conducted, nor was a scientific justification provided for the absence of these studies. Abortion and embryolethality were seen in nonclinical developmental and reprotoxicty studies with Neupogen (filgrastim) and other G-CSF products, approved either in the U.S., or in other countries. All of these products are labeled with adequate nonclinical developmental and reprotoxicity information; however, TEVA presented draft labeling absent this important information, and the raising both regulatory and ethical concerns. FDA's Office Chief Counsel and CDER's Office of Regulatory Policy have been tasked to provide a legal opinion as to whether TEVA would need to conduct Neutroval-specific nonclinical developmental and reprotoxicity studies prior to Neutroval approval as a regulatory requirement, or if existing (b) (4) nonclinical reprotoxicity data available in the public domain can be used to meet a fundamental regulatory requirement for approval under section 301(a) of the Public Health Act.

FDA recognized the shortcomings of pregnancy and lactation information in drug labeling and as a result, drafted and published the Proposed Pregnancy and Lactation Labeling Rule (PLLR) in May 2008. The goal of the PLLR when finalized, is to provide more comprehensive information in all prescription drug labeling for making prescribing decisions and for counseling women who are pregnant, breast-feeding, or of child-bearing age about using prescription medications. It would be remiss of the Agency to omit informative pregnancy risk information in a supportive therapy product because the supportive product is only intended to be used with drugs that have greater known reprotoxic risks. Pregnant women along with their clinicians should receive adequate information in all drug labeling to allow informed risk/benefit decision making.

In conclusion, the MHT is unable to review the pregnancy and nursing mothers subsections of Neutroval labeling until Teva submits adequate data for review. When a legal decision is rendered by OCC/ORP regarding the source of nonclinical reprotoxicty data that can be used to support the Neutroval application, Teva should submit that data (product-specific study data or a literature review of existing filgrastim nonclinical reprotoxicity data available in the public domain) for review, along with revised Neutroval pregnancy and nursing mothers labeling.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 16, 2010
To:	Patricia Keegan, MD, Director Division of Biologic Oncology Products
Through:	Kristina A. Toliver, PharmD, Team Leader Kaysoliver 8/16/10 Denise P. Toyer, PharmD, Deputy Director Carol A. Holquist, RPh, Director for CHolquist 8/16/10 Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA) 8/16/10
Subject:	Label and Labeling Review
Drug Name:	Neutroval (b) (4) Injection 300 mcg/0.5 mL and 480 mcg/0.8 mL
Application Type/Number:	BLA 125294
Applicant/sponsor:	Teva Pharmaceuticals
OSE RCM #:	2009-2469

1 INTRODUCTION

This review responds to a request from the Division of Biologic Oncology Products for DMEPA's assessment of the container labels, carton and insert labeling for Neutroval ((b) (4)) Injection (BLA 125294).

2 METHODS AND MATERIALS

DMEPA uses Failure Mode and Effects Analysis (FMEA) to evaluate container labels, carton and insert labeling. This review summarizes our evaluation of the container labels, blister pack and carton labeling submitted by the Applicant on November 30, 2009 (see Appendices C through F) and the proposed insert labeling submitted on March 26, 2010. Additionally, the Applicant provided working samples of the syringes with and without the needle guard for our review and comment (see Appendix G).

Furthermore, we conferred with the label and labeling reviewer in the Office of Biotechnology Products (OBP) prior to making our recommendations.

- Container Labels , 300 mcg/0.5 mL and 480 mcg/0.8 mL
- Blister Pack Labeling, 300 mcg/0.5 mL and 480 mcg/0.8 mL
- Carton Labeling, 300 mcg/0.5 mL and 480 mcg/0.8 mL (1-count, 5-count and 10-count)
- Insert Labeling (no image)
- Syringes, with and without the needle guard

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels, peel back labeling and carton labeling can be improved to minimize the potential for medication errors. We provide a comment on the insert labeling in Section 3.1 *Comments to the Division*. Section 3.2 *Comments to the Applicant* contains our recommendations for the container label, carton labeling, and syringes. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Sue Kang, at 301-796-4216.

3.1 COMMENTS TO THE DIVISION

Recommendations from DMEPA concerning Sections 3 *Dosage Forms and Strengths* and 16 *How Supplied/Storage and Handling* of the insert labeling were communicated to the Division in a labeling meeting held on May 21, 2010 (see Appendix A). Additionally, recommendations from DMEPA concerning Section 17, Patient Labeling of the insert labeling were communicated to the Division in a labeling meeting held on July 22, 2010 (see Appendix B). Below is our recommendation concerning the Highlights of Prescribing and Full Prescribing Information sections of the insert labeling.

A. Insert Labeling

1. Highlights of Prescribing and Full Prescribing Information

   a. The abbreviation "CTX" is used. We recommend the word "chemotherapy" be spelled out and not abbreviated since the abbreviation "CTX" has other meanings (e.g., Cytoxan, Cefotaxime, and chemotaxis) for which it may be confused.

3.2 COMMENTS TO THE APPLICANT

A. General Comment

Color is used to differentiate the 300 mcg statement of strength (blue) from the 480 mcg strength (grey). However, the proprietary name on both strengths is also blue in color which minimizes the effectiveness of the color differential of strength. We recommend you revise the color of the proprietary name on the 480 mcg labels and labeling to grey or use a color for the proprietary name that does not overlap with any of the colors used for strength.

B. General Comments for Blister Pack Labeling and Carton Labeling

1. Relocate the proper name to the line immediately below the proprietary name.
2. The statement "A recombinant Granulocyte Colony..." separates the proprietary name and proper name from the statement of strength. Relocate the statement "A recombinant Granulocyte Colony..." to a position below the route of administration.
3. Revise the dosage form statement [redacted (b) (4)] to read "Injection" and position the statement so that it is adjacent to the proper name (see below).

   "[redacted (b) (4)] injection".

4. Revise the route of administration statement to read: "For subcutaneous use".
5. Identify the location for the U.S. license number.
6. The triangle and rectangle on the right side of the 300 mcg and 480 mcg strengths, respectively, contain the dosage unit "mcg". Increase the size of the unit and place it to the right of the numerical designation (e.g., "300 mcg").
7. Revise the inactive ingredients statement from [redacted (b) (4)] to read: "Inactive ingredients: glacial acetic acid...."

C. Blister Pack Labeling

1. There are two pre-filled syringe configurations for the product, a syringe with a needle guard and a syringe without a needle guard, however, the labeling does not state the type of syringe that is inside the package. State on the labeling whether the blister pack contains a syringe with a needle guard or without a needle guard.
2. The statement "Peal Back" on the left side of the labeling contains the misspelled word "Peal". Correct the spelling to read: "Peel".

D. Carton Labeling (1-count, 5-count, and 10-count)

1. Add the statement "Discard unused portion" to the principal display panel.
2. The net quantity statements on the 10-count carton labeling for the syringes with a needle guard are inconsistent. The statement on the principal display panel reads, "Single-use pre-filled syringes with a *safety needle guard*" whereas the statement on

the side panels reads, [redacted] (b) (4)
Revise the statements on the side panels to correspond with the statement on the principal display panel.

3. The net quantity statements for both syringe configurations have a gray background and are not differentiated from one another. Use color or other means to differentiate the net quantity statements for the syringes with a needle guard from the syringes without a needle guard.

E. Syringes

1. The blue number markings are difficult to see due to a lack of contrast and the light font weight. We recommend the use of a darker color and heavier weight font for the markings (e.g., black) in order to increase the contrast and improve visibility.

2. [redacted] (b) (4)

3. The decimal points look like commas. Use a dot (.) as the decimal point designation.

APPENDICES

Appendix A: Insert Labeling Recommendations, Sections 3 and 16

1. Section 3, Dosage Forms and Strengths

   Add the dosage form "injection" to the statement

2. Section 16 How Supplied/Storage and Handling

   Revise the wording to include the statement "discard unused portion" to be placed conjunction with the statement "single use syringe" (i.e., "single-use syringe—discard unused portion").

Appendix B: Insert Labeling Recommendations, Section 17 Patient Labeling

1. Patient Information

(b) (4)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

CONSULT REVIEW

Date: July 27, 2010

From: William M. Burdick, Biomedical Engineer/Physicist
ODE/DAGID, General Hospital Device Branch

To: Danyal Chaudhry
CDER/OODP/Division of Biologic Oncology Products

Through: Nikhil Thakur
ODE/DAGID General Hospital Devices Branch
Team Leader, Comb. Prod.

Subject: **125294/S0022– Engineering Consult: Response from Teva following 6/30/10 teleconference**

BACKGROUND: 6/30/10 Teleconference
Below are the Minutes of the Meeting/Teleconference, verbatim.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 30, 2010

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 (b)(4) (Teleconference with Teva regarding the (b)(4) supplied Syringe)

Teleconference Date: June 30, 2010

Teleconference Requestor: FDA

Product: Neutroval

Proposed Use: For the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer
Teleconference Purpose: To communicate unresolved information requests regarding the safe use of the final finished syringe for the BLA.

Attendees:

FDA

Patricia Keegan, DBOP, Division Director
Suzanne Demko, DBOP, Clinical TL & CDTL
Thomas Herndon, DBOP, Clinical Reviewer
Erik Laughner, DBOP, Senior RPM
Nikhil Thakur, CDRH
Emily Shacter, DTP, CMC TL
Dov Pluznik, DTP, CMC Reviewer
Lana Shiu, OCP, Medical Advisor
Kathy Lee, DTP, CMC TL
Danyal Chaudhry, DBOP, RPM

Teva

Dennis Ahern, Director, US Regulatory Affairs
Diana Landa, Associate Director, Regulatory Affairs
Noa Avisar, R & D Project Manager, Israel

DISCUSSION:

FDA stated that their previous information requests to Teva regarding the syringe delivery system were still not propery addressed.

FDA stated that the proposed delivery system for the Neutroval BLA was a pre-filled syringe with or without a needle guard. FDA noted that components of the (b) (4) syringe did not meet current ISO standards, (b) (4) (b) (4) Teva confirmed that a sub-cutaneous injection was the only current route proposed in the BLA. FDA acknowledged and noted that while (b) (4) (b) (4)

FDA noted that Neutroval is (b) (4) (b) (4) Teva clarified that health professionals gave the drug. FDA noted that Teva would then have to provide data (b) (4) (b) (4)

Teva was requested to identify in either the BLA or (b) (4) master file (by right of reference) the specific section (page number),

(b) (4)
information needed by FDA to review the proposed syringe/device. If this information was not available, FDA requested that no new information be provided to the BLA for review at this time.

(b) (4)

FDA requested that Teva go back and investigate what performance information was contained in the current BLA or (b) (4) master file. FDA will provide CDRH Guidance documents regarding relevant information needed for the review of the drug delivery system.

(b) (4)

(b) (4)

CDRH notes that based upon further clarification from the Sponsor, and through discussions with CDER, Neutroval has been designated to be delivered through a pre-filled syringe with the needle already attached. CDRH has modified our review, and our recommendation to reflect this fact.

Following the teleconference the sponsor was requested to address a number of remaining issues concerning their BLA. Two of these issues are consequences of my original review and are addressed in the next section.

ENGINEERING ASSESSMENT AND DISCUSSION POINTS

The following two engineering issues resulted from the aforementioned teleconference.

FDA Question #1: Since the (b) (4) syringe (b) (4) (b) (4) it apparently does not meet the current ISO standards for pre-filled syringes. FDA does not specifically require that the ISO standards are met for the

device components (without drug); however, they're concerned and need proof that the device is capable of safely delivering Teva's product. What data, regarding performance criteria, for delivery with reference to ISO standards exists for Neutroval?

Teva response: For the purpose of syringe performance, Teva considers the most significant performance criteria for the syringe unit to be the volume delivered as to ensure appropriate dosage administered to the patient. Additionally, for those syringes provided with the safety device, a proper functioning of the safety device is considered critical. Accordingly, the following checks are performed routinely:

1. In-Process test (please refer to **Module 3.2.P.3.3** for DP Manufacturing Procedure)

(b) (4)

2. DP Release and Stability (please refer to **Module 3.2.P.5.1** and **Module 3.2.P.8.2**)

• Extractable volume is performed on release on every lot of DP. Additionally, the test is repeated at the 24-month and 36-month time stations on all annual batches placed on stability. The specifications for extractable volume are actually tighter than those specified in the USP, thus providing maximum assurance of delivery of a proper dose to the patient.

• Functional Test of Needle Safety Device is performed to ensure that the safety device is functioning properly upon activation and fully covers the needle after injection. This test is also performed on every lot of the DP at Release as well as the 24-month and 36-month time stations on all annual batches placed on stability.

Additionally, please note (b) (4) are performed at the Teva manufacturing site. All packaging components undergo verification of vendor's Certificate of Compliance to ensure compliance with all vendor's specifications, visual inspection to ensure cleanliness and

physical integrity of the component, and release testing, which incorporates a battery of chemical, physical as well as functional tests, according to the specifications provided in the original BLA.

Please refer to the following locations within the BLA for component specifications:

Component Teva Specifications (Location within BLA)
Syringe Unit **Appendix 3.2.P.7-8**
Stopper **Appendix 3.2.P.7-15**
Plunger Rods **Appendix 3.2.P.7-19** and **20**
Needle Safety Guard **Appendix 3.2.P.7-30**

Please note that the design of the syringe unit and safety device has been solely the responsibility of the component suppliers, (b) (4) (b) (4) respectively, (i.e., Teva did not require any customizations to the syringe and purchased the syringe from the supplier from common parts obtained through the suppliers catalog). Teva chose the syringe and the safety device based on performance characteristics described above, i.e. ability to deliver the proper dose and maintain proper functionality throughout shelf-life. It is Teva's belief that all important functionality aspects are controlled and ensured by testing currently in place for all packaging components and the packaged drug product.

My Assessment
They still have not provided adequate information concerning the analysis of their device closure system. For example, they 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 that can affect the amount delivered. Given the fact that this specific (b) (4) glass syringe is currently under Agency scrutiny regarding connection incapabilities, identified by the medical community, coupled with the fact that these syringes appear to not have been subjected to current FDA consensus standards regarding syringes and needles, I feel they need to meet the requirements of applicable specifications in the standards OR provide valid scientific and/or clinical reasons for not meeting the specifications.

FDA Question #3: (b) (4)

Teva response: (b) (4)

s.

My Assessment

(b) (4)

(b) (4)

CONCLUSION AND RECOMMENDATION

To facilitate incorporation into CDER's *Complete Response* letter, CDRH has worded our deficiencies in a manner that directly addresses the Sponsor. Please convey the following deficiencies regarding the medical device constituent of this combination product:

1. You have not provided adequate information concerning the analysis of your device closure system. Based on our assessment of your response, 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 the (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) (b) (4)), it appears that your syringes may not conform to current FDA consensus standards regarding syringes and needles.

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

    - (b) (4)

    b. FDA also believes that certain aspects of other syringe standards may still apply to your device. Specifically, we note that the device constituent of this combination product consists of a (b) (4) glass syringe with the needle pre-attached. In this capacity, the all specifications of the current consensus standards such as (b) (4) 4) However, you must still consider the application of specific elements of these standards as they impact your device. (b) (4)

(b) (4)

. You should 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).

2. (b) (4)

William M. Burdick

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	**July 21, 2010**
To:	**Patricia Keegan, MD, Director**
	Division of Biologic Oncology Products
Through:	Mary, Willy PhD. Deputy Director 7/21/10
	Division of Risk Management (DRISK)
	Sharon R. Mills, BSN, RN, CCRP
	Senior Patient Labeling Reviewer, Acting Team Leader
	Division of Risk Management
From:	Steve L. Morin, RN, BSN
	Patient Labeling Reviewer
	Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Instructions for Use),
Drug Name(s):	NEUTROVAL® (b) (4)
Application Type/Number:	BLA 125294
Applicant/sponsor:	Teva Pharmaceuticals USA
OSE RCM #:	2009-2468

1 INTRODUCTION

Teva Pharmaceuticals on November 30, 2009 submitted a new Biologic License Application, BLA 125-294 for NEUTROVAL® (b) (4) . This is a formulation of (b) (4) [Recombinant N-methionyl human granulocyte colonystimulating factor (r-metHuG-CSF).

This review is written in response to a request by the Division of Biologic Oncology Products (DBOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Instructions for Use for NEUTROVAL® (b) (4) (b) (4) . (b) (4) ;, DBOP notified DRISK that they intend to only have Patient Instructions for Use for the product.

2 MATERIAL REVIEWED

- Draft NEUTROVAL® (b) (4) (b) (4) Prescribing Information (PI) submitted November 30, 2009, revised by the Review Division throughout the current review cycle and provided to DRISK on July 9, 2010.
- Draft NEUTROVAL® (b) (4) (b) (4) Patient Instruction for Use submitted on November 30, 2009, revised by the review division throughout the review cycle and provided to DRISK on July 9, 2010.

3 RESULTS OF REVIEW

In our review of the IFU's, we have:

- simplified wording and clarified concepts where possible
- removed unnecessary or redundant information
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- referenced the approved Patient Instructions for Use for Neupogen dated 2006. The currently approved PI dated March 2, 2010 does not include Patient Instructions for Use.
- referenced the DRISK review of the Neulasta Patient Labeling (PPI and IFU) dated, February 5, 2010

Our annotated IFU is appended to this memo. Please send these comments to the Applicant and copy DRISK on the correspondence. Let us know if DBOP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

Any additional revisions to the PI should be reflected in the IFU.

Please let us know if you have any questions.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 20, 2010

From: Suchitra Balakrishnan, M.D., Ph.D.
Hao Zhu, Ph.D.

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Danyal Chaudhry/Eric Laughner
Regulatory Project Manager
Division of Biologic Oncology Products Products

Subject: QT-IRT Consult to BLA 125294

This memo responds to your consult to us dated July 2, 2010 regarding [redacted] (b) (4), Neutroval (XM02), sponsored by Teva Pharmaceuticals. The QT-IRT received and reviewed the following materials:

- Your consult
- [redacted] (b) (4)
- Previous reviews by the QT-IRT for BLA 125294

QT-IRT Comments for DBOP

- [redacted] (b) (4)
- However, if XM02 is being assessed as an NME then a QT assessment is still recommended. It can be conducted in patients at the maximum tolerated dose if a study in healthy volunteers is not feasible. As stated in our previous consult, it can be conducted as a PMC since we don't expect QT liability to be high with XM02.

BACKGROUND

Neutroval (XM02) is a formulation of filgrastim; which is a recombinant human granulocyte colony stimulating factor produced in E. coli, yielding a protein without glycosylation and with an N-terminal methionyl extension (r-metHuG-CSF).1t has a molecular weight of 18,799 Dalton and is a single chain of (b) (4)-amino acid polypeptide. XM02 was developed as a biosimilar (with Neupogen® being the reference product) under EMEA guidance. XM02 was approved in the Europe Union in September 2008. The sponsor reports that XM02 was developed to be similar to Neupogen®; (b) (4)

In a previous review dated May 6, 2010, the QT-IRT recommended a QT evaluation for XM02 based on smaller size compared to monoclonal antibodies and our understanding regarding current regulatory process for biosimilars. (b) (4)

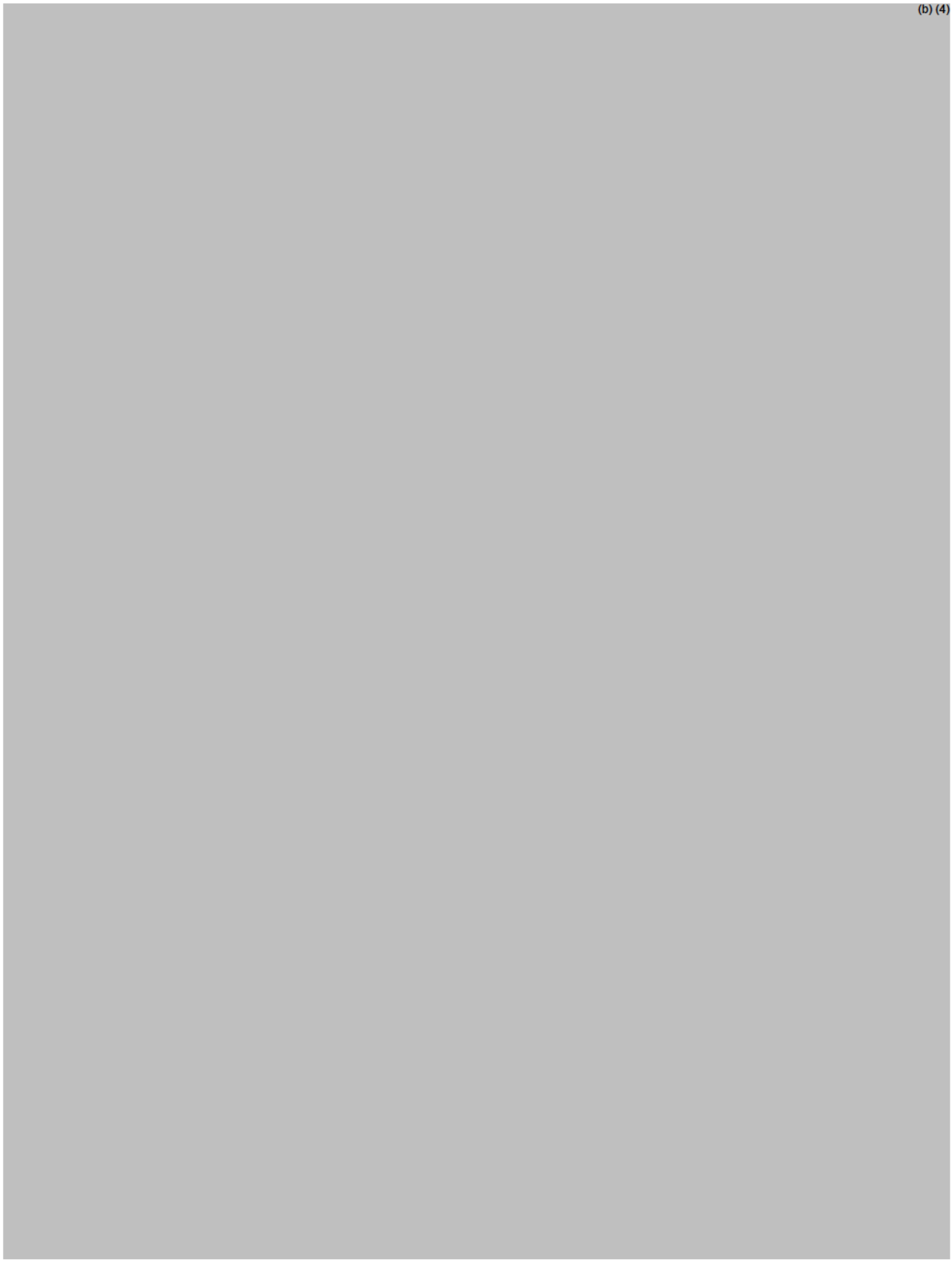
(b) (4)

(b) (4)

Reviewers Comments:
The clinical ECG and safety data obtained in the XM02 program have already been discussed in our previous review dated May 6, 2010.
ECGs were collected only in the healthy volunteer studies. They are not very informative since they were only collected at screening and follow-up and not during treatment. It would have been preferable to collect baseline and periodic on-therapy ECGs in the patient studies to exclude large cardiovascular effects.

SPONSOR'S PROPOSAL

(b) (4)



Reviewer's Comment: The sponsor's rationale for hERG liability seems reasonable; however pro-arrhythmic effects through other mechanisms cannot be excluded.

(b) (4)

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

*****Pre-Decisional Agency Information *****

Date: July 1, 2010

To: Danyal Chaudhry, Regulatory Project Manager
Division of Biologic Oncology Products

From: Division of Drug Marketing, Advertising, and Communications (DDMAC)

Package Insert:
Nisha Patel, Pharm.D., Regulatory Review Officer Nisha Patel 7/1/10
Sheila Ryan, Pharm.D., Group Leader

Patient Labeling:
Cynthia Collins, Ph.D., Regulatory Review Officer Cynthia Collins 07-01-10.

Subject: **Neutroval®** (b) (4)
BLA 125294

DDMAC has reviewed the proposed product labeling, including the package insert (PI), and patient labeling for Neutroval® (b) (4), dated June 28, 2010, and we offer the following comments. We have also taken into consideration the labeling for Neupogen® (filgrastim) and Neulasta® (pegfilgrastim).

DDMAC has also reviewed the proposed patient labeling, consisting of the Patient Instructions for Use (the Patient Package Insert was deleted from the proposed labeling at the June 25, 2010, labeling meeting). DDMAC has no comments on the Patient Instructions for Use at this time.

If you have any questions, please contact Nisha Patel (Package Insert) at 301-796-3715 or Cynthia Collins (Patient Labeling) at 301-796-4284.

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

CONSULT REVIEW

Date: May 4, 2010

From: William M. Burdick, Biomedical Engineer/Physicist WMB
ODE/DAGID, General Hospital Device Branch

To: Jee Chung
CDER/Division of Biologic Oncology Products

Through: Nikhil Thakur
ODE/DAGID General Hospital Devices Branch

Subject: **CON100799, BLA 125294– Engineering Consult: Review of Pre-Filled Syringe**

IMPORTANT NOTE: I reviewed the physical and engineering information and data that I received. Most of this described the tests to which the System was subjected including the test protocols, the test results, an interpretation of the significance of the testing and subsequent results, and the resulting impact on the safety and effectiveness of the System.

Information which I did not review and which we customarily defer to the expertise of CDER included the following:

- **Biocompatibility**
- **Sterility**
- **Compatibility between the Material Comprising the Device and Contacting Drug**
- **Stability of the Drug in the Device**
- **Microbiological Testing**
- **Chemical Testing**
- (b) (4) **Filling of Syringes**
- **Labeling**

Generally, we defer to CDER regarding the above testing, because CDER has many more in-house scientists who are familiar with and eminently qualified to perform the types of analyses required to assess such testing. If you would like to contact CDRH experts in these fields, I will provide you the names of available personnel with whom I am familiar.

We also defer to CDER regarding drug labeling.

BACKGROUND

A pre-filled syringe is intended to deliver recombinant human granulocyte colony stimulating factor (b) (4) -DP) for the reduction of the duration of severe neutropenia and the incidence

of febrile neutropenia in nonmyeloid cancer patients receiving myelosuppressive chemotherapy. The product will be available as either 300 mcg/0.5 ml or 480 mcg/0.8ml amounts (b) (4)

DEVICE DESCRIPTION

Over-all Description of Container Closure System

(b) (4) DP will be supplied in a pre-filled syringe. The container closure system selected for

Table 3.2.P.2.4-1: Validated Container Closure and Delivery Systems for (b) (4) -DP

Component	Specifications	Supplier
Syringe Unit	(b) (4)	(b) (4)

the product is distributed by (b) (4) The container closure system includes the syringe barrel with fixed needle and needle shield, and plunger stopper. The validated container closure system is presented in Table 1.

TABLE 1: VALIDATED CONTAINER CLOSURE AND DELIVERY SYSTEMS FOR (b) (4) DP		
COMPONENT	**SPECIFICATION**	**SUPPLIER**
Syringe Unit	(b) (4)	
Needle Shield		
Plunger Stopper		

The (b) (4) -DP pre-filled syringes for both 300 mcg/0.5 mL and 480 mcg/0.8 mL strengths employ the following components in their container/closure:

- (b) (4) glass (Type I) syringe barrel
- (b) (4) steel needle (supplied as a unit with the syringe)
- (b) (4) needle shield (supplied as a unit with the syringe)
- (b) (4) rubber plunger stopper
- (b) (4) plunger rod*

• UltraSafe Passive™ Needle Guard, manufactured by (b) (4)

(b) (4)

Syringe Barrel

(b) (4)

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RECOMMENDATION

I recommend that the sponsor be requested to provide the following additional information:

1. Please provide verification, validation, and testing information related to your final, finished product. You provided substantial information regarding the assessment of the manufacturing of your device, but you did not provide information related to design, development, and validation of your device related to its intended use. Information we require is covered in the following FDA guidance and industry standards:

   - (b) (4)

   DMF (b) (4) was cited in your submission but DMF (b) (4) is a huge document, and specification of the volumes and pertinent sections relating to the subject device was not cited in the document. If any or all of the verification, validation, and testing information covered in the preceding guidance document and standards is assessed in DMF (b) (4) or any other document, please provide the appropriate volumes and pertinent sections. We need this information in order to continue the review of your BLA.

   (b) (4)

2. (b) (4)

William M. Burdick

William M. Burdick

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Biologic Oncology Products

Application Number: Original BL 125294/0

Name of Drug: Neutroval (b) (4)), 300mcg/0.5 ml & 480 mcg/0.5 ml, (b) (4) S.C. Injection

Applicant: TEVA Pharmaceuticals USA

Material Reviewed:

Submission Date(s): November 30, 2009

Receipt Date(s): November 30, 2009

Submission Date of Structure Product Labeling (SPL): November 30, 2009

Type of Labeling Reviewed: WORD/SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

This is a preliminary review of the proposed labeling submitted in this application. The RPM review is composed of PLR formatting edits which are embedded in the attached label. This label also contains edits and comments made by the CDTL.

Recommendations

This red-lined label with embedded comments to Sponsor will be provided with the 74-day letter. The sponsor should address the identified deficiencies/ issues and resubmit labeling by March 19, 2010.

28 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

2/19/10

Danyal Chaudhry
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Karen D. Jones 2/19/10

Karen Jones
Chief, Project Management Staff

Drafted: Danyal Chaudhry/1-21-10
Revised/Initialed:
Finalized:
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY ADDENDUM

DATE: December 16, 2011

TO: Erik Laughner, Regulatory Project Manager
Robert Thomas Herndon, Medical Officer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

BLA: 125294/0

APPLICANT: Teva Pharmaceuticals

DRUG: Neutroval (XM02)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: The reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer.

CONSULTATION REQUEST DATE: 2/3/2010
DIVISION ACTION GOAL DATE: 07/31/2010
PDUFA DATE: 09/30/2010

ADDENDUM To CIS:
This is an addendum to the finalized Clinical Inspection Summary with Addendum for BLA 125294, dated September 15, 2010. The basis for this addendum is to provide the results of the inspection of (b) (4) and revise OSI's recommendation of data integrity for Study XM02-02-INT.

Background: Previously, on (b) (4), FDA inspected the study sponsor's (BioGeneriX AG) conduct of Protocol XM02-02-INT, entitled, "Efficacy and Safety of XM02 Compared to Filgrastim In Patients With Breast Cancer Receiving Chemotherapy. A Multinational, Multicentre, Randomized, and Controlled Study," in support of BLA 125294. During that inspection the FDA field investigator was not able to verify the integrity of the clinical database maintained by a CRO, (b) (4) The sponsor did not have adequate documentation that demonstrated sponsor-authorized/justified database manipulations, nor could they provide documentation that described exactly what was altered in the clinical database. A Complete Response Letter, dated September 29, 2010, was issued to the BLA 125294 Applicant, Teva Pharmaceuticals U.S.A., and included this observation as a deficiency (CR LTR, Item 1).

Update: The inspection of CRO (b) (4) was conducted by FDA field investigators on (b) (4) (b) (4) as a follow up to the inspection of study sponsor, to verify the integrity of the clinical database for Study XM02-02.

Results of the (b) (4) inspection revealed that there were clear failures to control access to the database via the locking and unlocking processes, and failure to adequately document significant steps in the control of the database. However, the audit trail of the clinical database, assessed during the (b) (4) inspection, confirmed that no inappropriate changes were made to the database during time periods when it was in unlocked status. The inspection findings conclude that the primary efficacy data were verifiable and there was no evidence of underreporting of SAEs. The remaining regulatory violations noted during the inspection of (b) (4) are considered unlikely to importantly impact data integrity.

Assessment of data integrity: The data generated at this site, as it pertains to Study XM02-02-INT were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The inspection findings support that the data from this CRO submitted to the agency as part and in support of BLA 125294 appear reliable.

/Lauren Iacono-Connors, Ph.D./
Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

/Susan Leibenhaut, M.D./
Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

/Tejashri Purohit-Sheth, M.D./
Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Attachment

Clinical Inspection Summary with Addendum, dated September 15, 2010

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 6, 2010

From: Suchitra Balakrishnan, M.D., Ph.D.
Hao Zhu, Ph.D.
CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Danyal Chaudhry/Erik Laughner
Regulatory Project Managers
Division of Biologic Oncology Products

Subject: QT-IRT Consult to BLA 125294

This memo responds to your consult to us dated March 26, 2010 regarding ECG assessments for Neutroval (b) (4) sponsored by Teva Pharmaceuticals. The QT-IRT received and reviewed the following materials:

- Your consult
- eCTD summaries including summary of clinical safety (eCTD 2.7.4)
- Study report for XM02-05-DE

QT-IRT Comments for DBOP

- The ECGs collected in the healthy volunteer studies are not very informative since they were only collected at follow-up and not during treatment.
- For monoclonal antibodies (mAb), we recommend periodic ECG monitoring in the clinical trials to exclude to exclude large cardiovascular effects instead of a thorough QT study (TQT) assessment. All other biologics are assessed on a case-by-case basis. (b) (4) is about one-tenth as large as a monoclonal antibody. We do not have a molecular weight cut-off to date. We base our decision for mAB based on size and target specificity. Since we are not sure about the latter in this case we will recommend requesting a TQT. We feel requesting the Thorough ECG assessment as a PMR is reasonable since we have some experience with the reference compound (Neupogen) and we do not expect QT liability to be high.

- We recommend that the sponsor conduct TQT study to assess the QTc prolongation risk. A single-dose cross-over study using the maximum tolerated dose should be possibly adequate. The sponsor should submit the study protocol for QT-IRT to review.

BACKGROUND

Neutroval (XM02) is a formulation of filgrastim; which is a recombinant human granulocyte colony stimulating factor produced in *E. coli*, yielding a protein without glycosylation and with an N-terminal methionyl extension (r-metHuG-CSF). It has a molecular weight of 18,798.98 Dalton and is a single chain of (b) (4)-amino acid polypeptide. XM02 was developed as a biosimilar (with Neupogen® being the reference product) under EMEA guidance. XM02 was approved in the Europe Union in September 2008 and is marketed as TevaGrastim® and Ratiograstim®.

Filgrastim is used for reducing the duration of neutropenia and the incidence of febrile neutropenia (FN) in patients undergoing myelosuppressive chemotherapy (CTX) for malignant diseases and for reducing the duration of neutropenia in patients undergoing myeloablative therapy prior to bone marrow transplantation who are at risk of prolonged severe neutropenia. Filgrastim is also used to mobilize peripheral blood stem cells as monotherapy or after myelosuppressive CTX, and in long-term treatment of severe congenital, cyclical or idiopathic neutropenia.

Non-Clinical Experience

Source: Pharmacology Written Summary

A single s.c. injection of XM02 administered to male Beagle dogs at a dose level of 3,500 µg/kg resulted in no treatment-related clinical signs, nor was there any effect on hemodynamic measures during the 48-h observation period. The electrocardiographic interpretation showed no treatment-related changes.

The sponsor also reports no effects on the electrocardiograms in the 26-week toxicity study in monkeys but no further details are available.

Previous clinical experience

As part of the clinical development program 5 clinical studies were completed, in which safety of XM02 was evaluated in a total of 877 subjects. Since XM02 was developed as a biosimilar in Europe the safety of XM02 was compared to that of Neupogen® (filgrastim). There were 2 phase I studies in healthy volunteers (studies XM02-01-LT and XM02-05-DE included 200 subjects), and 3 phase III studies in 677 CTX treated cancer patients with breast cancer (study XM02-02-INT), lung cancer (study XM02-03-INT), or Non-Hodgkin Lymphoma (NHL) (study XM02-04-INT), who received G-CSF support in addition to CTX.

Cardiac AEs

Table 4.3.1: TEAEs by system organ class and preferred term - Cancer patients set

System Organ Class / Preferred Term	XM02 only (N=356) N	%	E	Filgrastim only (N=136) N	%	E	Filgrastim /XM02 (1) (N=115) N	%	E	Placebo /XM02 (2) (N=72) N	%	E	Any XM02 (N=541) N	%	E	Overall (N=677) N	%	E	p-value
Period: Overall																			
BLOOD AND LYMPHATIC SYSTEM DISORDERS																			
THROMBOCYTHAEMIA	5	1.4	5	1	0.7	1	0			1	1.4	1	6	1.1	6	7	1.0	7	0.634
THROMBOCYTOPENIA	31	8.7	85	4	3.0	7	17	14.8	28	4	5.6	5	52	9.6	118	56	8.3	125	0.003
CARDIAC DISORDERS																			
Any TEAE	36	10.1	53	7	5.2	7	12	10.4	17	7	9.7	8	53	9.8	76	62	9.2	85	0.282
ANGINA PECTORIS	3	0.8	3	1	0.7	1	1	0.9	1	2	2.8	2	6	1.1	6	7	1.0	7	1.000
ARRHYTHMIA	0			0			1	0.9	1	0			1	0.2	1	1	0.1	1	0.190
ATRIAL FIBRILLATION	5	1.4	6	0			2	1.7	2	0			7	1.3	8	7	1.0	8	0.327
ATRIAL FLUTTER	1	0.3	1	0			0			0			1	0.2	1	1	0.1	1	1.000
BRADYCARDIA	1	0.3	1	0			0			0			1	0.2	1	1	0.1	1	1.000
CARDIAC FAILURE	1	0.3	1	0			2	1.7	2	0			3	0.6	3	3	0.4	3	0.133
CARDIAC FAILURE ACUTE	0			0			1	0.9	1	0			1	0.2	1	1	0.1	1	0.190
CARDIAC FAILURE CONGESTIVE	2	0.6	2	0			0			0			2	0.4	2	2	0.3	2	1.000
CARDIAC TAMPONADE	1	0.3	1	0			0			0			1	0.2	1	1	0.1	1	1.000
CARDIO-RESPIRATORY ARREST	2	0.6	2	0			1	0.9	1	1	1.4	1	3	0.6	3	4	0.6	4	0.566
CARDIOMYOPATHY	1	0.3	1	0			0			0			1	0.2	1	1	0.1	1	1.000
CARDIOPULMONARY FAILURE	0			0			2	1.7	2	0			2	0.4	2	2	0.3	2	0.036
CONGESTS	3	0.8	3	0			0			0			3	0.6	3	3	0.4	3	0.769
MYOCARDIAL INFARCTION	0			1	0.7	1	1	0.9	1	0			1	0.2	1	2	0.3	2	0.169
MYOCARDIAL ISCHAEMIA	2	0.6	4	0			0			0			2	0.4	4	2	0.3	4	1.000
PALPITATIONS	3	0.8	4	3	2.2	3	0			1	1.4	1	4	0.7	5	7	1.0	8	0.251
PERICARDIAL EFFUSION	1	0.3	1	0			1	0.9	1	0			2	0.4	2	2	0.3	2	0.393
SINUS TACHYCARDIA	2	0.6	2	0			1	0.9	1	0			3	0.6	3	3	0.4	3	0.566

(continued)
N, % = number and % of patients with TEAEs (% based on patients exposed to drug), E = number of events. AEs were coded using MedDRA 7.1.
p-value: 2-sided p-value of Fisher's exact test comparing the first 3 actual treatment groups, excluding 'Placebo/XM02'
(1) Received both Filgrastim and XM02, no placebo. All but 4 patients got Filgrastim in cycle 1, XM02 thereafter.
(2) Placebo (cycle 1), XM02 thereafter, including 2 patients without XM02 and 12 patients who got also Filgrastim.

19OCT06:10:33 //projects/biogs81909/stats/programs/tables/t_advrsc_events.rtf 86

Table 4.3.1: TEAEs by system organ class and preferred term - Cancer patients set

System Organ Class / Preferred Term	XM02 only (N=356) N	%	E	Filgrastim only (N=136) N	%	E	Filgrastim /XM02 (1) (N=115) N	%	E	Placebo /XM02 (2) (N=72) N	%	E	Any XM02 (N=541) N	%	E	Overall (N=677) N	%	E	p-value
Period: Overall																			
CARDIAC DISORDERS																			
SUPRAVENTRICULAR EXTRASYSTOLES	1	0.3	1	0			0			0			1	0.2	1	1	0.1	1	1.000
TACHYCARDIA	16	4.5	19	1	0.7	1	3	2.6	3	4	5.6	4	22	4.1	25	24	3.5	27	0.098
VENTRICULAR EXTRASYSTOLES	1	0.3	1	0			1	0.9	1	0			2	0.4	2	2	0.3	2	0.393
VENTRICULAR TACHYCARDIA	0			1	0.7	1	0			0			0			1	0.1	1	0.412

(From the ISS)

Reviewers's Comments: There were no reports of sudden death or significant ventricular arrhythmias in the ISS and summary of safety. The sponsor attributed all cases of cardiorespiratory arrest or cardiopulmonary failure to the underlying disease. There appears to be an imbalance in the number of events in the cardiac disorders SOC for XM02 alone and overall XM02 compared to filgrastim alone (10% v.s. 5%). Specifically, tachycardias were seen more frequently in the XM02 group but these could have mulifactorial etiologies (infusion reactions, anemia, etc.).

ECGs

ECGs were routinely collected only in the healthy volunteer studies.

XM02-01 was a phase I, single center, single blind, single dose, randomized, two-period crossover, two arm study in 56 healthy male subjects to compare PK and pharmacodynamic profiles of XM02 and Neupogen®. Study subjects received either s.c. 5 µg/kg or s.c. 10 µg/kg of study drug. The crossover design included 2 treatment periods, separated by a 2-week washout period. ECG monitoring was done at screening and at follow up and no significant changes were noted in QT, QRS, or PR.

Study XM02-05 was a study on the bioequivalence of 5 μg/kg or 10 μg/kg of XM02 and Neupogen®, each after intravenous or subcutaneous administration and was a multi-center, randomized, single dose, single-blind, two-way crossover design. The study was carried out in two study periods lasting 16 days each, with administration on Study Day 1 of each period and a washout period of at least 3 weeks between the first and second administration. There were 36 planned subjects per group and 144 total subjects. Subjects were monitored using a 12 lead EKG at screeening and at follow-up. Mean and median values of ECG parameters remained within normal limits under all treatments.
Reviewer's Comments: These ECGs in healthy volunteers are not very informative since they were only collected at follow-up and not during treatment. It would have been preferable to collect baseline and periodic on-therapy ECGs in the patient studies to exclude large cardiovascular effects.

Post-marketing experience
The Periodic Safety Update Report submitted by the sponsor for filgrastim parenteral formulations was reviewed. No cardiac AEs were reported
MGPS datamining analysis
This reviewer conducted an MGPS data mining analyses of AERS for cardiac arrhythmias associated with filgrastim. The signal scores (EBGM values) for most PT's were under 2 indicated incidence less than twice the background rate, except for supraventricular arrhythmias (EBGM-2.1) and sudden cardiac death (EBGM-1.94). Even for these events the lower bound of the confidence interval (EB05 value), was less than 1.

Configuration: CBAERS BestRep (S) (v2) **Run :** Generic (S) **Run ID:** 2726
Dimension: 2 **Selection Criteria:** Generic name(...) + PT(...) **Where:** EBGM > 1.0
20 rows Sorted by Generic name, EBGM desc

Generic name	PT	HLT	N	EBGM	EB05	EB95
Filgrastim	Arrhythmia supraventricular	Supraventricular arrhythmias	4	2.10	0.921	4.28
Filgrastim	Sudden cardiac death	Death and sudden death	3	1.94	0.757	4.29
Filgrastim	Tachycardia	Rate and rhythm disorders NEC	85	1.64	1.37	1.95
Filgrastim	Conduction disorder	Cardiac conduction disorders	2	1.42	0.464	3.55
Filgrastim	Atrial fibrillation	Supraventricular arrhythmias	24	1.33	0.943	1.83
Filgrastim	Cardio-respiratory arrest	Ventricular arrhythmias and cardiac arrest	14	1.33	0.847	2.00
Filgrastim	Bundle branch block bilateral	Cardiac conduction disorders	1	1.32	0.307	4.14
Filgrastim	Atrioventricular dissociation	Cardiac conduction disorders	1	1.27	0.297	3.97
Filgrastim	Tachycardia paroxysmal	Rate and rhythm disorders NEC	1	1.23	0.288	3.83
Filgrastim	Supraventricular tachycardia	Supraventricular arrhythmias	6	1.18	0.599	2.15
Filgrastim	Bradyarrhythmia	Rate and rhythm disorders NEC	1	1.10	0.258	3.42
Filgrastim	Ventricular arrhythmia	Ventricular arrhythmias and cardiac arrest	2	1.02	0.332	2.54
Pegfilgrastim	Arrhythmia supraventricular	Supraventricular arrhythmias	3	1.55	0.605	3.42
Pegfilgrastim	Tachycardia	Rate and rhythm disorders NEC	33	1.52	1.13	2.00
Pegfilgrastim	Sinus tachycardia	Supraventricular arrhythmias	7	1.38	0.730	2.41
Pegfilgrastim	Supraventricular tachycardia	Supraventricular arrhythmias	5	1.32	0.630	2.53
Pegfilgrastim	Tachyarrhythmia	Rate and rhythm disorders NEC	2	1.20	0.393	3.00
Pegfilgrastim	Atrial flutter	Supraventricular arrhythmias	3	1.12	0.436	2.46
Pegfilgrastim	Sudden death	Death and sudden death	6	1.09	0.553	1.99
Pegfilgrastim	Atrial fibrillation	Supraventricular arrhythmias	22	1.07	0.749	1.50

ID:	2726
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S) (v2)
Configuration description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As of date:	04/15/2010 00:00:00
Item variables:	Generic name, PT
Stratification variables:	Standard strata
Highest dimension:	2

Minimum count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base counts on cases:	Yes
Use "all drugs" comparator:	No
Apply Yates correction:	Yes
Stratify PRR and ROR:	No
Fill in hierarchy values:	Yes
Exclude single itemtypes:	Yes
Fit separate distributions:	Yes
Save intermediate files:	No
Created by:	Empirica Signal Administrator
Created on:	04/24/2010 06:25:38 EDT
User:	Suchitra Balakrishnan
Source database:	Source Data: CBAERS data from Extract provided by CBER as of 04/15/2010 00:00:00 loaded on 2010-04-23 02:45:42.0

Dimension: 2 **Selection Criteria:** Generic name(Filgrastim, Filgrastim And G-Csf Unspecified, Filgrastim And Gm-Csf Unspecified, Pegfilgrastim) + PT(Accelerated idioventricular rhythm, Accessory cardiac pathway, Adams-Stokes syndrome, Agonal rhythm, Anomalous atrioventricular excitation, Arrhythmia, Arrhythmia neonatal, Arrhythmia supraventricular, Atrial conduction time prolongation, Atrial fibrillation, Atrial flutter, Atrial tachycardia, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Atrioventricular extrasystoles, Bifascicular block, Bradyarrhythmia, Bradycardia, Bradycardia foetal, Bradycardia neonatal, Brugada syndrome, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Cardiac arrest, Cardiac arrest neonatal, Cardiac death, Cardiac fibrillation, Cardiac flutter, Cardio-respiratory arrest, Cardio-respiratory arrest neonatal, Chronotropic incompetence, Conduction disorder, Electromechanical dissociation, Extrasystoles, Foetal arrhythmia, Foetal heart rate deceleration, Foetal heart rate disorder, Heart alternation, Heart block congenital, Long QT syndrome, Long QT syndrome congenital, Lown-Ganong-Levine syndrome, Neonatal tachycardia, Nodal arrhythmia, Nodal rhythm, Pacemaker complication, Pacemaker generated arrhythmia, Parasystole, Paroxysmal arrhythmia, Postural orthostatic tachycardia syndrome, Rebound tachycardia, Reperfusion arrhythmia, Rhythm idioventricular, Sick sinus syndrome, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus bradycardia, Sinus tachycardia, Sudden cardiac death, Sudden death, Supraventricular extrasystoles, Supraventricular tachyarrhythmia, Supraventricular tachycardia, Tachyarrhythmia, Tachycardia, Tachycardia foetal, Tachycardia paroxysmal, Torsade de pointes, Trifascicular block, Ventricular arrhythmia, Ventricular asystole, Ventricular extrasystoles, Ventricular fibrillation, Ventricular flutter, Ventricular pre-excitation, Ventricular tachyarrhythmia, Ventricular tachycardia, Wandering pacemaker, Withdrawal arrhythmia, Wolff-Parkinson-White syndrome, Wolff-Parkinson-White syndrome congenital) **Where:** EBGM > 1.0

SELECT * FROM OutputData_2726 WHERE (DIM=2 AND EBGM>1.0 AND ((P1='D' AND ITEM1 IN ('Filgrastim','Filgrastim And G-Csf Unspecified','Filgrastim And Gm-Csf Unspecified','Pegfilgrastim') AND P2='E' AND ITEM2 IN ('Accelerated idioventricular rhythm','Accessory cardiac pathway','Adams-Stokes syndrome','Agonal rhythm','Anomalous atrioventricular excitation','Arrhythmia','Arrhythmia neonatal','Arrhythmia supraventricular','Atrial conduction time prolongation','Atrial fibrillation','Atrial flutter','Atrial tachycardia','Atrioventricular block','Atrioventricular block complete','Atrioventricular block first degree','Atrioventricular block second degree','Atrioventricular conduction time shortened','Atrioventricular dissociation','Atrioventricular extrasystoles','Bifascicular block','Bradyarrhythmia','Bradycardia','Bradycardia foetal','Bradycardia neonatal','Brugada syndrome','Bundle branch block','Bundle branch block bilateral','Bundle branch block left','Bundle branch block right','Cardiac arrest','Cardiac arrest neonatal','Cardiac death','Cardiac fibrillation','Cardiac flutter','Cardio-respiratory arrest','Cardio-respiratory arrest neonatal','Chronotropic incompetence','Conduction disorder','Electromechanical dissociation','Extrasystoles','Foetal arrhythmia','Foetal heart rate deceleration','Foetal heart rate disorder','Heart alternation','Heart block congenital','Long QT syndrome','Long QT syndrome congenital','Lown-Ganong-Levine syndrome','Neonatal tachycardia','Nodal arrhythmia','Nodal rhythm','Pacemaker complication','Pacemaker generated arrhythmia','Parasystole','Paroxysmal arrhythmia','Postural orthostatic tachycardia syndrome','Rebound tachycardia','Reperfusion arrhythmia','Rhythm idioventricular','Sick sinus syndrome','Sinoatrial block','Sinus arrest','Sinus arrhythmia','Sinus bradycardia','Sinus tachycardia','Sudden cardiac death','Sudden death','Supraventricular extrasystoles','Supraventricular

tachyarrhythmia','Supraventricular tachycardia','Tachyarrhythmia','Tachycardia','Tachycardia foetal','Tachycardia paroxysmal','Torsade de pointes','Trifascicular block','Ventricular arrhythmia','Ventricular asystole','Ventricular extrasystoles','Ventricular fibrillation','Ventricular flutter','Ventricular pre-excitation','Ventricular tachyarrhythmia','Ventricular tachycardia','Wandering pacemaker','Withdrawal arrhythmia','Wolff-Parkinson-White syndrome','Wolff-Parkinson-White syndrome congenital')))) ORDER BY ITEM1,EBGM desc

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

APPENDIX
Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen. The recommended dose of Neutroval is 5 μg/kg/day administered subcutaneously at 24 hours following myelosuppressive chemotherapy (CTX). Daily dosing should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range	
Maximum tolerated dose	Include if studied or NOAEL dose Neutroval has been used in clinical studies at doses of 5 and 10 μg/kg/day. Higher doses have not been tested. The clinical studies were designed to demonstrate similar safety and efficacy to an active comparator (Neupogen). The mechanism of action and the clinical dosing of filgrastim/ Neutroval are well known so MTD dosing was not explored. In preclinical studies Neutroval was used at doses of up to 500 μg/kg/day in rats and up to 125 μg/kg/day in monkeys for 26 weeks. Toxicity was related to the exaggerated pharmacology of the product and has been observed for other filgrastim products.	
Principal adverse events	Include most common adverse events; dose limiting adverse events Most of the adverse events in the oncology clinical trials were related to the chemotherapy (nausea, alopecia, neutropenia, diarrhea, asthenia and vomiting). Bone pain can result from Neutroval treatment and is presumed to be a consequence of increased proliferation of hematopoietic cells in the bone marrow.	
Maximum dose tested	Single Dose	Specify dose 10 μg/kg
	Multiple Dose	Specify dosing interval and duration 5 μg/kg/day In all 3 phase III studies, starting the day after the end of CTX within a cycle, the patients received daily subcutaneous (s.c.) injections of Neutroval (5 μg/kg/day), for a minimum of 5 days and a maximum of 14 days. The study drug had to be stopped earlier, if an ANC of 10 x 10^9/L after nadir was reached.

<table>
<tr><td rowspan="2">Exposures Achieved at Maximum Tested Dose</td><td>Single Dose</td><td>Mean (%CV); specify dosing regimen
In the study reports of the phase I studies 01 and 05, the CV values are given for the PK parameters Cmax and AUC, see PK appendix of the report.
The highest dose used was 10 µg/kg that was used both SC and IV in Studies XM02-01 and XM02-05.
<table>
<tr><td>Geometric mean</td><td>Study XM02-01</td><td>Study XM02-05</td><td>Study XM02-05</td></tr>
<tr><td></td><td>10 µg/kg SC</td><td>10 µg/kg SC</td><td>10 µg/kg IV</td></tr>
<tr><td>Cmax [ng/mL]</td><td>55.74</td><td>46.24</td><td>231.14</td></tr>
<tr><td>$AUC_{0-\infty}$ [ng/mL/h]</td><td>530.67</td><td>472.24</td><td>1057.42</td></tr>
</table></td></tr>
<tr><td>Multiple Dose</td><td>Mean (%CV); Cmax and AUC
In Studies XM02-02, 03 and 04, PK was measured in a subset of patients not only after the first dose but also in a so-called "second profile" on the day the ANC had reached at least 2 x 10 to the 9/L after nadir. This was in the majority of patients between day 9 and 11. PK data can be found in patients after multiple dosing. Samples for a first and second profile were taken in cycle 1 and cycle 4. Even though these patients received Neutroval for multiple days starting on day 1 after chemotherapy, the PK data was acquired on the day 2 of each cycle. Thus, this PK data does not reflect multiple doses.</td></tr>
<tr><td>Range of linear PK</td><td colspan="2">Specify dosing regimen
The range of linear PK and accumulation at steady state are not applicable for Neutroval.</td></tr>
<tr><td>Accumulation at steady state</td><td colspan="2">Mean (%CV); specify dosing regimen
No specific multiple dose studies to describe accumulation at steady-state were performed. After multiple dosing in the breast cancer study XM02-02 for 9 to 11 days, the AUC 0-24h was slightly lower (geometric means) than after the first injection, i.e. a trend of accumulation was not observed. A trend of accumulation was not observed in the two other phase III studies XM02-03 and XM02-04.</td></tr>
<tr><td>Metabolites</td><td colspan="2">Include listing of all metabolites and activity
Neutroval is a protein that acts via a specific G-CSF receptor on hematopoietic cells to increase the number of neutrophils. In general proteins are metabolized in vivo to peptides and amino acids. The metabolic fate of G-CSF has not been fully determined and it is not known if the drug is metabolized or how it is eliminated from the body. It has been suggested that the level of circulating neutrophils in the body may affect the half-live and clearance of G-CSF, decreasing and increasing, respectively, as neutrophil counts increase.</td></tr>
<tr><td>Absorption</td><td>Absolute/Relative Bioavailability</td><td>Mean (%CV)
The absolute bioavailability of Neutroval was 33% and 45% for the single 5 µg/kg and 10 µg/kg s.c. doses, respectively [Study XM02-05].</td></tr>
</table>

		Relative bioavailability of Neutroval compared to Neupogen is 112% and 104% following single 5 μg/kg and 10 μg/kg sc dosing in healthy subjects, respectively [Study XM02-01]. Results are given in the study report.
	Tmax	• Median (range) for parent 4 hours (1.5 to 6) following subcutaneous Neutroval 5 μg/kg [Study XM02-01] 6 hours (3 to 8) following subcutaneous Neutroval 5 μg/kg [Study XM02-05] 6 hours (2 to 12) for subcutaneous Neutroval 5 μg/kg in the three oncology studies combined. • Median (range) for metabolites Not applicable
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV) As Neutroval is a therapeutic protein, protein binding is not determined.
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent 2.16 hours for subcutaneous Neutroval 5 μg/kg [Study XM02-01] 8.5 hours (%CV= 38.14) for subcutaneous Neutroval 5 μg/kg [Study XM02-05] 3.7 hours (%CV= 37.36) for subcutaneous Neutroval 5 μg/kg in the three oncology studies combined. • Mean (%CV) for metabolites Not applicable
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC There is no apparent difference of Neutroval efficacy based on age. See the response below.
	Sex	Specify mean changes in Cmax and AUC Gender related differences cannot be confirmed at this time. See the response below.
	Race	Specify mean changes in Cmax and AUC There is no apparent difference of Neutroval efficacy based on age. See the response below.
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC In the primary efficacy study, XM02-02, there were no patients with renal impairment and only 4 patients with hepatic impairment (defined as having a baseline ALT > 3 times the upper normal limit or baseline AST > 3 times the

		upper normal limit). Thus evaluation of efficacy for those with hepatic impairment was not carried out due to low sample size.
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC Drug interactions between Neutroval and other drugs have not been fully evaluated. No specific *in vivo* pharmacokinetic drug interaction studies were conducted. Neutroval is intended to reduce the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer. Neutroval should not be administered concurrently with chemotherapy but rather the day after chemotherapy.
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat) Neutroval is intended to be administered subcutaneously. No specific food effect studies were conducted.
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose. Doses of Neutroval that increase the ANC beyond 10 x 10^9/L may not result in any additional clinical benefit. To avoid the potential risks of excessive leukocytosis, Neutroval therapy should be discontinued if the ANC surpasses 10 x 10^9/L after the chemotherapy-induced ANC nadir has occurred.	

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # BLA# 125294	NDA Supplement #:S- BLA STN # 0	Efficacy Supplement Type SE- N/A
Proprietary Name: Neutroval Established/Proper Name: (b) (4) Dosage Form: Injection Strengths: 300 mcg/0.5 mL & 480 mcg/0.8 mL		
Applicant: Teva Pharmaceuticals USA Agent for Applicant (if applicable):		
Date of Application: November 30, 2009 Date of Receipt: November 30, 2009 Date clock started after UN:		
PDUFA Goal Date: September 30, 2010	Action Goal Date (if different):	
Filing Date: January 29, 2010	Date of Filing Meeting: January 12, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): For the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***		☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☒ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): N/A	
List referenced IND Number(s): Pre-IND 103188 (no IND submitted)	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***			NA	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			User Fee Paid (verified by Carla Vincent)

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☐ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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

Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			N/A	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*			N/A	

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?			**N/A**	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			**N/A**	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	N/A			
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? *If yes, date consult sent to the Controlled Substance Staff:*			**N/A**	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**N/A**	

Forms and Certifications				
__Electronic__ forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, __paper__ forms and certifications with hand-written signatures must be included. __Forms__ include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); __Certifications__ include: debarment certification, patent certification(s), field copy certification, and pediatric certification.				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?			X	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			N/A	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***		X		
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***				Not sure about this
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***				

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	X			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			N/A	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
REMS consulted to OSE/DRISK?		X		No REMS in this application
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			DDMAC, SEALD, OSE & DSI (all sent 12-22-09)

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** November 25, 2008 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 30, 2009

BLA/NDA/Supp #: 125294/0

PROPRIETARY NAME: Neutroval

ESTABLISHED/PROPER NAME: (b) (4)

DOSAGE FORM/STRENGTH: Injection, 300 mcg/0.5 mL & 480 mcg/0.8 mL

APPLICANT: Teva Pharmaceuticals, USA

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): For the reduction in the duration of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer

BACKGROUND: XM02 was developed in Europe as a similar biological product to the innovator filgrastim (Neupogen). Pre-IND/pre-BLA meeting held with DBOP on 25-Nov-2008. Multiple studies completed before approaching the agency. Application submitted 11/30/09 with PDUFA action date of 9/30/10

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Erik Laughner & Danyal Chaudhry	Y
	CPMS/TL:	Karen Jones	Y
Cross-Discipline Team Leader (CDTL)	Jeff Summers		Y
Clinical	Reviewer:	Thomas Herndon	Y
	TL:	Jeff Summers	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial*	Reviewer:		

products)			
	TL:		

Clinical Pharmacology	Reviewer:	Sarah Schrieber	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Hong (Laura) Lu	Y
	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mary Jane Masson-Hinrichs	Y
	TL:	Anne Pilaro	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	Laura Salazar-Fontana	Y
	TL:	Susan Kirshner	Y
Product Quality (CMC)	Reviewers:	Jee Chung and Dov Pluznik & Baolin Zhang	Jee Chung present
	TL:	Emily Shacter	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:	Kimberly Rains	Y
	TL:		
Facility Review/Inspection	Reviewer:	Anastasia Lolas (DS) & Kalavati Suvarna (DP)	Y
	TL:	Patricia Hughes	Y
OSE/DMEPA (proprietary name)	Reviewer:	Loretta Holmes	Y
	TL:	Kristina Arnwine	Y
OSE/DRISK (REMS)	Reviewer:	Jessica Diaz	N
	TL:	Sharon Mills	N
Bioresearch Monitoring (DSI)	Reviewer:	Constance Lewin & Tejashri Purohit-Sheth	N
	TL:		

Other reviewers (Product)		
Other attendees	DDMAC: Cynthia Collins Maternal Health: Jeanine Best CDRH: William Burdick SEALD:	Y for Cynthia Collins and N for Jeanine Best and William Burdick

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: Electronic submission, no comments	☐ Not Applicable
CLINICAL **Comments**: Adequacy of data for characterization of treatment effect for non-U.S. licensed active control	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: **If no, for an original NME or BLA application, include the reason. For example:** o **this drug/biologic is not the first in its class** o **the clinical study design was acceptable** o **the application did not raise significant safety**	☐ YES Date if known: ☒ NO ☐ To be determined Reason:This biologic is not the first in its class

or efficacy issues ○ **the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease**	

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: Comment regarding additional sub-group analysis	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**: Multiple comments for 74-day letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: Multiple comments for 74-day letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

Environmental Assessment	☐ Not Applicable
• Categorical exclusion for environmental assessment (EA) requested?	☒ YES ☐ NO
If no, was a complete EA submitted?	☐ YES ☐ NO
If EA submitted, consulted to EA officer (OPS)?	☐ YES ☐ NO
Comments:	
Quality Microbiology (for sterile products)	☒ Not Applicable
• Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☐ YES ☐ NO
Comments:	
Facility Inspection	☐ Not Applicable
• Establishment(s) ready for inspection?	☒ YES ☐ NO
▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?	☒ YES ☐ NO
Comments:	
Facility/Microbiology Review (BLAs only)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE
Comments:	☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only)	
Comments: Label with comments communicated to sponsor with 74-day letter	☒ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, Office Director, OODP **21st Century Review Milestones (see attached)** (optional): a. Filing Action Letter: January 29, 2010 b. Deficiencies Identified Letter (74 day letter): February 12, 2010 c. Action Letter: September 30, 2010 **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74

☐	Other