CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125294Orig1s000

CHEMISTRY REVIEW(S)

Center for Drug Evaluation and Research - Food and Drug Administration
Office of Biotechnology Products, Office of Pharmaceutical Science
29 Lincoln Drive, Bethesda, MD 20892

BLA STN:	125294
DATE:	8/2/12
FROM:	Jee Chung, Ph.D.
THROUGH:	Kathy Lee, M.S.
PRODUCT:	Recombinant N-Methionyl Human Granulocyte Colony Stimulating Factor (r-metHuG-CSF); Produced in E. coli; (b) (4)
INDICATION:	To prevent infection as manifested by febrile neutropenia in patients with non-myeloid malignancies undergoing chemotherapy regimen
ROUTE OF ADMIN:	s.c.
DOSAGE FORM:	Pre-filled syringes at 30 MIU/0.5 ml (300 ug G-CSF) and 48 MIU/0.8 ml (480 ug G-CSF); DP is (b) (4) Sorbitol, Polysorbate 80, pH 4.2
DOSE REGIMEN:	5 mcg/kg/day
SPONSOR:	SICOR Biotech UAB

DATES FOR REVIEW PROCESS:
Received: March 2, 2012
Decision: August 2, 2012

Post-Marketing Commitments For the Sponsor:

The following are 5 draft Post-Marketing Commitments (PMCs). The final version of the PMCs will be in the Approval Letter.

1. 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. These data will be submitted by MM/DD/YYYY.

2. 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. These SVPs data and risk assessment will be submitted to the agency by MM/DD/YYYY.

3. 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. The validation study report, protocol, and specifications will be submitted by MM/DD/YYYY.

4. To conduct a quantitative (ppb and ppm) leachables study and risk assessment of leachates to the drug product and/ (b) (4) in the final container closure system using methods that are suitably validated for its intended purpose. The leachables study data as well as a risk assessment will be submitted to the agency by MM/DD/YYYY.

5. 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. The laboratory study data will be submitted to the agency by MM/DD/YYYY.

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/s/

JEE Y CHUNG
08/02/2012

MARY K W LEE
08/02/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

From:	**Kathy Lee, M.S.** **Division of Therapeutic proteins (DTP)**
Through:	**Emanuela Lacana, Ph.D.**
BLA Number:	**125294**
Product:	**XM02**
Sponsor:	**SICOR Biotech UAB**
Date of Review:	**August 1, 2012**
Due Date of CDTL Memo:	**August 9, 2012**

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA125294 for G-CSF recombinantly produced in Escherichia coli and manufactured by SICOR Biotech UAB. Since at the time of this review no trademark or proper name was assigned, the product will be referred to in the review with its company code, XM02. Once a name is determined an addendum will be placed in DARRTS with the name. The data submitted in this application are adequate to support the conclusion that the manufacture of XM02 is well controlled, and leads to a product that is pure and potent. There are several CMC issues that the sponsor should address which are not required for approval of this application (see draft PMC's listed below). For final PMC language see Approval Letter.

SICOR has appropriately characterized the XM02 molecule through a series of characterization studies using both stressed and unstressed molecules. SICOR used these studies, in addition to data from their manufacturing history and clinical trial material, to support the release and stability specifications for XM02. The release and stability specifications appropriately control product and process variants that are the result of the manufacturing process (e.g., host cell DNA) and long-term storage (e.g., methionine oxidation and deamidation).

The manufacturing process is well controlled and consistently produces pure and potent XM02. Teva demonstrated manufacturing consistency for the drug substance through process validation and 69 commercial scale ((b) (4) lots produced at the cGMP facility in Lithuania. The manufacturing consistency for the drug product was demonstrated through process validation studies conducted with two full-scale drug product batches. The two drug product batches represent the 300 µg/0.5 ml and 480 µg/0.8 ml strengths. In addition, Teva included in-process data as well as batch analysis data from four drug product batches manufactured at a pilot scale. Teva provided data demonstrating comparability between the manufacturing scale and pilot scale lots of the drug product.

The proposed storage conditions and expiration dates are supported by stability data. The recommended storage condition for (b) (4) the drug substance (b) (4) (b) (4) XM02 drug substance is stable when stored (b) (4) for up to (b) (4) and the drug product is stable when stored at 5°C ± 3°C for up to 36 months.

The product used in the pivotal clinical trials was derived from drug substance process A, which was used to manufacture clinical lots P-04-025 and P-04-024 and process C which was used to manufacture clinical lots P-05-002 and P-05-003. For commercial distribution, drug substance processes changes included (b) (4) (b) (4) All clinical lots of drug product were produced at (b) (4). The commercial drug product will be produced at

Kfar Saba, Israel. For commercial distribution, the drug product process changes included [redacted]. Comparability between the product used in the pivotal clinical trials and the product used for market distribution was determined by a robust physico-chemical and biological characterization of the pre and post change products.

II. APPROVAL LETTER INFORMATION

Drug Substance (DS) Manufacturer:
SICOR Biotech UAB,
Molėtų pl. 5
LT-08409 Vilnius
Lithuania

DUNS Number: 565487722

Drug Product (DP) Manufacturer:
TEVA Pharmaceutical Industries, Ltd
64 Hashikma St.,
Industrial Zone
Kfar Saba, Israel 44102

FDA Registration Number: 3002721084

DUNS Number: 533065814

The USAN and marketed names have not been determined at this time (August 1, 2012).

The recommended storage condition for [redacted] the drug substance [redacted] XM02 drug substance is stable when stored at [redacted] and the drug product is stable when stored at 5°C ± 3°C for up to 36 months.

The post-approval stability scheme for XM02 DS [redacted] to be performed on one commercial batch per year includes the following time points: 0, 3, 6, 9, and 12 months. The Post-approval stability protocol for XM02 DP (5 ± 3 °C) will be performed on one commercial batch per year and includes the following time points: 0 3, 6, 9, 12, 18, 24, and 36 months.

III. DRAFT POST MARKETING COMMITMENTS

1. 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. These data will be submitted by MM/DD/YYYY.

2. 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. These SVPs data and risk assessment will be submitted to the agency by MM/DD/YYYY.

3. 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. The validation study report, protocol, and specifications will be submitted by MM/DD/YYYY.

4. To conduct a quantitative (ppb and ppm) leachables study and risk assessment of leachates into the drug product and/ (b) (4) in the final container closure system using methods that are suitably validated for its intended purpose. The leachables study data as well as a risk assessment will be submitted to the agency by MM/DD/YYYY.

5. To formulate drug product, at laboratory scale, using polysorbate 80 at or above (b) (4) and evaluate the effects of the polysorbate 80 on product quality over time. The laboratory study data will be submitted to the agency by MM/DD/YYYY.

IV. EXECUTIVE SUMMARY

SICOR was provided a Complete Response (CR) letter for this BLA on September 29, 2010 for clinical data integrity issues, device related issues and lack of nonclinical embryo-fetal toxicity testing. No CMC issues rose to the level of a CR. There were six information requests (IR) provided to the sponsor concerning CMC in the CR letter. This memo provides a summary of the complete responses from the sponsor for the CMC issues. The original IRs provided to the sponsor will be summarized.

Additionally, see Appendix 1 for the original Executive Summary which outlines the following information:

- Description of XM02
- Mechanism of Action
- Complexity of XM02
- Stability
- Summary of DS and DP specifications
- Reference Standards
- Method Validation
- Plasmid Construct and Cell Banks
- Manufacturing Process
- Adventitious Agent Control
- Comparability

Information Request Comments

The IR comments will be listed by the corresponding number in the September 29, 2010 CR letter.

Number 13, asked SICOR to provide additional data verifying that the SEC assay can accurately "measure aggregate content through the product's shelf life and conditions of use…" It was suggested to the sponsor that they "stress the product under multiple conditions…and determine if SEC provides an accurate assessment of aggregate contents as compared to AUC."

SICOR responded that they will generate stress samples and measure the aggregate content using an orthogonal method. According to the sponsor these data will be provided to the agency by third quarter 2012. Since this is after the PDUFA date, a PMC is being negotiated with the sponsor.

Number 14, asked SICOR to provide a risk assessment of potential impact of subvisible particles (SVPs) "on the quality safety and efficacy…" of their product and to "propose a strategy that provides an appropriate level of control." Additionally, we recommended that they "conduct a robust characterization of the subvisible particle content at release, on stability and in use." using orthogonal techniques.

SICOR responded that they will study SVPs using orthogonal techniques and propose a control strategy. According to the sponsor these data will be provided to the agency by third quarter 2012. Since this is after the PDUFA date, a PMC is being negotiated with the sponsor.

Number 15, asked SICOR to "revise the peptide mapping assay to include quantitative acceptance criteria for peak areas, relative peak heights, and new peaks." and when validating the method for purity, to base the acceptance criteria on more than one lot of drug substance and drug product.

SICOR stated that the validation study is being conducted and these data will be provided to the agency by third quarter 2012. Since this is after the PDUFA date, a PMC is being negotiated with the sponsor.

Number 16, asked SICOR to assess the risk to product quality from leachables at the end-of-shelf-life, in the final container closure system in the presence of the drug product and (b) (4) alone.

SICOR provided a qualitative extractables study conducted by (b) (4) ((b) (4) Qualitative evaluation of the extractables is acceptable as a basis for the leachables study. These data provide a worst case scenario and guidance on the types of compounds that may be leached into the DP or the DP (b) (4).

The (b) (4) study evaluated the pre-filled syringe system, which consist of the glass barrel, needle shield, and the needle.

Each of these was exposed to three different solvents, water, isopropanol, and hexane. The methods used to detect extractables were the following:

- For semi-volatile organic extractables: Gas Chromatography/Mass spectrometry (GC/MS) direct injection
- For volatile organic extractables: GC/MS headspace analysis
- For organic extractables: High performance liquid chromatography with photodiode array spectroscopy and MS (HPLC/PDA/MS)
- Extractable metals: Inductively-coupled plasma/optical emission spectroscopy (ICP/OES)
- For non-volatile residue extractables: Fourier-Transform Infrared Spectroscopy (FT-IR)

SICOR states that the leachables study is currently underway. Based on the data generated by the (b) (4) studies the risk to patient safety due to exposure of the extracted compounds are low. Therefore, the leachables study data will be a PMC.

Number 17, SICOR was asked to optimize the assay or develop a new one for the determination of plasmid copy number due to a discrepancy between plasmid copy number for the master cell bank (b) (4)), working cell bank (b) (4)), and end-of-production cells (b) (4)).

SICOR provided a new method to determine the plasmid copy number (PCN) in *E. coli* host cells. The new method is a qPCR method. The method does not give an absolute number of plasmids/cell due to the presence of several chromosomal replication forks occurring at same time within exponentially growing cells. The PCN is the ratio of the amount of plasmid to chromosome at the time of sampling. SICOR validated the method appropriately. This method will be used to qualify new MCB, WCB and EOP cells that will be generated from the new cell banks.

Number 18, SICOR was asked to provide data to support the proposed release and retest specification for polysorbate 80 to be not more than (b) (4)
We also noted that their investigation procedures were inadequate to assess XM02 product quality in that "you do not require affected lots to be placed on stability." We asked them to revise their "investigation procedure to include a provision of assessing long-term stability of the product when formulated with expired polysorbate 80."

SICOR stated that they have created an alert limit of (b) (4) and an action limit of (b) (4). Each polysorbate lot will be tested at (b) (4) intervals. When the polysorbate 80 reaches the alert limit, the Quality Assurance (QA) unit will be notified and the use of the polysorbate lot will be assessed for suitability for production of the drug product. If the action limit is reached for a polysorbate lot during a re-test, then the QA unit will be notified immediately and corrective actions will be determined accordingly.

SICOR stated that they will conduct a laboratory study using polysorbate 80 at or above (b) (4) and will formulate the drug product using this polysorbate 80. They will evaluate the effects of the polysorbate 80 on product quality. These data will be used to evaluate the appropriateness of the current specification.

SICOR stated that the study is being conducted and these data will be provided to the Agency after the PDUFA date, therefore a PMC is being negotiated with the sponsor.

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ADDENDUM TO PRIMARY CMC REVIEW MEMO

Center for Drug Evaluation and Research
Office of Pharmaceutical Science
Office of Biotechnology Products
Division of Therapeutic Proteins
HFD-122

BLA:	125294
Addendum Date:	September 23, 2010
FROM:	Jee Chung, Ph.D.
THROUGH:	Dov Pluznik, Ph.D. and Kathy Lee, M.S.
SPONSOR:	Teva Biopharmaceuticals USA
PRODUCT:	Recombinant Methionyl Human Granulocyte Colony Stimulating Factor (r-metHuG-CSF; XM02; Neutroval); Expressed in *E. coli*
PROPOSED USE:	To prevent infection as manifested by febrile neutropenia in patients with non-myeloid malignancies undergoing chemotherapy regimen
CLINICAL DIVISION:	Division of Biologic Oncology Products (DBOP)
REVIEW TEAM:	
MO:	Thomas Herndon and Suzanne Demko
P/T:	Mary Jane Masson-Hinrichs and Anne Pilaro
Product Team:	Jee Chung, Dov Pluznik, Baolin Zhang, Laura Salazar-Fontana, Kimberly Rains, Kathy Lee, Joslyn Brunelle, Jennifer Shen, Jennifer Dickey, Maria Teresa Gutierrez-Lugo, Emily Shacter, and Susan Kirshner
Facilities:	Anastasia Lolas (DS), Kalavati Suvarna (DP), and Patricia Hughes
Clinical Pharmacology:	Sarah Schrieber and Hong Zhao
Statistical:	Hong (Laura) Lu, Yuan Li Shen, and Mark Rothmann
RPM:	Erik Laughner and Danyal Chaudhry

MKL for
Dov Pluznik 9/23/10
Jee Chung 9/23/10
MKL 9/23/10

This is an addendum to the Primary CMC review memo. The original memo did not address the claim of Categorical Exclusion for this application.

Teva provided a Claim Of Categorical Exclusion per 21 CFR 25.31(c) and (d). We find that the product meets the conditions for a categorical exclusion as stated in the above mentioned regulations. Therefore an environmental assessment is not necessary.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drug Evaluation and Research - Food and Drug Administration
Office of Biotechnology Products, Office of Pharmaceutical Science
29 Lincoln Drive, Bethesda, MD 20892

The Quality Team Leader's Executive Summary

From:	**Dov Pluznik, Ph.D. and Kathy Lee. M. S.** **Division of Therapeutic proteins (DTP)**
Through:	**Emily Shacter, Ph.D.** **Barry Cherney, Ph.D.** **Amy Rosenberg, MD**
BLA Number:	**125294**
Product:	**Neutroval (XM02)**
Sponsor:	**Teva Pharmaceuticals USA**
Date of Review:	**September 17, 2010**

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of 125294 for Neutroval (XM02) manufactured by Teva Pharmaceuticals USA. The data submitted in this application are adequate to support the conclusion that the manufacture of Neutroval (XM02) is well controlled, and leads to a product that is pure and potent. There are several CMC issues that the sponsor should address which are not required for approval of this application, listed below.

Teva has appropriately characterized the XM02 molecule through a series of characterization studies using both stressed and unstressed molecules. Teva used these studies, in addition to data from their manufacturing history and clinical trial material, to support the release and stability specifications for XM02. The release and stability specifications appropriately control product and process variants that are the result of the manufacturing process (e.g., host cell DNA) and long-term storage (e.g., methionine oxidation and deamidation).

The manufacturing process is well controlled and consistently produces pure and potent XM02. Teva demonstrated manufacturing consistency for the drug substance through process validation and 69 commercial scale (b) (4) lots produced at the cGMP facility in Lithuania. The manufacturing consistency for the drug product was demonstrated through process validation studies conducted with two full-scale drug product batches. The two drug product batches represent the 300 µg/0.5 ml and 480 µg/0.8 ml strengths. In addition, Teva included in-process data as well as batch analysis data from four drug product batches manufactured at a pilot scale. Teva provided data demonstrating comparability between the manufacturing scale and pilot scale lots of the drug product.

The proposed storage conditions and expiration dates are supported by stability data. The recommended storage condition fo (b) (4) the drug substance (b) (4) (b) (4) XM02 drug substance is stable when stored at (b) (4) and the drug product is stable when stored at 5°C ± 3°C for up to 36 months.

The product used in the pivotal clinical trials was derived from drug substance process A which was used to manufacture clinical lots P-04-025 and P-04-024 and process C which was used to manufacture clinical lots P-05-002 and P-05-003. For commercial distribution, drug substance processes changes included (b) (4) All clinical lots of drug product were produced at (b) (4). The commercial drug product will be produced at Kfar Saba, Israel. For commercial distribution, the drug product process changes included (b) (4) Comparability

between the product used in the pivotal clinical trials and the product used for market distribution was determined by a robust physico-chemical and biological characterization of the pre and post change products.

Teva is being asked to perform a Post Marketing Requirement (PMR) for immunogenicity issues related to their antibody assay. This is not an approvability issue because immunogenicity-related adverse events such as extended neutropenia or loss of efficacy were not observed in the Neutroval clinical trials. 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 through post-marketing studies. At the same time, it is critical that the data be obtained so that the safety profile of the drug can be more fully understood. 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.

For the PMR Teva will assess the induction of anti-GCSF antibodies in serum from treated patients using validated assays. The Sponsor will:

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

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

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

II. RESOLVED CMC ISSUES

a. Information request *discussed with the sponsor during a T-con on 8/6/10. The applicant committed to provide the answers to our comments by 8/20/10 and August 27, 2010.*

1. Residual DNA is not being tested as part of the release of the DS or as an in process control. The data that you have provided in the BLA were not sufficient to support the removal of this assay from testing. It is possible that G-CSF protein and any remaining host cell DNA could interact (ie. bind together) in the DS, which could decrease the specificity of the qRT-PCR assay to measure host cell DNA. We note that in your validation study you did not provide details on assay robustness. Please comment on the effect that varying protein concentrations, incubation times, etc. have on the sensitivity of the qRT-PCR assay for measurement of host cell DNA. Additionally, based on spiking studies you have determined that the limit of quantification is (b) (4). Yet, the datum is reported as (b) (4). Please provide the numerical results for each of the 49 DS batches that were reported as (b) (4). Include a discussion of how the data from

these 49 batches provide sufficient assurance that the product will meet expectations regarding residual DNA content or add this test to the drug substance specifications.

Reviewer Comment: Teva provided the requested data. Residual DNA levels from historical 48 DS lots were consistently well below the limit of quantitation (b) (4) providing sufficient assurance that the product meets expectations regarding residual DNA levels.

2. You have provided data showing that the elution gradient in the RP-HPLC method can be modified so that the retention time (RT) of system suitability main peak remains within a RT window (b) (4), the assay is validated for quantification of all product variants detected by RP-HPLC. However, your SOP does not specify the composition and step gradients that may be modified by an operator to remain with in the acceptance criteria of the system suitability run. Please revise your SOP to specify exactly how much an operator can modify the elution gradient to ensure reliable quantification of the G-CSF main peak and variants and submit the revised SOP in your response to the Complete Response Letter.

Reviewer Comment: Teva revised the SOP to specify exactly allowable gradient adjustments to ensure reliable quantification of the G-CSF main peak and variants.

3. You state that the resolution of the G-CSF and (b) (4) (relative RT (b) (4) (b) (4)) peaks in the RP-HPLC method is visually controlled by a valley between these two peaks. However, this is not described in your SOP. Please include a reference chromatogram in your SOP to graphically represent acceptable resolution between G-CSF and (b) (4) and submit the revised SOP in your response to the Complete Response Letter.

Reviewer Comment: Teva revised the SOP to include a reference chromatogram.

4. You have provided data demonstrating that G-CSF becomes deamidated at (b) (4) under stress conditions and is detectable by RP-HPLC at relative RT of (b) (4). The RP-HPLC method has been validated for the quantification of this and other product related variants (oxidized, deamidated, etc). However you have not set a release or stability specification for this variant. Please establish release and stability specifications for (b) (4) deamidated variants and submit the revised specifications.

Reviewer Comment: Teva has established release and stability specifications for (b) (4) deaminated variants corresponding to the LOQ of the analytical methods (b) (4) for the DS and (b) (4).

b. Additional CMC comments for sponsor not required for the approval of XM02

1. You use SE-HPLC to measure aggregates in the DS and DP. This assay detects monomers, dimers and high molecular weight (HMW) species. You have validated the assay for the detection of monomers and dimers using AUC as your orthogonal method. We note that you did this study using release (unstressed) samples. Because of the low

amount of aggregates at release, there is little sensitivity for determining whether the assay provides accurate results regarding aggregate content. Because AUC may monitor species of aggregates that are not detected by SEC 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. **Please commit to** providing data indicating that SEC provides an accurate measure of aggregate content through the product's shelf life and conditions of use, or consider use of an alternative assessment of aggregate content. As one possible approach, we suggest that you stress 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.

2. You are proposing to set specifications for sub-visible particles after 12 batches of the DP have been produced. Instead, we suggest you provide a risk assessment of the potential impact these particulates may have on the quality, safety and efficacy of your product and propose a strategy that provides an appropriate level of control. As part of the risk assessment, we suggest that you conduct a robust characterization of the subvisible particle content at release, on stability and in use. This characterization should include the use of multiple orthogonal techniques to quantitate the amount and types of particulates and the use of multiple stress conditions to fully understand the propensity to form large protein aggregates. **You should provide timelines** in your response to the Complete Response letter for submission of a protocol and data supporting your risk assessment and proposed control strategy.

3. You currently use peptide mapping as an identity test. However, when appropriately analyzed, the peptide map data also provide a measure of the purity of the drug substance and drug product. Please revise the peptide mapping assay to include quantitative acceptance criteria for peak areas, relative peak heights, and new peaks **and provide a timeline in your response to** the Complete Response letter when this information will be submitted to the application. 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.

4. You have provided extractable/leachable data for the stoppers used for the container closure system of the drug product. You did not provide extractable/leachable data on the (b) (4) in the presence of the drug product (b) (4). Because the presence of leachates in the drug product may impact product quality in multiple ways,, you should assess risk to product quality posed by such leachates. Please commit to including leachable testing at the end-of-shelf-life for the drug product in the final container closure system in presence of the drug product (b) (4)t alone and **provide a timeline** in your response to the Complete Response letter for submission of these data and your evaluation of the risk to product quality.

Reviewer Comment: One CMC item that the Division deemed inadequate was the sponsor's proposed qualification protocol for new cell banks. The sponsor was contacted on August 10, 2010 and were informed that the qualification protocol for new cell banks present in the application should be withdrawn from the application and resubmitted as a PAS following

approval. Teva agreed to withdraw the protocol and commit to optimizing or develop a new plasmid copy number assay.

5. The plasmid copy number varies between the Master Cell Bank [redacted] Working Cell Bank [redacted] and batches of end-of-production cells [redacted] copies/cell). Please **provide a timeline** in your response to the Complete Response letter for the submission of optimization data for the current assay used to determine plasmid copy number or develop a new assay.

Reviewer Comment: Teva was asked this question during our August 6, 2010 teleconference. However it was not adequately addressed; see below.

You have provided release and retest data demonstrating that the [redacted] values present in Polysorbate 80 used to formulate the final drug product are not more [redacted] However your release/retest specification is [redacted] You have not provided data to support the upper limit of [redacted]. Please provide data showing that Polysobate 80 with [redacted] values at or close to the upper limit of the specification does not impact the quality of your G-CSF product over time or tighten this specification based on your current experience.

Reviewer Comment: Teva reviewed historical data for lots of Polysorbate 80 which have been utilized in the manufacturing of the DP. The highest amount of [redacted] in the Polysorbate 80 used in the production of DP was [redacted]. The sponsor also supplied Polysorbate 80 stability data where the Polysorbate 80 was stored in an open container and tested for [redacted] levels at T=0, 6 and 12 months. All values were at or below [redacted]. Additionally, Teva retests the Polysorbate 80 every [redacted]. If a lot is found to be out of specification, an investigation will be initiated and QA will assess which batches are affected and determine which batches should be placed on hold until the investigation has been completed and disposition has been determined. Finally, they supplied initial and retest values for Polysorbate 80 the highest value was [redacted] on retest. Based on these data, Teva has agreed to reduce the specification to NMT [redacted] This specification is acceptable. However, given that increased levels [redacted] in the Polysorbate 80 will only affect XM02 product quality attributes (i.e., oxidation) after storage, the change in specification and the investigation SOP are inadequate. We still do not understand the impact on product quality when XM02 is formulated with Polysorbate 80 at the highest allowable level of [redacted] over time. Teva will need to supply this data. Additionally, any investigation into this issue should include placing all lots on stability to assess long-term affects.

6. You have revised the release and retest specification for in Polysorbate 80 to be not more than (NMT) [redacted] g and you have submitted information on how an investigation will be conducted for any lots formulated with out of specification Polysorbate 80. However you have not provided long-term product quality data for XM02 formulated with Polysorbate 80 at the upper limit of [redacted]. Also, your investigation procedure is inadequate to assess XM02 product quality in that you do not require affected lots to be placed on stability.

Please **provide a timeline** in your response to the Complete Response letter for submission of data showing that Polysobate 80 (b) (4) values at or close to the upper limit of the specification does not impact the quality of your G-CSF product over time. In addition please consider revising you investigation SOP to include a provision for assessing long-term stability of the product when formulated with expired Polysorbate 80. Please note, if lots have been released with out of specification Polysorbate 80, you will need to submit a Biologic Product Deviation Report to the Agency.

III. EXECUTIVE SUMMARY

A. Description of Neutroval (XM02)

The product, XM02, is recombinant Human N-Methionyl-Granulocyte-Colony Stimulating factor (r-metHu-G-CSF), expressed in *E. coli* cells (b) (4) (b) (4). The drug product (DP) is supplied as two strengths, 300 µg/0.5 ml or 480 µg/0.8 ml, in pre-filled syringes. The proposed route of administration is sub-cutaneous injections. Both the drug substance (DS) and drug product (b) (4) The tables below describe the constituents of DP, their function. The product indication is to prevent or reduce severe neutropenia in patients receiving chemotherapy for non-myeloid malignancies.

The drug product is described in the tables below:

Table 2.3.P-2: (b) (4) DP Excipients

Excipient	Concentration (mg/mL)
Acetic acid, glacial	(b) (4)
Sorbitol	(b) (4)
Polysorbate 80	(b) (4)
Sodium hydroxide	q.s. (to pH 4.20)
Water for injection	300 mcg/ 0.5 mL: q.s. to 0.5 mL 480 mcg/ 0.8 mL: q.s. to 0.8 mL

Table 2.3.P-4: Final (b) (4) -DP Formulation

Excipient	Quantity	Purpose
Acetic acid	(b) (4)	(b) (4)
Sodium hydroxide	*q.s. ad* pH 4.20	
Sorbitol	(b) (4)	
Polysorbate 80	(b) (4)	
Water for Injection	(b) (4)	

The DP is supplied in PFS see table below for details:

Table 3.2.P.7-2: Primary Packaging Components: Description			
Component	**Description**	**Compliance Reference**	**DMF/ BMF #**
(b) (4)			

The product label claims that the DP is supplied as 300 mcg/0.5 ml and 480 mcg/0.8 ml. The PFS are filled to a target fill volume (b) (4) and (b) (4) respectively. Teva was asked to justify the overfill of (b) (4) per syringe. They have provided fill weight data generated during the manufacture of the pivotal batches of XM02-DP. The data show for the 0.5 mL PFS the average weight is (b) (4) with a STD (b) (4) For the 0.8 mL PFS the average weight is (b) (4) and a STD (b) (4) Given this data Teva states that tightening of the fill weight limits beyond the original limits is operationally not feasible.

Reviewer Comment: These data indicate that the variation in the stated content is well within USP recommendations for "excess" volume and thus the applicant meets the requirements under 21CFR 201.51(g).

XM02 is 175 amino acids long (b) (4)

(b) (4)

B. Clinical Trial Information

[1] (b) (4)

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V. SIGNATURE BLOCK (BLA ONLY)

Name and Title	Signature and Date
Amy Rosenberg, MD Director Division of Therapeutic Proteins	9-17-10
Barry Cherney, Ph.D. Deputy Director, Division of Therapeutic Proteins	9-17-10
Emily Shacter, Ph.D. Laboratory Chief, Laboratory of Biochemistry, Division of Therapeutic Proteins	9/17/10
Kathy Lee, M.S., Associate Laboratory Chief, and Jee Chung, Ph.D., Biologist and Dov Pluznik, Ph.D. Biologist, Division of Therapeutic Proteins	9/17/10 9/17/10 9/17/10

Center for Drug Evaluation and Research
Office of Pharmaceutical Science
Office of Biotechnology Products
Division of Therapeutic Proteins
HFD-122

BLA:	125294
START DATE:	2/12/10
FINISH DATE:	4/29/10
REVISION DATE:	5/13/10, June, July, August and September 2010
FROM:	Jee Chung, Ph.D.
THROUGH:	Dov Pluznik, Ph.D. and Kathy Lee, M.S. DSLP 9/17/10
SPONSOR:	Teva Biopharmaceuticals USA
PRODUCT:	Recombinant Methionyl Human Granulocyte Colony Stimulating Factor (r-metHuG-CSF; XM02; Neutroval); Expressed in *E. coli*
PROPOSED USE:	(b) (4) febrile neutropenia in patients with non-myeloid malignancies undergoing chemotherapy regimen
CLINICAL DIVISION:	Division of Biologic Oncology Products (DBOP)
GRMP TIMELINE:	
Filing Meeting:	1/12/10
74th Day:	2/12/10
Mid-Cycle Meeting:	5/10/10
Labeling Meeting:	6/17/10 (final)
Wrap-Up:	
Labeling Tcon with Applicant:	
Primary Reviews/Draft CDTL Memo Due:	7/30/10
Secondary Reviews/Draft CDTL Memo Due:	8/9/10
CDTL Memo Due:	Mid-August
PDUFA Action Date:	9/30/10

REVIEW TEAM:

MO:	Thomas Herndon and Suzanne Demko
P/T:	Mary Jane Masson-Hinrichs and Anne Pilaro
Product Team:	Jee Chung, Dov Pluznik, Baolin Zhang, Laura Salazar-Fontana, Kimberly Rains, Kathy Lee, Joslyn Brunelle, Jennifer Shen, Jennifer Dickey, Maria Teresa Gutierrez-Lugo, Emily Shacter, and Susan Kirshner
Facilities:	Anastasia Lolas (DS), Kalavati Suvarna (DP), and Patricia Hughes
Clinical Pharmacology:	Sarah Schrieber and Hong Zhao
Statistical:	Hong (Laura) Lu, Yuan Li Shen, and Mark Rothmann
RPM:	Erik Laughner and Danyal Chaudhry

TABLE OF CONTENTS

Reviewer Comment: This memo does not cotain the summary basis of approval. For information on the approvability of this application see the CTDL secondary CMC memo.

I. SUMMARY OF QUALITY ASSESSMENTS

(b) (4)

[redacted]

380 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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: 08/09/2010

To: File: BLA 125,294

From: Laura I. Salazar-Fontana, Ph.D. 8/9/10
Susan L. Kirshner, Ph.D. Susan L. Kirshner 8/9/10
Associate Chief, Laboratory of Immunology
Division of Therapeutic Proteins
Office of Biotech Products
CDER/FDA

Through: Amy Rosenberg, Director, DTP Mary Gray for A. Rosenberg

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)

REVIEWER RECOMMENDATIONS:

The immunogenicity assays are not adequate, therefore the patient test results provided by the Sponsor cannot be considered reliable. We recommend that samples be retested once the assays have been appropriately validated. This will be addressed in a Post Marketing requirement:

1. To assess the induction of anti-GCSF antibodies in serum from treated patients using validated assays. The Sponsor will:

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

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

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

As we have extensive comments regarding the immunogenicity assays we recommend that these be transmitted in an advice letter to the Sponsor. Draft comments for the advice letter are provided.

ADVICE LETTER COMMENTS TO THE SPONSOR:

- According to the general immunogenicity scheme provided, samples that screen positive in the ELISA assay will be confirmed in the western blot (WB assay). Samples that confirm positive or that have questionable results in the Western blot assay are then tested in the Luminex, Biacore and neutralizing assays. However you state in the safety summary that patient 50-513-01 was ELISA negative but positive in the Luminex, WB and NAb assays. Please provide a clear explanation of the testing paradigm that you are using to assess immunogenicity.

- Given the results with patient 50-513-01, it appears that your ELISA is an inadequate screening assay. Please address this concern.

- The Western blot assay characterizes by the identification of denatured proteins, priorly transferred to a nitrocellulose membrane, by a specific antibody. Not all antibodies are able to recognize their epitope/antigen under Western Blot analysis, therefore the Agency would recommend that a confirmatory assay is developed and implemented as a competition assay of the method used for the screening assay to avoid selection of anti-drug antibodies that only recognize linear/denatured epitopes.

- The validation of the Luminex assay is mentioned during the validation of your screening ELISA assay, but also metioned as method to quantitate the amount of antibodies in samples confirmed positive in your WB assay. Please clarify.

- It is not clear if the BIAcore assay has been used only in the screening of samples during the follow up period of your Phase 3 clinical trial but also as a method to measure anti-drug antibody affinity in those samples that were confirmed positive by your WB confirmatory assay. Please explain.

Regarding your ELISA screening assay:

- The raw data used for the recalculation of your assay cut point value has not been provided therefore the statistical relevance of the value provided cannot assessed. We recommend that calculation of the cut point is done using a sample size ranging from 50-100 samples.

- The sensitivity of the ELISA screening assay has not been estimated in mass per units despite the use of a positive quality control of known Ab concentration. The Sponsor should be able to provide a quantitative value for the ELISA sensitivity in a similar manner as it has provided a mass/unit sensitivity value for the Luminex assay, given the fact that both assays have been qualified using the same quality control.

- The specificity of the ELISA screening assay has been evaluated by comparing the detection of XM02 versus Neupogen®. This approach does not demonstrate specificity of your assay towards the product. For guidance on how to determine assay specificity please refer to Mire-Sluis. et al.

The absence of key assay parameters such as sensitivity, specificity, and cut point value in the target patient population does not allow the unequivocal identification of antibody positive samples, and therefore safety or lost of efficacy due to the presence of neutralizing antibodies against the recombinant or the endogenous G-CSF cannot be addressed.

Regarding your neutralizing assay:

- Please clarify the final dose used for the maintenance and growth of (b) (4) cells line while determining the neutralizing activity of serum samples from Phase 3 clinical trial. Given the fact that bioassays show high variability and limited dynamic range, please, provide an explanation for the effect of this saturating concentration of G-CSF in the sensitivity of your assay.

- Please address the effect of (b) (4) in the viability of (b) (4) cell line by performing your neutralizing assay in the presence of (b) (4) antibody.

- The determination of the neutralizing assay cutoff value is inadequate. Please recalculate following the comments provided in the review.

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 Methyonine residue in the N-terminal portion. 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.

XM02 is indicated for the treatment of severe neutropenia in cancer patients undergoing myelosuppressive chemotherapy (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.

Drug Product batches of XM02 used during Phase III clinical trials have been well characterized and tightly controlled by the sponsor to limit the amount of oxidized and deamidated variants, and stability studies to evaluate aggregate formation have been requested to the Sponsor and will be provided to the Agency.

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 does 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 and cannot account for the appropriate screening of samples for the presence of neutralizing antibodies. The inability to detect neutralizing antibodies against the product can result in (1) lost of efficacy; (2) but also, development of neutralizing antibodies against endogenous G-CSF can have serious clinical sequelae in off-label use of hr-G-CSF, such as immune-mediated neutropenia in healthy donors participating in allogeneic bone marrow transplantation.

The safety database for XM02 does not indicate that there were patients who lost efficacy or developed neutropenia during the course of the trial. Therefore 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.

OVERVIEW:

The immunogenicity testing scheme provided by the Sponsor plans to detect the presence of binding and neutralizing antibodies against the product XM02. The screening of binding antibodies present in patient serum samples is done using a direct binding ELISA. ELISA positive samples are further confirmed by Western blot for human IgG and IgM antibody isotypes. Confirmed positive or questionable samples are then tested for the presence of neutralizing antibodies by measuring the inhibition of growth of the G-CSF (b) (4) (b) (4) cell line (b) (4) The Sponsor has also presented data regarding the validation of two additional assays: one for the quantitation of binding antibodies (Luminex platform) and a second one, BIAcore®, planed to use in follow up immunogenicity studies. It is not clear if the Luminex assay has also been used for preliminary screening of samples.

None of the assays was appropriately validated. Specific details can be found in the continuation of the review below. In addition the patient data provided by the Sponsor is inconsistent with the testing scheme they describe (a patient who was negative in the ELISA was nevertheless tested using the Western blot, Luminex and neutralizing assays). The Sponsor is being asked to address these issues as a post-marketing requirement.

REFERENCES:

D'Souza, A. et al., Transfusion Medicine Reviews, 2008, 22-4: 280 - 290.

Kröger, N. and Zander, A.R., Leuk Lymphoma, 2002, 43-7: 1391 - 1394.

Martinez, C. et al., Bone Marrow Transplant, 1999, 24-12: 1273 - 1278.

Li H and d'Anjou M, Curr. Op. Biotech., 2009, 20: 1-7.

Rosenberg AS, AAPS J, 2006, 8: E501-507.

Mire-Sluis A, et al. Journal of Immunological Methods, 2004, 289: 1 - 16.

Shankar G, et al. Journal of Pharmaceutical and Bioanalytical Analysis, 2008, 48: 1267 - 1281.

Gupta S, et al. Journal of Immunological Methods, 2007, 321: 1 - 18

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number: 125294 Applicant: Teva Pharmaceuticals USA Stamp Date: 11/30/09

Established/Proper Name: None BLA/NDA Type: Original BLA

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed	Y N	Defer to RPM
❑ including list of all establishment sites and their registration numbers	Y N	
Comprehensive Table of Contents	Y	Per Section
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y N	Defer to RPM
Labeling:	Y	
❑ PI –non-annotated	Y	
❑ PI –annotated	Y	
❑ PI (electronic)	Y N	
❑ Medication Guide	Y N	
❑ Patient Insert	Y N	
❑ package and container	Y	
❑ diluent	N	Not applicable
❑ other components	N	Not applicable
❑ established name (e.g. USAN)	N	Sponsor has not applied yet
❑ proprietary name (for review)	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
❑ legible	Y	
❑ English (or translated into English)	Y	
❑ compatible file formats	Y	
❑ navigable hyper-links	Y	
❑ interpretable data tabulations (line listings) & graphical displays	Y	
❑ summary reports reference the location of individual data and records	Y	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing arrangement	N	Not Applicable

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

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

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

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
o justification of specifications	Y	
o stability	Y	
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	
❑ characterization of drug substance	Y	
❑ control of drug substance	Y	
o specifications	Y	
o justification of specs.	Y	
o analytical procedures	Y	
o analytical method validation	Y	
o batch analyses	Y	
❑ reference standards	Y	
❑ container closure system	Y	
❑ stability	Y	
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval	Y	
o protocol	Y	
o results	Y	
o method validation	Y	
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
o preservative effectiveness	N	Not Applicable
o container-closure integrity	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y	
❑ controls of critical steps and intermediates	Y	
❑ process validation including aseptic processing & sterility assurance:	Y	
o Filter validation	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
○ Component, container, closure depyrogenation and sterilization validation	Y	
○ Validation of aseptic processing (media simulations)	Y	
○ Environmental Monitoring Program	Y	
○ Lyophilizer validation	N	Not Applicable
○ Other needed validation data (hold times)	Y	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
❑ reference standards or materials	Y	
❑ container closure system [3.2.P.7]	Y	
○ specifications (vial, elastomer, drawings)	Y	
○ availability of DMF & LOAs	Y	
○ administration device(s)	N	Not Applicable
❑ stability	Y	
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval	Y	
○ protocol	Y	
○ results	Y	
○ method validation	Y	
Diluent (vials or filled syringes) [3.2P']		
❑ description and composition of diluent	N	Not Applicable
❑ pharmaceutical development	N	Not Applicable
○ preservative effectiveness	N	Not Applicable
○ container-closure integrity	N	Not Applicable
❑ manufacturers (names, locations, and responsibilities of all sites involved)	N	Not Applicable
❑ batch formula	N	Not Applicable
	N	Not Applicable

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	N	Not Applicable
❑ controls of critical steps and intermediates	N	Not Applicable
❑ process validation including aseptic processing & sterility assurance:	N	Not Applicable
o Filter validation	N	Not Applicable
o Component, container, closure depyrogenation and sterilization validation	N	Not Applicable
o Validation of aseptic processing (media simulations)	N	Not Applicable
o Environmental Monitoring Program	N	Not Applicable
o Lyophilizer sterilization validation	N	Not Applicable
o Other needed validation data (hold times)	N	Not Applicable
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	N	Not Applicable
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	N	Not Applicable
❑ reference standards	N	Not Applicable
❑ container closure system	N	Not Applicable
o specifications (vial, elastomer, drawings)	N	Not Applicable
o availability of DMF & LOAs	N	Not Applicable
❑ stability	N	Not Applicable
❑ summary	N	Not Applicable
❑ post-approval protocol and commitment	N	Not Applicable
❑ pre-approval	N	Not Applicable
o protocol	N	Not Applicable
o results	N	Not Applicable
Other components to be marketed (full description and supporting data, as		

CTD Module 3 Contents	Present?	If not, justification, action & status
listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	 N N	 Not Applicable Not Applicable
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	 Y N Y Y Y N N N N	 Defer to BMT/DMPQ Not Applicable Not Applicable Not Applicable Not Applicable
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y Y N	 Not Applicable
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y	
Describes changes in the manufacturing	Y	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

Examples of Filing Issues	Yes?	If not, justification, action & status
process, from material used in clinical trial to commercial production lots		
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y	
Certification that all facilities are ready for inspection	Y N	Defer to BMT/DMPQ
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	Y N	Defer to BMT/DMPQ
❑ LAL instead of rabbit pyrogen	Y N	Defer to BMT/DMPQ
❑ mycoplasma	Y N	Defer to BMT/DMPQ
❑ sterility	Y N	Defer to BMT/DMPQ
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	Defer to BMT/DMPQ
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	Defer to BMT/DMPQ

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? (Yes) No

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Lee Chung Doak K. Pluzynski — 1/12/10
Product ~~Quality~~ Reviewer(s) — Date

Ernest Kaclik — 1/12/10
Branch Chief/Team Leader/Supervisor — Date

Amy Rosenberg — 1-12-10
Division Director — Date