

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125294Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125294/0 Supplement Number: NA NDA Supplement Type (e.g. SE5): NA

Division Name: DBOP PDUFA Goal Date: 9/30/10 Stamp Date: 11/30/2009

Proprietary Name: Neuroval

Established/Generic Name: (b) (4)

Dosage Form: Injection

Applicant/Sponsor: TEVA Pharmaceuticals USA

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) NA
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

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

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Population	minimum	maximum	Ready for Approval in Adults
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. __ mo.	17 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

 Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

Disease/condition does not exist in children

Too few children with disease/condition to study

Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

Original BLA 125,494
Product: Neutroval (b) (4)
Indication: Neutropenia

1.3.3 DEBARMENT CERTIFICATION

Re: **BLA 125,294**

Recombinant N-methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF, E. coli) [TevaGrastim, XM02, (b) (4)]

Debarment Certification Statement

In response to the requirements of the Generic Drug Enforcement Act of 1992 (GDEA), I hereby certify on behalf of Teva Pharmaceuticals USA (Teva), that we did not use and will not use in connection with this Biologic License Application, the services of any person in any capacity debarred under section 306 (a) or (b) of Federal Food, Drug, and Cosmetic Act (FD&C Act).

Sincerely,



Deborah A. Jaskot, MS, RAC
Vice President, Regulatory Affairs
TEVA Pharmaceuticals USA

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # N/A BLA # 125294	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: None Established/Proper Name: Tbo-filgrastim Dosage Form: Injection		Applicant: Sicor Biotech UAB Agent for Applicant (if applicable): Teva Pharmaceuticals, USA
RPM: Lara Akinsanya		Division: Hematology Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>N/A</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>N/A</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: N/A</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>August 29, 2012</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None CR - Sept. 29, 2010

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input checked="" type="checkbox"/> Yes, dates Aug. 7, 2012
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
<p>❖ Copy of this Action Package Checklist⁴</p>	<p>August 29, 2012</p>
Officer/Employee List	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
Action Letters	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) Approval -August 29, 2012 CR - September 29, 2010</p>
Labeling	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>November 30, 2009</p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	<p>N/A</p>

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	August 24, 2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	November 30, 2009
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	August 27, 2012
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Non-acceptability letter - 7/16/12, 3/22/10 7/16/12, 3/19/10
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 6/5/12, 2/19/10 <input checked="" type="checkbox"/> DMEPA 7/24/12, 8/16/10 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 8/8/12, 7/21/10 <input checked="" type="checkbox"/> ODPD (DDMAC) 8/7/12, 7/1/10 <input checked="" type="checkbox"/> SEALD 8/18/10 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews MHT - 8/17/10 PEDS - 5/17/12 OBP Carton & Container Review- 8/29/12, 9/22/10
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	1/12/10
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) N/A <input type="checkbox"/> Not a (b)(2) N/A
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>8/11/10</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>) 	8/20/12, 8/3/12, 8/2/12, 8/2/12, 8/2/12, 7/25/12, 7/25/12, 7/24/12, 6/25/12, 6/20/12, 6/13/12, 6/13/12, 6/1/12, 5/31/12, 5/31/12, 5/30/12, 3/26/12, 3/15/12, 2/17/12, 5/3/11, 2/2/11, 8/17/10, 8/10/10, 8/6/10, 7/16/10, 7/12/10, 7/6/10, 6/30/10, 6/30/10, 6/21/10, 5/27/10, 5/25/10, 5/24/10, 5/19/10, 5/12/10, 5/12/10, 4/30/10, 4/21/10, 4/20/10, 4/6/10, 4/5/10, 4/2/10, 3/31/10, 3/26/10, 3/24/10, 3/22/10, 3/19/10, 2/19/10, 2/19/10, 2/12/10, 2/3/10, 1/29/10, 1/29/10, 1/29/10, 1/22/10, 1/15/10, 1/15/10, 1/12/10, 1/11/10, 12/31/09, 12/17/09, 12/14/09, 12/10/09, 12/9/09, 12/4/09
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, etc. 	8/2/12, 7/23/12, 7/27/10, 7/22/10, 6/28/10, 6/25/10, 6/17/10, 6/14/10, 5/25/10, 5/21/10, 5/14/10, 5/10/10, 4/30/10, 3/12/10, 1/12/10, 12/16/09
Minutes of Meetings	
<ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A or no mtg 7/15/11, 1/12/11
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg Pre-IND/Pre-BLA Mtg, 11/25/08
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	None
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> • 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 8/29/12, 9/29/10
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 8/29/12, 9/27/10
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 8/29/12, 9/22/10
<ul style="list-style-type: none"> PMR/PMC Development Templates (<i>indicate total number</i>) 	<input type="checkbox"/> None 14

Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	7/24/12
• Clinical review(s) (<i>indicate date for each review</i>)	7/24/12, 8/6/10
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 16 of Clinical Review dated 8/16/10
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None CDRH - 7/23/12, 5/31/12, 7/27/10, 5/4/10
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested Review Summaries- 12/16/11 9/15/10 & 8/24/10
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/27/12, 7/30/10
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/27/12, 7/30/10
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/27/12, 7/29/10
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/29/12, 8/9/10
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/1/12, 5/25/12, 8/9/10
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/1/12, 5/25/12, 8/9/10 QT/IRT - 5/15/12, 7/20/10, 5/6/10
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None

⁶ Filing reviews should be filed with the discipline reviews.

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/28/12, 9/29/10
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Addendum dated 9/29/10, 8/9/10
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/26/12, Addendum dated 9/29/10, 8/9/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/17/10
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/6/12, 9/17/10
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/2/12, Addendum dated 9/23/10 regarding the environmental assessment, 9/17/10
❖ Microbiology Reviews	<input type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	Facilities Secondary Review 8/10/10 Facilities Primary Review (DP) 8/6/10, Facilities Primary Review (DS) 8/2/10, 8/1/12
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input type="checkbox"/> None Immunogenicity - 8/17/12, 8/9/10
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Refer to the addendum to the primary CMC review dated 9/23/10
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	

❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁷)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)	Date completed: 7/25/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

MONSURAT O AKINSANYA
08/30/2012



BLA 125294/0

GENERAL ADVICE

Sicor Biotech UAB
Attention: Diana Landa (Authorized U.S. Agent)
Director, Regulatory Affairs
Teva Branded Pharmaceutical Products, R&D
425 Privet Road
P.O. Box 1005
Horsham, PA 10944

Dear Diana Landa:

Please refer to your Biologics License Application (BLA) dated November 30, 2009, received November 30, 2009, submitted under section 351(a) of the Public Health Service Act for “xxx-filgrastim.”

We also refer to your February 29, 2012, submission, containing your complete response to our September 29, 2010, action letter.

We have reviewed your proposals for a distinguishing prefix as part of the nonproprietary name for your proposed product for which you are seeking approval in BLA 125294. Of the four proposed prefixes, we have no objection to:

- tbo-filgrastim
-  (b) (4)
- 

We also encourage you to conduct due diligence on your proposed prefix(es) to ensure there are no restrictions on its use in this context.

Submit your final proposal for a distinguishing prefix to be used as part of the nonproprietary name for the product filed under this BLA by noon on August 7, 2012, as part of the revised labeling and carton and container labels that you were requested to submit in our August 2, 2012, communications to you.

If you have any questions, call Lara Akinsanya, M.S., at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Edvardas Kaminskas, M.D.
Deputy Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

EDVARDAS KAMINSKAS
08/03/2012

Akinsanya, Lara

From: Akinsanya, Lara
Int: Thursday, August 02, 2012 5:36 PM
To: 'Diana Landa'
Cc: Akinsanya, Lara
Subject: STN 125294/0/32 (Neuroval) - FDA Proposed PMRs and PMCs - DUE August 7, 2012

Attachments: FDA proposed PMRs and PMCs for BLA 125294.doc

Dear Diana Landa,

As we continue our review of your NDA, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief summaries are intended to describe the main trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by teleconference if needed.

Upon mutual agreement, we will ask you to submit an official copy of the PMR trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Milestones only need month and year. For milestone calculations purposes only, assume that an approval occurs on the PDUFA date.

Final PMR designation numbers will be assigned later.



FDA proposed
s and PMCs for..

If you have any questions regarding any item on the list, please let me know by email before you make your official submission electronically.

Please respond by Noon on **Tuesday, August 7, 2012.**

Thanks
Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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/s/

MONSURAT O AKINSANYA
08/02/2012

PMR #4

PMR Description:

To conduct an assessment for the presence of anti-[INSERT NAME] and anti-native human G-CSF binding antibodies using a validated assay in at least 500 patients enrolled/to be enrolled in one or more clinical trials. To conduct an assessment for neutralizing antibodies using a validated assay in all patients with binding antibodies to [INSERT NAME] or native G-CSF and in all patients with evidence of unexplained, persistent neutropenia. Teva should provide a listing of the clinical trials in which this assessment will be conducted.

PMR Schedule Milestones:

Final protocol Submission Date: MM/YYYY
Study Completion Date: MM/YYYY
Final Report Submission Date: MM/YYYY
Other: _____ MM/YYYY

FDA proposed Post Marketing Commitments for BLA 125294

Product Name:

Neuroval (generic name not determined)

PMC #1

PMC Description:

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

PMC Schedule Milestones:

Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

PMC #2

PMC Description:

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

PMC Schedule Milestones:

Final Protocol Submission: MM/YYYY
Study Completion: MM/YYYY
Final Report Submission: MM/YYYY

PMC #3

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 figrastim bioburden and endotoxin data for the (b) (4) following the proposed changes.

PMC #7

PMC Description:

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

PMC Schedule Milestones:

Final Protocol Submission:	<u>MM/YYYY</u>
Study/Trial Completion:	<u>MM/YYYY</u>
Final Report Submission:	<u>MM/YYYY</u>
Other: <u>Assay Development Findings</u>	<u>MM/YYYY</u>

PMC #8

PMC Description:

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

PMC Schedule Milestones:

Final Protocol Submission:	<u>MM/YYYY</u>
Study/Trial Completion:	<u>MM/YYYY</u>
Final Report Submission:	<u>MM/YYYY</u>
Other: <u>Assay Development Findings</u>	<u>MM/YYYY</u>

Akinsanya, Lara

From: Akinsanya, Lara
Int: Thursday, August 02, 2012 5:34 PM
To: 'Diana Landa'
Cc: Akinsanya, Lara
Subject: STN 125294/0/32 (Neuroval) - FDA Proposed PI - - DUE August 7, 2012

Attachments: BLA 125294_draft-labeling_FDA Proposed_080212.doc

Dear Diana Landa,

Please see attached revised draft (additional revisions to the PI may be sent at a future date as negotiations proceed) of the PI for STN 125294.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)



BLA
94_draft-labeling_FL

After you have made the changes, please send me the revised tracked change before you make your official submission electronically.

Please provide a revised PI to me by Noon on **Tuesday, August 7, 2012**.

Thanks
Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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/s/

MONSURAT O AKINSANYA

08/02/2012

Akinsanya, Lara

From: Akinsanya, Lara
Int: Thursday, August 02, 2012 5:09 PM
To: 'Diana Landa'
Cc: Akinsanya, Lara
Subject: CMC-labeling/ Information Request : STN 125294/0/32 (Neutroval) - DUE August 7, 2012

Dear Diana Landa,

Please respond to the following CMC Labeling information request:

1. Please add the statement, "No U.S. standard of potency" to each carton per 21 CFR 610.61(r).
2. As defined in 21 CFR 600.3(t), manufacturer is the "applicant." The name, address and license number of the manufacturer must be listed on labeling per 21 CFR 610.61(b) and 21 CFR 201.57. Per 21 CFR 610.64 the marketer may be listed with the manufacturer. The U.S. License number must follow the manufacturer's address.

Please respond to this information request by Noon on **Tuesday, August 7, 2012.**

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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/s/

MONSURAT O AKINSANYA
08/02/2012

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, July 25, 2012 2:40 PM
To: Diana Landa
Cc: Akinsanya, Lara
Subject: BMAB - Information Request : STN 125294/0/32 (Neuroval) - DUE July 31, 2012

Dear Diana Landa,

Please respond to the following information request from the Biotechnology Manufacturing Assessment Branch:

1. You have indicated in response to item 6 in the complete response letter that you are implementing changes to the drug substance manufacturing process to improve microbial control and the data to support proposed changes would be available by 3Q 2012. Please provide an update relating to when the changes were implemented and how many batches have been manufactured since implementation of the change. Please also provide the date when the complete information would be submitted to the Agency.

Please respond to this information request by **Tuesday, July 31, 2012**.

Thanks
Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA
07/25/2012

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, July 25, 2012 8:34 AM
To: Diana Landa
Cc: Akinsanya, Lara
Subject: DMEPA - Information Request : STN 125294/0/32 (Neuroval) - DUE July 30, 2012

Dear Diana Landa,

Please respond to the following information request from the Division of Medication Error Prevention and Analysis:

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.

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 300 mcg. 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

Please respond to this information request by **Monday, July 30, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MONSURAT O AKINSANYA
07/25/2012

Akinsanya, Lara

F : Akinsanya, Lara
S : Tuesday, July 24, 2012 10:11 AM
To: Diana Landa
Cc: Akinsanya, Lara
Subject: Clinical - Information Request : STN 125294/0/32 (Neuroval) - DUE TODAY

Dear Diana Landa,

We are reviewing your submission and have the following information request. We request a written response via email **by 5:00 PM Today** in order to continue our evaluation of your BLA. You will also need to follow up with a formal response to the BLA.

- Provide a tabular listing of all study subjects enrolled from all of the clinical studies that had an adverse event of neutropenia associated with a positive assay (validated or unvalidated) result for antibodies to XM-02 and a listing of the number of patients with positive antibody assays and of those neutralizing antibodies regardless of association of an adverse event.

Thank you
Lara

I (Monsurat) Akinsanya, M.S.
Laboratory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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/s/

MONSURAT O AKINSANYA
07/24/2012



BLA 125294

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Sicor Biotech UAB
c/o Teva Branded Pharmaceutical Products R&D
425 Privet Road
P.O. Box 1005
Horsham, PA 10944

ATTENTION: Diana Landa
Director, Regulatory Affairs

Dear Ms. Landa:

Please refer to your Biologics License Application (BLA) dated February 29, 2012, received February 29, 2012, submitted under section 351 of the Public Health Service Act, for (b) (4) 300 mcg/0.5 mL and 480 mcg/0.8 mL.

We also refer to your April 17, 2012, correspondence, received April 17, 2012, requesting review of your proposed proprietary name, Neutroval. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

1. Neutroval and Neupogen

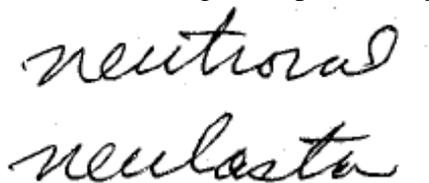
The proposed proprietary name is orthographically similar to Neupogen (filgrastim injection). Neutroval and Neupogen are similar in length (9 vs. 8 letters) and share the beginning letter string, 'neu'. Moreover, the name pair has identical product characteristics such as indication (to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever), dosage form (solution for injection), (b) (4) strengths (300 mcg/0.5 mL, 480 mcg/0.8 mL), dose (5 mcg/kg/day), frequency of administration (once daily), and product presentation (single use prefilled syringe). However, the two products are not interchangeable.

Although the ending letter strings differ, there is significant overlap with product characteristics. Therefore, we are concerned with name confusion based on prior errors with name pairs that share the

same beginning letter string but end differently (Neuroval vs. Neulasta, Neupogen, or Neumega). These name pairs also shared product characteristics such as dosage form, route of administration, indication, patient population, and product presentation. Thus, confusion between this name pair may result in medication errors if both are marketed.

2. Neuroval and Neulasta

The proposed proprietary name is orthographically similar to Neulasta (pegfilgrastim injection). Neuroval and Neulasta are similar in shape (3 up strokes), length (9 vs. 8 letters), and share the beginning letter string, 'neu'. Moreover, the name pair shares product characteristics including dosage form (solution for injection), route of administration (subcutaneous), indication (decrease in incidence of febrile neutropenia), patient population (patients receiving myelosuppressive anti-cancer drugs), and product presentation (single use prefilled syringes).

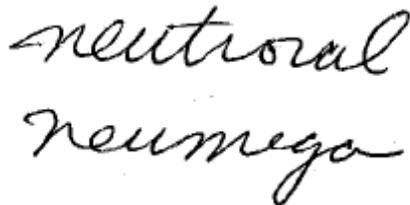


The image shows two lines of handwritten text in cursive. The top line reads 'neuroval' and the bottom line reads 'neulasta'. The handwriting is fluid and somewhat slanted, with the 'n' in both words starting with a similar upward stroke.

The minor orthographic differences in the endings of the names may not sufficiently distinguish the name pair given the orthographic similarities stated previously. Thus, confusion between this name pair may result in medication errors if both are marketed as demonstrated by post marketing medication error.

3. Neuroval and Neumega

The proposed proprietary name is orthographically similar to Neumega (oprelvekin for injection). Neuroval and Neumega are similar in length (9 vs. 7 letters) and share the beginning letter string, 'neu'. The two products have similar product characteristics including route of administration (subcutaneous), patient population (cancer patients), similarity in dose (5 mcg/kg vs. 50 mcg/kg), and frequency of administration (once daily).



The image shows two lines of handwritten text in cursive. The top line reads 'neuroval' and the bottom line reads 'neumega'. The handwriting is fluid and somewhat slanted, with the 'n' in both words starting with a similar upward stroke.

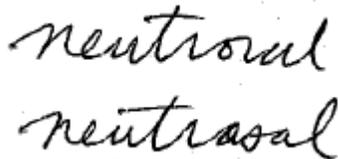
The minor orthographic differences in the endings of the names may not sufficiently distinguish the name pair given the orthographic similarities stated previously. Thus, confusion between this name pair may result in medication errors if both are marketed as demonstrated by post marketing medication error data.

4. Neuroval and Neutrasal

The proposed proprietary name, Neuroval, is orthographically and phonetically similar to the marketed product, Neutrasal. Neutrasal (powder for supersaturated calcium phosphate rinse) is a 510(k) product marketed as a device. Indications for use are¹:

- NeutraSal[®] is also indicated as an adjunct to standard oral care in relieving the discomfort associated with oral mucositis that may be caused by radiation or high dose chemotherapy. Relief of dryness of the oral mucosa in these conditions is associated with the amelioration of pain.
- NeutraSal[®] may be used for relief of dryness of the oral mucosa when hyposalivation results from the following: surgery, radiotherapy near the salivary glands, chemotherapy, infection or dysfunction of the salivary glands; emotional factors such as fear or anxiety; obstruction of the salivary glands; Sjogren's Syndrome .
- NeutraSal[®] is also indicated for the dryness of the mouth (hyposalivation, xerostomia).
- NeutraSal[®] is indicated for dryness of the oral mucosa due to drugs such as antihistamines, atropine, and other anticholinergic agents that suppress salivary secretion.

The orthographic and phonetic similarities stem from the fact that the name pair has the same length (9 letters) and are nearly identical with only differences in the two letters as indicated here (Neuroval vs. Neutrasal). Thus the names appear and sound similar when scripted and spoken.



The two products also have similar product characteristics such as overlapping patient population (cancer patients) and prescribers. We carefully considered whether differences in product characteristics such as dosage form, strength, and route and frequency of administration for your product compared to NeutraSal would minimize the potential for error between Neuroval and NeutraSal. We concluded that these aspects will not eliminate the potential for name confusion and medication errors.

Although Neutrasal has some differences in product characteristics, because the name pair has such strong orthographic and phonetic similarities, differences in product characteristics are not enough to overcome the similarities. We identified post marketing confusion between products with different product characteristics when strong orthographic and phonetic similarities exist. For example, ISMP recently published a report where Arixtra (fondaparinux) was confused with Arista (a device used in surgical procedures as an adjunctive hemostatic device to assist when control of capillary, venous, and arteriolar bleeding).¹ The report demonstrates that differing product characteristics cannot overcome overwhelming orthographic and/or phonetic similarities, particularly for products used in the same setting of care. Thus, confusion between this name pair may result in medication errors if both products are marketed.

¹ <http://neutrasal.com/>

¹ <http://www.ismp.org/newsletters/acutecare/issues/20120517.pdf>

5. Neutroval and Pending Proprietary Name

The proposed proprietary name, Neutroval, is also vulnerable to name confusion that could lead to medication errors with a pending proposed proprietary name due to orthographic similarity and shared product characteristics.

We acknowledge that the conclusions of this review differ from the March 22, 2010 correspondence in which the proprietary name Neutroval was found conditionally acceptable. This difference is accounted for by the recently identified medication error reports among Neupogen and Neulasta as well as Neupogen and Neumega. Because your name is constructed similar to these name pairs and share similar product characteristics, we have determined that these reports indicate your name is prone to confusion with Neupogen, Neulasta, and Neumega. Additionally, two new names (i.e. NeutraSal and pending proprietary name) were identified during this review cycle that were not available for review during the previous review cycle. Therefore we conclude that the proposed proprietary name, Neutroval, is not acceptable from a safety perspective.

If you intend to have a proprietary name for this product, we recommend that you submit an alternate proprietary name for review as soon as possible. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Lara Akinsanya at (301) 796-9634.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/16/2012

Akinsanya, Lara

From: Nguyen, Quynh Nhu
Sent: Monday, July 23, 2012 12:58 PM
To: Akinsanya, Lara
Cc: Deisseroth, Albert; Kaye, Ron D.; Story, Molly
Subject: RE: Sponsor's Response to your IR - CDRH Consult Request: STN 125294 (Neuroval) - CDRH
(b) (4)



QuynhNhu Nguyen
Lieutenant, U.S. Public Health Service

Biomedical Engineer/Combination Products Human Factors Specialist
Office of Device Evaluation
Center for Devices and Radiological Health
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO66, Room 2531
Silver Spring, MD 20993
quynhT.nguyen@fda.hhs.gov
301-796-6273

From: Akinsanya, Lara
Sent: Tuesday, July 10, 2012 4:35 PM
To: Nguyen, Quynh Nhu
Subject: FW: Sponsor's Response to your IR - CDRH Consult Request: STN 125294 (Neuroval)

Thanks for the call - I completed the consult form right away for you - see attached and I will check it into DARRTS as well.

8 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

MONSURAT O AKINSANYA
07/23/2012

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, March 15, 2012 11:43 AM
To: 'Diana Landa'
Cc: Akinsanya, Lara
Subject: OMPQ - Information Request : STN 125294/0/32 (Neuroval)

Dear Diana Landa,

Please respond to the following information request from the Office of Manufacturing and Product Quality:

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

Please respond to this information request by **Thursday, April 5, 2012**.

Thank you
Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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/s/

MONSURAT O AKINSANYA
03/15/2012



BLA 125294/0

GENERAL ADVICE

Teva Pharmaceuticals U.S.A.
Attention: Diana Landa, M.S.
Director, Regulatory Affairs
425 Privet Road
P.O. Box 1005
Horsham, PA 19044

Dear Ms. Landa:

Please refer to your Biologics License Application (BLA) dated November 30, 2009, received November 30, 2009, submitted under section 351 of the Public Health Service Act for **NEUTROVAL™ (XM02; (b) (4)**.

We also refer to your July 12, 2010, submission, containing your response to an information request from the Division of Biologic Oncology Products (via Danyal Chaudhry) on March 24, 2010 regarding your proposed pediatric plan.

We have reviewed the referenced material and have the following comments:

1. FDA notes that the deferred studies were to include PK/PD and safety studies in 50 patients from 1 month to 16 years, not 1 month to 18 years as stated in Teva's study plan. This will require justification at the time of the Response to CR submission.
2. The PK/PD portion of the study is an important aspect of the Pediatric Study Plans. FDA refers you to the Guidance for Industry, *General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072114.pdf>)
3. At the time of the Response to CR submission, provide a protocol for the PK/PD and safety studies including a statistical analysis plan and justification for approval in terms of number of patients, sampling, endpoints, and analysis

If you have any questions, call me at (301) 796-9634.

Sincerely,
{See appended electronic signature page}

Lara Akinsanya, M.S.
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MONSURAT O AKINSANYA
02/17/2012

Akinsanya, Lara

From: Akinsanya, Lara
nt: Monday, June 25, 2012 12:16 PM
o: 'Diana Landa'
Cc: Akinsanya, Lara
Subject: CDRH - Information Request : STN 125294/0/32 (Neuroval) - DUE July 6, 2012

Dear Diana Landa,

Please respond to the following information request from the Center for Devices and Radiological Health:

Your response to FDA letter dated September 29, 2010 states the following (in quotes):

(b) (4)



Please respond to this information request by **Thursday, July 6, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager

Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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/s/

MONSURAT O AKINSANYA
06/25/2012

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, June 20, 2012 4:08 PM
To: 'Diana Landa'
Cc: Akinsanya, Lara; Boehmer, Jessica
Subject: Pharmacology/Toxicology - Information Request : STN 125294/0/32 (Neuroval) - DUE June 26, 2012

Dear Diana Landa,

Please respond to the following Pharmacology/Toxicology information request:

- Regarding Study AA99241 (embryofetal toxicity study in rabbits)- In section 5.6 (page 32 of 512), Module 4, submission date of February 29, 2012, you state that blood samples were collected for ADA analysis. We could not locate the results of this analysis. Please indicate the location of the data in your submission or submit the data for our review.
- Please provide human AUCs and propose animal-to-human AUC ratios to be incorporated in section 8.1 of the label.

Please respond to this information request by **Tuesday, June 26, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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/s/

MONSURAT O AKINSANYA
06/20/2012

Akinsanya, Lara

From: Akinsanya, Lara
nt: Wednesday, June 13, 2012 12:02 PM
o: 'Diana Landa'
Cc: Akinsanya, Lara; Boehmer, Jessica
Subject: DMEPA - Information Request : STN 125294/0/32 (Neuroval) - DUE June 27, 2012

Dear Diana Landa,

Please respond to the following information request from the Division of Medication Error Prevention and Analysis:

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, "Single-use pre-filled syringes with a *needle safety guard*". 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.  (b) (4)
3. The decimal points look like commas. Use a dot (.) as the decimal point designation.

F. Package Insert

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”).

Please respond to this information request by **Wednesday, June 27, 2012.**

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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/s/

MONSURAT O AKINSANYA
06/13/2012

Akinsanya, Lara

From: Akinsanya, Lara
Int: Wednesday, June 13, 2012 11:52 AM
To: 'Diana Landa'
Cc: Akinsanya, Lara; Boehmer, Jessica
Subject: Labeling - Information Request : STN 125294/0/32 (Neutroval) - DUE June 27, 2012
Attachments: BLA 125294_RPM Review_draft-labeling.doc

Dear Diana Landa,

Please respond to the following information request regarding the PI that was submitted:

- Please look at the attached revised PI (with changes tracked) and make the format changes as requested.



BLA 125294_RPM
Review_draft-la...

Please make your changes to the attached version - in tracked mode.

Please respond to this information request by **Wednesday, June 27, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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/s/

MONSURAT O AKINSANYA
06/13/2012

Akinsanya, Lara

From: Akinsanya, Lara
nt: Friday, June 01, 2012 2:20 PM
o: 'Diana Landa'
Cc: Akinsanya, Lara; Boehmer, Jessica
Subject: CMC - Information Request : STN 125294/0/32 (Neuroval) - DUE June 29, 2012

Dear Diana Landa,

Please respond to the following Chemistry, Manufacturing and Controls' information request:

-  (b) (4)

Please respond to this information request by **Wednesday, June 29, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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/s/

MONSURAT O AKINSANYA
06/01/2012

Akinsanya, Lara

From: Akinsanya, Lara
nt: Thursday, May 31, 2012 1:23 PM
to: 'Diana Landa'
Cc: Akinsanya, Lara; Boehmer, Jessica
Subject: IRT - Information Request : STN 125294/0/32 (Neutroval) - DUE June 27, 2012

Dear Diana Landa,

Please respond to the following information request from the **FDA Interdisciplinary Review Team (IRT)** regarding the proposed protocol :

(b) (4)



Please respond to this information request by **Wednesday, June 27, 2012.**

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager

Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
 (1) 796-9849 (fax)

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/s/

MONSURAT O AKINSANYA
05/31/2012

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Thursday, May 31, 2012 1:07 PM
To: 'Diana Landa'
Cc: Akinsanya, Lara; Boehmer, Jessica
Subject: CDRH - Information Request : STN 125294/0/32 (Neuroval) - DUE June 21, 2012

Dear Diana Landa,

Please respond to the following information request from the Center for Devices and Radiological Health:

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.

Please respond to this information request by **Thursday, June 21, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA
05/31/2012

Akinsanya, Lara

From: Akinsanya, Lara
Sent: Wednesday, May 30, 2012 11:08 AM
To: 'Diana Landa'
Cc: Akinsanya, Lara
Subject: OMPQ - Information Request : STN 125294/0/32 (Neuroval) - DUE June 27, 2012

Dear Diana Landa,

Please respond to the following information request from the Office of Manufacturing and Product Quality:

1.  (b) (4)
2. It appears from the  (b) (4) in the shipping qualification protocol (SQP-009) that  (b) (4) Please explain why  (b) (4)


Please respond to this information request by **Wednesday, June 27, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
(301) 796-9634 (phone)
(301) 796-9849 (fax)

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/s/

MONSURAT O AKINSANYA
05/30/2012



BLA 125294/0/32

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

Teva Pharmaceuticals U.S.A.
Attention: Diana Landa, M.S.
Director, Regulatory Affairs
425 Privet Road
P.O. Box 1005
Horsham, PA 19044

Dear Ms. Landa:

We have received your February 29, 2012 resubmission to your supplement to your biologics license application for **NEUTROVAL™** on February 29, 2012.

The resubmission contains additional information addressing all deficiencies and information requests identified by the Agency in our September 29, 2010 complete response letter.

We consider this a complete, class 2 response to our September 29, 2010, action letter. Therefore, the user fee goal date is August 30, 2012.

If you have any questions, call me at (301) 796-9634.

Sincerely,
{See appended electronic signature page}

Lara Akinsanya, M.S.
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MONSURAT O AKINSANYA
03/26/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Our STN: 125294/0

July 20, 2011

Teva Pharmaceuticals U.S.A.
Attention: Deborah A. Jaskot, M.S., R.A.C.
Vice President, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Ms. Jaskot:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Neutroval. We also refer to the teleconference held on July 15, 2011, between representatives of your firm and the FDA. A copy of the official minutes is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact me at (301) 796-1393.

Sincerely,

A handwritten signature in black ink, appearing to read "Erik Laughner", with a long horizontal flourish extending to the right.

/Erik Laughner/

Erik Laughner, M.S. RAC (US)
Senior Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures: FDA Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 15, 2011; 11:00 AM -12:00 PM ET
APPLICATION: BLA STN 125294/0
SPONSOR: Teva Biopharmaceuticals USA [Teva]
DRUG NAME: Neutroval (rmetHuG-CSF)
TYPE OF MEETING: Type C; Teleconference
MEETING CHAIR: Susan L. Kirshner
MEETING RECORDER: Erik Laughner

FDA ATTENDEES:

Erik Laughner, Senior Regulatory Health Project Manager, DBOP/OODP
Suzanne Demko, Medical Team Leader, DBOP/OODP
Thomas Herndon, Medical Officer, DBOP/OODP
Jee Chung, Product Reviewer, DTP/OBP
Laura Salazar-Fontana, Immunogenicity Reviewer, DTP/OBP
Susan L. Kirshner, Immunogenicity Team Leader, DTP/OBP

TEVA ATTENDEES:

Name	Title	Organization
Dennis Ahern, MS	Senior Director, Regulatory Affairs	Teva Branded Pharmaceutical Products (Horsham, PA)
(b) (4)		
Patrick Liu, MD, Ph.D	Senior Director, Global Head of Bioassays	Teva Global Branded Products (Rockville, MD)

1.0 MEETING OBJECTIVES:

To discuss comments 8-11 pertaining to immunogenicity from the September 29, 2010 Complete Response (CR) letter for BLA STN 125294 (Neutroval).

2.0 BACKGROUND:

On November 30, 2009, Teva submitted for FDA review, BLA STN 125294 for Neutroval (recombinant N-methionyl human granulocyte colony-stimulating factor; rmetHuG-CSF). The proposed indication was 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 September 29, 2010, FDA sent a Complete Response (CR) letter to Teva regarding a number of deficiencies (items 1-5 of letter) which prevented approval. FDA also provided a number of information requests (items 6-22 of letter).

On April 21, 2011, Teva requested a Type C teleconference with FDA to specifically discuss the following information requests from the September 29, 2010 letter:

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 Neutroval. 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.

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-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.

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-Neutroval 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.

11. *Provide a plan for assessing for the presence, persistence, and effects of anti-Neuroval 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:*
 - a. *Date of submission of the protocol for clinical immunogenicity assessment*
 - b. *Date of completion of the study*
 - c. *Final report submission date*

The meeting briefing packages were submitted to the BLA file on June 15, 2011. Draft FDA responses were communicated to Teva on July 14, 2011. On July 14, 2011, Teva notified FDA via electronic mail (email) that the responses were reviewed. Teva only required one additional clarification and provided a written response (incorporated below on page 8). Actual **meeting discussion** immediately follows.

3.0 DISCUSSION:

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSE:

1. Teva is retracting Question 1 that was submitted with the Type C meeting request on April 21, 2011. After further internal discussions, Teva has decided to develop a new positive control using XM02 versus utilizing a commercially-available product (Neupogen®, Amgen GmbH).

FDA Response Provided On July 14, 2011: Acknowledged.

2. The following relates to item 8 and 9 of FDA's September 29, 2010 CR letter in terms of the request for validation of the assay to include sensitivity and specificity for detection of anti-Neuroval antibodies that are also cross-reactive with the native human G-CSF.

Based on the development work performed by Teva, the sensitivity of the screening assay will be between [REDACTED] (b) (4)

Detection of anti-Neuroval antibodies that are also cross-reactive with human G-CSF will be validated in the confirmatory step using an additional competition assay with recombinant human G-CSF as a competitor. In this assay a recombinant human G-CSF protein, which is produced from Chinese Hamster Ovarian cells (CHO cells), will be used as competitor.

- a. Does FDA accept the proposed assay format?

FDA Response Provided On July 14, 2011: Yes, the Agency agrees with the proposed assay format.

- b. G-CSF used in this assay as competitor is produced from mammalian CHO cells. Is it acceptable to use this product as a competitor to confirm the specificity for detection of anti-Neutroval antibodies that are cross-reactive with native human G-CSF?

FDA Response Provided On July 14, 2011: According to the meeting briefing document, (b) (4)

[Redacted text block]

- 3. The following relates to item 10 of FDA's September 29, 2010 CR letter in terms of the request for validation of the assay to include the sensitivity and specificity for detection of anti-Neutroval antibodies that are also cross-reactive with and neutralize the bioactivity of native human G-CSF.

The sensitivity of the assay will be determined during the validation.

[Redacted text block] (b) (4)

Is it acceptable to use recombinant human G-CSF in the neutralizing antibody assay as cell growth stimulator to confirm the specificity for detection of anti-Neutroval antibodies that are cross-reactive with and neutralize the bioactivity of human G-CSF?

FDA Response Provided On July 14, 2011: Please refer to FDA's response to question 2 above. The acceptability of the assay is a review issue. However, provided Teva submits validation data demonstrating the assay performs suitably when cells are stimulated with either XM02 or the native sequence rhG-CSF produced in CHO, FDA agrees.

4. The following relates to item 11 of FDA's September 29, 2010 CR letter in terms of a plan for assessing the presence, persistence, and effects of anti-Neuroval and anti-native human G-CSF binding and neutralizing antibodies using validated assays in at least 500 patients enrolled or to be enrolled in one or more clinical trials.

a. Does the agency consider the planned immunogenicity assay cascade being adequate to evaluate the presence, persistence, and effects of anti-Neuroval and anti-native human G-CSF binding and neutralizing antibodies?

FDA Response Provided On July 14, 2011: FDA agrees with the overall immunogenicity cascade provided in this meeting package.

b. Does the agency accept data gained with the planned immunogenicity assay cascade and the proposed assays, as described under request 8-10?

FDA Response Provided On July 14, 2011: Given the limited information presented in this meeting package, the adequacy of the data obtained using the new immunogenicity scheme is considered a review issue. Therefore, its significance will be evaluated when all the data is submitted to the Agency.

c. Does the agency agree that the number of enrolled patients from XM02 clinical trials, being less than initially requested, is sufficient to accommodate FDA's request for additional information on the presence, persistence, and effects of anti-Neuroval and anti-native human G-CSF binding and neutralizing antibodies?

FDA Response Provided On July 14, 2011: Teva proposes to test samples from 426 patients. That number is sufficient to detect an immunogenicity rate of approximately 1% and is therefore acceptable.

Teva July 14, 2011, Written Response:

(b) (4)



Can this product be used as the competitor referring to the question (response 2b) and as cell growth stimulator (response 3)?

Meeting Discussion: FDA acknowledged Teva's written response and agreed that use of this product was likely acceptable. However, final acceptability would be a review issue when the data was formally submitted and reviewed by FDA. Teva acknowledged and noted that this product was well characterized and had a certificate of compliance.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125294/0

MEETING REQUEST GRANTED
May 3, 2011

Teva Pharmaceuticals U.S.A.
Attention: Deborah A. Jaskot, M.S., R.A.C.
Vice President
North American Regulatory Affairs
Policy and Governance
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454-1090

Dear Ms. Jaskot:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Neutroval.

We also refer to your April 21, 2011, correspondence requesting a teleconference to discuss comments 8-11 from our September 29, 2010 Complete Response (CR) letter pertaining to immunogenicity. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The teleconference is scheduled as follows:

Date: Friday, July 15, 2011

Time: 11:00 AM-12:00 PM ET

Phone Arrangements: Please provide a CALL-IN NUMBER and PASSCODE to the FDA

CDER participants:

Patricia Keegan, Division Director, DBOP/OODP
Erik Laughner, Senior Regulatory Health Project Manager, DBOP/OODP
Suzanne Demko, Medical Team Leader, DBOP/OODP
Thomas Herndon, Medical Officer, DBOP/OODP
Jee Chung, Product Reviewer, DTP/OBP
Laura Salazar-Fontana, Immunogenicity Reviewer, DTP/OBP
Daniela Verthelyi, Immunogenicity Team Leader, DTP/OBP

Submit background information for the meeting (one formal electronic copy to the eCTD application and 10 desk copies to Erik Laughner) by June 15, 2011. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by June 15, 2011, we may cancel or reschedule the meeting.

Submit the 10 desk copies to the following address:

Erik Laughner, M.S. RAC (US)
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2319
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If you have any questions, contact me at (301) 796-1393.

Sincerely,

A handwritten signature in black ink, appearing to read 'E. Laughner', written in a cursive style.

/Erik Laughner/
Erik Laughner, M.S. RAC (US)
Senior Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125294/0

February 2, 2011

Teva Pharmaceuticals U.S.A.
Attention: Deborah A. Jaskot, M.S., R.A.C.
Vice-President, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Ms. Jaskot:

Please refer to your Biologics License Application (BLA) dated November 30, 2009, received November 30, 2009, submitted under section 351 of the Public Health Service Act for "Neuroval." We also refer to our deficiency comments 2 and 3 identified in the September 29, 2010, Complete Response (CR) letter and to the recent teleconference held on January 12, 2011, between Teva Pharmaceuticals U.S.A, representatives (b) (4), and the FDA regarding the proposed container closure system for Neuroval. We provide the following comment which delineates your responsibility as the applicant.

The product described in this BLA application meets the regulatory definition of a combination product (see 21 CFR Part 3) comprised of a prefilled syringe with a staked needle (device constituent) filled with Neuroval (biologic constituent). As the applicant of the marketing application (BLA), you (Teva Pharmaceuticals U.S.A.) assume responsibility for compliance with all applicable standards and data to ensure safety and efficacy of the product submitted in this BLA (i.e., all constituent parts and the combination product as a whole). For guidance related to the marketing application applicant and master files, please refer to FDA Guidance to Industry, "Container Closure Systems for Packaging Human Drugs and Biologics;" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf>

BL 125294/0

Page 2

If you have any questions contact Erik Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

A handwritten signature in cursive script that reads "Patricia Keegan".

/Patricia Keegan/

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN
SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Our STN: 125294/0/27

January 28, 2011

Teva Pharmaceuticals U.S.A.
Attention: Deborah A. Jaskot, M.S., R.A.C.
Vice- President, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Ms. Jaskot:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Neutroval. We also refer to the teleconference held on January 12, 2011, between representatives of your firm and the FDA. A copy of the official minutes is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact me at (301) 796-1393.

Sincerely,

A handwritten signature in black ink, appearing to read "Erik Laughner".

/Erik Laughner/

Erik Laughner, M.S. RAC (US)
Senior Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures: FDA Minutes



**DEPARTMENT OF HEALTH & HUMAN
SERVICES**

Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 12, 2011; 3:30-4:00 PM ET
APPLICATION: BLA STN 125294
SPONSOR: Teva Biopharmaceuticals USA [Teva]
DRUG NAME: Neuproval (rmetHuG-CSF)
TYPE OF MEETING: Type A; Teleconference
MEETING CHAIR: Patricia Keegan
MEETING RECORDER: Erik Laughner

FDA ATTENDEES:

Patricia Keegan, Division Director, DBOP/OODP
Erik Laughner, Senior Regulatory Health Project Manager, DBOP/OODP
Suzanne Demko, Medical Team Leader, DBOP/OODP
Thomas Herndon, Medical Officer, DBOP/OODP
Kalavati Suvarna, Facilities Reviewer, DMPQ/OC
Anastasia Lolas, Facilities Reviewer, DMPQ/OC
William M. Burdick, Biomedical Engineer/Physicist, ODE/DAGID/GHDB
Lana Shiu, Medical Officer, OSMP/OCP

TEVA ATTENDEES:

Diana Landa, Director, Regulatory Affairs
Dennis Ahern, Senior Director, Regulatory Affairs
Peter Bias, Global Clinical Program Leader for Biosimilars
Ayelet Altman, Senior Director, Head of Operations, Global Innovative Products
Eric Strauss, Director, Quality, Global Generic Resources

(b) (4)



1.0 MEETING OBJECTIVES:

To discuss comment #3 from FDA's September 29, 2010 Complete Response (CR) letter for STN 125294 pertaining to the container/ closure system for Neutroval.

2.0 BACKGROUND:

On November 30, 2009, Teva submitted for FDA review, BLA STN 125294 for Neutroval (recombinant N-methionyl human granulocyte colony-stimulating factor; rmetHuG-CSF). The proposed indication was 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 September 29, 2010, FDA sent a Complete Response (CR) letter to Teva regarding a number of deficiencies which prevented approval.

On November 23, 2010, Teva requested a Type A teleconference with FDA to specifically discuss the following comment (#3) from the CR letter which pertained to the Neutroval container/closure system:

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) [redacted] 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) [redacted]), it appears that your syringes may not conform to current FDA consensus standards regarding syringes and needles.*

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

- [redacted] (b)(4)
- [redacted]
- [redacted]

(b) (4)

[Redacted text block]

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).

Draft FDA responses were communicated to Teva on January 10, 2011. On January 11, 2011, Teva indicated that the teleconference would focus on the Agency's concerns as stated in question #3.

3.0 DISCUSSION:

SPONSOR SUBMITTED BACKGROUND PREAMBLE, QUESTIONS AND FDA RESPONSE:

Neuroval® is supplied as a pre-filled syringe in two fill sizes: 300 mcg/0.5 mL and 480 mcg/0.8 mL. The main components of the final drug product container/ closure system are a

(b) (4)

[Redacted text block]

On May 12, 2010, the Agency has requested information pertaining to the design, development and validation of the syringe. Teva responded to the request via Sequence 0015, submitted on June 11, 2010, where it was clarified that Teva purchases the syringe from (b) (4) and therefore, all technical information pertaining to the device is considered proprietary and confidential and is contained within (b) (4) master file # (b) (4) and DMF # (b) (4) Letter of Authorization and contact information for (b) (4) were provided as part of the response.

Further, reference is made to June 30, 2010 Teleconference held between Teva and FDA and subsequent Sequence 0022, dated July 20, 2010, in which Teva provided information regarding functional testing performed on in-process basis as well as on drug product release and stability to assess performance and functionality of the syringe and safety device in routine production. Teva further clarified that the design of the syringe unit and safety device has been solely the responsibility of the component suppliers, (b) (4) and (b) (4) respectively, i.e. Teva did not require any customization to the syringe unit. Teva considers the most important performance characteristic of the syringe to be the ability to deliver the proper dose

and maintain proper functionality throughout shelf-life. Documentation delineating testing in place for all packaging components and the packaged drug product was provided as part of Sequence 0022.

The request for documentation demonstrating compliance of the device with ISO standards was communicated by the Agency as part of the Complete Response letter (Item #3), received on September 29, 2010.

Subsequently, Teva discussed the issue with (b)(4) and it was agreed upon by both parties that in order to maintain confidentiality of (b)(4) data and to expedite the resolution of Agency's concerns pertaining to the syringe, Teva hereby respectfully requests that the Agency issues (b)(4) a DMF deficiency letter, which will prompt (b)(4) to amend their DMF with any required information. Please note that (b)(4) has expressed willingness to accept such DMF deficiency letter and stand ready to submit any necessary data to demonstrate compliance of the (b)(4) with all relevant current FDA regulations and ISO standards.

1. Based on the fact that the safety device manufactured by (b)(4) is the subject of FDA-approved 510(k), Teva understands that the Agency's concerns regarding device conformance to ISO standards are limited to (b)(4) syringe components (without the safety device) only. Does the Agency concur?

FDA Draft Response Provided on January 10, 2011: Yes.

Meeting Discussion: There was no further discussion.

2. Further, Does the Agency agree to Teva's proposal that FDA issue (b)(4) a deficiency letter to DMF (b)(4) so that (b)(4) can work to resolve all issues requested by FDA for the pre-filled syringe and assure that performance is adequate for the pre-filled syringe with staked needle?

FDA Draft Response Provided on January 10, 2011: FDA agrees to issue (b)(4) a deficiency letter regarding DMF (b)(4)

Meeting Discussion: FDA confirmed that the DMF letter issued to (b)(4) would contain the same issues previously communicated to Teva in the CR letter.

3. Finally, does the Agency concur that the scope of data presented herein is adequate to address all FDA's concerns regarding Teva's drug product in the proposed packaging configuration?

FDA Draft Response Provided on January 10, 2011: FDA is unable to concur at this time. CDRH has concerns with the (b)(4) syringe due to performance issues that appear to be related to the design of the device. Performance issues, including but not limited to syringe tip breakage/blockage, incompatibility with needleless connectors, etc. have surfaced over the past year. Since the introduction of the (b)(4) syringe, CDRH's requirements for the design have evolved to reflect the current consensus of the

scientific/technical committee regarding the dimensional and performance aspects of syringes. This consensus is reflected in FDA's guidance document and industry standards to which conformance is required.

These documents were cited in FDA's CR comment #3 in the September 29, 2010, letter:

- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]
- [REDACTED]

CDRH requires that the syringe Teva has chosen either meet the specifications stated in these above documents or that valid scientific, technical, or clinical rationale for not meeting the specifications be provided for review. As stated in CR comment #3 in the September 29, 2010 letter, FDA is not currently able to determine whether the syringe meets all of the requirements, especially for the integrity of the connection between the syringe and staked needle.

Meeting Discussion: Teva acknowledged FDA's response and a representative from [REDACTED] (b) (4) requested clarification/confirmation from FDA that concerns regarding the [REDACTED] (b) (4) were not applicable to the [REDACTED] (b) (4) syringe chosen by Teva. [REDACTED] (b) (4) noted that this issue was recently discussed with FDA on November 1, 2010. [REDACTED] (b) (4)

[REDACTED] (b) (4). FDA's CDRH reviewer acknowledged and agreed [REDACTED] (b) (4) concerns are not a concern and will not be part of the DMF letter that will issued to [REDACTED] (b) (4). CDRH did request, however, that the protocol, pass/fail criteria, and results of testing the security/strength of attachment between the staked needle and the syringe tip be provided for review. This information is necessary to assure that the needle does not disengage from the syringe during clinical use.

[REDACTED] (b) (4) noted that some of the ISO standards cited in FDA's response may not be relevant, and agreed to submit any needed information to the DMF which could demonstrate compliance of relevant technical aspects of the ISO standards of this specific [REDACTED] (b) (4) syringe. FDA's representative from the Office of Combination Products stated that aspects such as dead space volume and bond strength evaluation should be performed on the syringe with the drug product and Teva as the manufacturer of the final filled syringe would ultimately be responsible for these tests. Furthermore, as a combination product, Teva would have to ensure compliance with both the drug and the device regulations.

(b) (4)

A large rectangular area of the document is completely redacted with a solid grey fill.

(b) (4)

A large rectangular area of the document is completely redacted with a solid grey fill.

FDA summarized that a letter to the (b) (4) Master File would formally identify those issues previously communicated to Teva regarding the syringe. In addition, FDA agreed to provide a letter to Teva (under the BLA) which would state Teva's responsibility as the applicant. FDA anticipated that the letters would issue within two weeks.

FDA Post-Meeting Addendum: Please refer to the link related to the prefilled glass syringe public health communication:

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm234219.htm>



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE of DECISION: January 12, 2010

FROM: Patricia Keegan, M.D.
Director
Division of Biological Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Designation of BLA application review status
Sponsor: TEVA Pharmaceuticals USA
Product: Neuroval (b)(4)

TO: BLA file STN 125294/0

The review status of this file submitted as a BLA application is designated to be:

Standard (10 Months)

Priority (6 Months)

Patricia Keegan, M.D.: Patricia Keegan

Date: 1-12-2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: August 17, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Verification of Integrity of Clinical Data Base for Study XM02-02-INT)

From: Chaudhry, Danyal
Sent: Tuesday, August 17, 2010 4:16 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: Diana.Landa@tevausa.com; Laughner, Erik; Chaudhry, Danyal
Subject: Information Request: Teva BLA STN 125294/0 (Neuroval (b) (4): Verification of Integrity of Clinical Data Base for Study XM02-02-INT

Dennis -- please make note of the following information request. We are requesting a response by Friday, August 27, 2010.

Information Request: For Study XM02- 02-INT

1. Define the oversight and management of the study database.
2. Define the composition of data recorded in the database.
3. Provide database SOPs to include but not be limited to routine use, quality control, security and access.
4. Provide CRO contract for database support between (b) (4) and Study Sponsor.
5. Provide detailed accounting of all database integrity events; locking, unblinding, unlocking, modification of composition of data, and relocking. Provide documentation supporting authorization and justification for the integrity events, and documentation for all database manipulations. Please ensure that your response specifically addresses the following FDA inspectional findings associated with potential database integrity breaches, in addition to any other unlocking of the database events not captured below:
 - a. Initial locking and unblinding – January 2, 2006
 - b. Initial unlocking of the database after unblinding – January 17, 2006
 - c. Initial relocking of the database – January 23, 2006
 - d. Unlocking of the database – on or after January 23, 2006
 - e. Final database lock – February 27, 2006
6. Provide current status and management of the database.

Please confirm receipt of this e-mail.

Danyal



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: August 10, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Follow up CMC information request in reference to the 8/6/10 CMC teleconference with the sponsor)

From: Chaudhry, Danyal
Sent: Tuesday, August 10, 2010 3:33 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: Chaudhry, Danyal; Diana.Landa@tevausa.com; Laughner, Erik
Subject: CMC Teleconference 8/6/10: Follow On Information Request

Dennis -- in reference to the August 6, 2010, teleconference to discuss outstanding CMC issues, please find below a follow up CMC information request regarding your BLA 125294:

The plasmid copy number varies between the Master Cell Bank (b) (4) Working Cell Bank (b) (4) and batches of end-of-production cells (b) (4) copies/cell). You state that this is due to the assay variability. Given that you have provided process validation and batch analysis demonstrating that the manufacturing produces highly similar XM02 drug substance batches you have submitted sufficient information to support the use in manufacturing of this working cell bank. However, you have also included a protocol for qualification of new working cell banks where the acceptance criterion for plasmid copy number is (b) (4). This protocol can not be evaluated because the acceptance criteria appear to be based on an unreliable assay for plasmid copy number. We recommend that you withdraw the current protocol for qualification on new cell banks from your application and optimized the assay used to determine plasmid copy number or develop a new assay. Using the new assay we suggest you revise the cell bank qualification protocol to include acceptance criterion for plasmid copy number that better reflects your actual manufacturing experience. This information should be submitted in a prior approval supplement following approval of your application.

Kindly confirm receipt of this e-mail and note that we request a response by or before August 20, 2010 as associated with other items from the August 6, 2010, teleconference.

Danyal



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: August 6, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Teleconference with Teva regarding CMC issues)

Teleconference Date: August 6, 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 CMC issues for the BLA

Attendees (tentative):

FDA

Dov Pluznik, DTP, CMC Reviewer
Kathy Lee, DTP, CMC TL
Danyal Chaudhry, DBOP, RPM

Teva

Dennis Ahern, Director, US Regulatory Affairs
Diana Landa, Associate Director, Regulatory Affairs

The following were discussed at the 8/6/10 teleconference between Teva and the FDA regarding unresolved CMC issues:

1. You have provided release and retest data demonstrating that the (b) (4) values present in Polysorbate 80 used to formulate the final drug product are not more (b) (4). However your release/retest specification is (b) (4). You have not provided data to support the upper limit of (b) (4).

(b) (4) Please provide data showing that Polysorbate 80 with (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 or tighten this specification based on your current experience.

Discussion:

Teva stated that the (b) (4) specification is in accordance with the European Pharmacopoeia. FDA clarified that Teva cannot rely on this general reference as each compound is specific. Teva stated that they will look to see if additional data is available to support the stated specification and if not Teva proposed to change the specification from (b) (4)

(b) (4). Teva further stated that based on available data they will provide additional information as a response to FDA's comment. FDA stated that the revised data provided by Teva will be reviewed for adequacy upon receipt.

2. 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 affect that varying protein concentrations, incubation times, etc. has on the sensitivity of the qRT-PCR assay to measure host cell DNA. Additionally, based on spiking studies you have determined that the limit of quantification is (b) (4) However, the data is reported as (b) (4) (b) (4) Please provide the numerical results for the 49 DS batches that were reported as (b) (4) Include a discussion of how these 49 batches provide sufficient information that the allowable range of in process control parameters described in your batch records will provide sufficient assurance that the product will meet expectations regarding residual DNA or add this test to the drug substance specifications.

Discussion:

Regarding the robustness of the qRT-PCR assay, Teva stated that they do not anticipate demonstrating full assay robustness for this assay as it is not for routine use and that currently they have data on assay robustness for two parameters, namely, the protein concentration and two of the reagents. Teva stated that the information pertaining to the robustness of the assay will be translated into English and provided to the FDA for review.

Regarding the limit of quantification, Teva stated that there may be misinterpretation relating to (b) (4) and clarified that this refers to (b) (4) (b) (4) of DNA in specific concentration of proteins. Teva stated that the data being reported as (b) (4) is in fact a true result and not a theoretical value. FDA advised Teva to create specifications based on their data. Teva agreed to review the data again and provide values for FDA to review.

3. 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 within 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.

Discussion:

Teva agreed to provide a red-lined version of the revised SOP incorporating the FDA suggested changes.

4. You state that the resolution of the G-CSF and (b) (4) (relative RT (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.

Discussion:

Teva agreed to provide a red-lined version of the revised SOP incorporating the FDA suggested changes.

5. You have provided data demonstrating that G-CSF becomes (b) (4) under stress stability 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 (b) (4). However you have not set a release or stability specification for this variant. Please establish release and stability specifications for (b) (4) variants and submit the revised specifications.

Discussion:

Teva agreed to provide a red-lined version of the revised SOP incorporating the FDA suggested changes.

Summary: Teva agreed to submit as a formal amendment the requested information by or before Friday, August 20, 2010.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: June 28, 2010

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 (b) (4) (Third Team Meeting)

Team meeting was held 6/28/10. Participants were present from all disciplines including, clinical, statistics, clinical pharmacology, pharmacology-toxicology, product, immunogenicity and facilities. Team accessed the progress of the reviews and discussed issues that were identified during the course of the review. It was decided to meet next at the wrap up meeting.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: July 27, 2010

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 f (b) (4) (Wrap Up Meeting)

Wrap Up meeting was held 7/27/10. It was also decided that a post-decision meeting will not be scheduled for this application. Participants were present from all disciplines including, clinical, statistics, clinical pharmacology, pharmacology-toxicology, product, immunogenicity and facilities.

Timelines for completion of reviews as per GRMP were discussed. All outstanding issues and resolution strategies and timeframes were also discussed.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: July 22, 2010

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 (b) (4) (Sixth Labeling Meeting)

DDMAC, OSE and SEALD changes were discussed at this meeting



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: July 16, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Request to rearrange data by clinical pharmacology for the renal position paper)

From: Chaudhry, Danyal
Sent: Friday, July 16, 2010 4:01 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: Diana.Landa@tevausa.com; Noa.Avisar@teva.co.il; Chaudhry, Danyal; Laughner, Erik
Subject: RE: Teva BLA STN 125294/0 (Neutroval/ (b) (4)): CDRH Guidance Documents

Dennis -- regarding your renal position paper, please expand Appendix 1, Tables 1-8 to include the individual (with subject ID #) PK data and geomean (CV%) for AUC and Cmax and median (range) for Tmax and t 1/2.

We are requesting this information by Tuesday, July, 20, 2010.

Please confirm receipt.

Danyal

From: Dennis.Ahern@tevausa.com [mailto:Dennis.Ahern@tevausa.com]
Sent: Thursday, July 08, 2010 3:49 PM
To: Chaudhry, Danyal

Cc: Diana.Landa@tevausa.com; Noa.Avisar@teva.co.il

Subject: RE: Teva BLA STN 125294/0 (Neuroval/[REDACTED] (b) (4)): CDRH Guidance Documents

Hi Danyal,

Attached, please find the cover letter for our submission today (S-0019) which details Teva's response to FDA's May 12th Clinical Pharmacology request regarding renal impairment.

Next week, we will submit the following outstanding items to FDA:

1. Pediatric Proposal: requested from FDA (March 24) via e-mail and due by July 12.
2. Responses to Dr. Keegan's questions regarding the 510K device, clarification on proper dose administered in clinical studies (based on mg/kg dosing), [REDACTED] (b) (4)

[REDACTED] Teva intends to submit a response to these items next week.

Best regards and have a nice weekend.

Dennis

(See attached file: Neuroval (XM02, [REDACTED] (b) (4) - BLA 125294 - Response to May 12, 2010 Clinical Pharmacology Information Request.pdf)

Dennis E. Ahern

TEVA Branded Pharmaceutical Products R&D

Director, U.S. Regulatory Affairs

T - 215-293-6339

M - [REDACTED] (b) (6)

"Chaudhry, Danyal" <Danyal.Chaudhry@fda.hhs.gov>

"Chaudhry,
Danyal"
<Danyal.Chaudhry@fda.hhs.gov>

To <Dennis.Ahern@tevausa.com>

06/30/2010
04:33 PM

cc

Subject RE: Teva BLA STN 125294/0
(Neuroval/[REDACTED] (b) (4)): CDRH Guidance Documents

Thanks, Dennis

Danyal

From: Dennis.Ahern@tevausa.com [mailto:Dennis.Ahern@tevausa.com]
Sent: Wednesday, June 30, 2010 4:31 PM
To: Chaudhry, Danyal
Subject: RE: Teva BLA STN 125294/0 (Neuroval/filgrastim): CDRH Guidance Documents

Hi Danyal,

Attached, please find a copy of the cover letter for our submission today that includes responses to clin pharm items TQT and DDI. I am meeting with my group tomorrow morning to (hopefully) conclude the renal response.

Have a nice evening!

Dennis

(See attached file: cover-rir.pdf)

Dennis E. Ahern
TEVA Branded Pharmaceutical Products R&D
Director, U.S. Regulatory Affairs
T - 215-293-6339
M - (b) (6)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: July 12, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b)(4) (EU Neupogen label request)

From: Chaudhry, Danyal
Sent: Monday, July 12, 2010 2:41 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: Diana.Landa@tevausa.com; Noa.Avisar@teva.co.il; Laughner, Erik; Chaudhry, Danyal
Subject: RE: Teva BLA STN 125294/0 (Neuroval/ (b)(4)); CDRH Guidance Documents

Dennis -- according to our reviewers the link to the EU Neupogen label takes you to the Tevagrastim information & not the EU Neupogen product label. An example of this can be found on pg 4 of the document. We are requesting that the link be corrected or the EU Neupogen product label be submitted. Please provide clarification regarding this issue.

Kindly confirm receipt and indicate an action date for the item above.

Danyal

From: Dennis.Ahern@tevausa.com [mailto:Dennis.Ahern@tevausa.com]
Sent: Thursday, July 08, 2010 3:49 PM
To: Chaudhry, Danyal
Cc: Diana.Landa@tevausa.com; Noa.Avisar@teva.co.il
Subject: RE: Teva BLA STN 125294/0 (Neuroval (b)(4)); CDRH Guidance Documents

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Attached, please find the cover letter for our submission today (S-0019) which details Teva's response to FDA's May 12th Clinical Pharmacology request regarding renal impairment.

Next week, we will submit the following outstanding items to FDA:

1. Pediatric Proposal: requested from FDA (March 24) via e-mail and due by July 12.
2. Responses to Dr. Keegan's questions regarding the 510K device, clarification on proper dose administered in clinical studies (based on mg/kg dosing), (b) (4)

(b) (4) Teva intends to submit a response to these items next week.

Best regards and have a nice weekend.

Dennis

(See attached file: Neuroval (XM02; (b) (4) - BLA 125294 - Response to May 12, 2010 Clinical Pharmacology Information Request.pdf)

Dennis E. Ahern
TEVA Branded Pharmaceutical Products R&D
Director, U.S. Regulatory Affairs
T - 215-293-6339
M - (b) (6)

"Chaudhry, Danyal" <Danyal.Chaudhry@fda.hhs.gov>

"Chaudhry,
Danyal"
<Danyal.Ch
audhry@fd
a.hhs.gov>

To <Dennis.Ahern@tevausa.com>

06/30/2010
04:33 PM

cc

Subject RE: Teva BLA STN 125294/0
(Neuroval, (b) (4); CDRH Guidance Documents

Thanks, Dennis

Danyal

From: Dennis.Ahern@tevausa.com [mailto:Dennis.Ahern@tevausa.com]
Sent: Wednesday, June 30, 2010 4:31 PM
To: Chaudhry, Danyal
Subject: RE: Teva BLA STN 125294/0 (Neuroval/ (b) (4)): CDRH Guidance Documents

Hi Danyal,

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Have a nice evening!

Dennis

(See attached file: cover-rir.pdf)

Dennis E. Ahern
TEVA Branded Pharmaceutical Products R&D
Director, U.S. Regulatory Affairs
T - 215-293-6339
M - (b) (6)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: July 6, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Facilities IR)

From: Chaudhry, Danyal
Sent: Tuesday, July 06, 2010 1:52 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: 'Diana.Landa@tevausa.com'; Laughner, Erik; Chaudhry, Danyal
Subject: Facilities Information Request: Teva BLA STN 125294/0 (Neuroval, (b) (4))

Dennis -- attached below is a Facilities information request regarding the Teva BLA STN 125294/0 (Neuroval (b) (4)). Please note that we are requesting this information by 7/20.

Kindly confirm receipt of this message.

Danyal



STN 125294
request for informa..

STN 125294/0 Request for information (date 7-6-2010):

1. The [REDACTED] (b) (4)
[REDACTED]
[REDACTED] The action limit should be based on process capability and should reflect data accumulated thus far. Please revise the [REDACTED] (b) (4) bioburden action limit to reflect data accumulated during commercial manufacture or [REDACTED] (b) (4) [REDACTED] set appropriate limits. The results should be reported as CFU/volume tested.
2. The procedure for microbial ingress test used to validate container closure integrity indicates that the number of microorganisms in the challenge suspension must not be less than [REDACTED] (b) (4) [REDACTED]. It is expected that a challenge of [REDACTED] (b) (4) CFU/mL be used in these studies. The test results in the submission suggest that the challenge suspension contained [REDACTED] (b) (4) CFU/mL and the test need not be repeated. However, if you plan to use the microbial ingress test for container closure integrity during stability studies, the microbial challenge suspension concentration in the test procedure should be revised and submitted to the BLA.
3. Regarding bioburden testing for [REDACTED] (b) (4) drug substance, please submit method qualification data summaries for 3 lots of drug substance.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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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 properly 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) did not meet current ISO standards, (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) may be responsible for performance characteristics of the various components for the device, Teva was the applicant for the final container closure system (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), containing (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)



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Center for Drug Evaluation and Research

Memorandum

Date: June 30, 2010

From: Danyal Chaudhry, M.P.H., DBOP/ODDP/CDER

Subject: BLA 125294 (b) (4) (links to 2 CDRH guidance documents regarding relevant information for the review of a syringe communicated to Teva in this e-mail)

From: Chaudhry, Danyal
Sent: Wednesday, June 30, 2010 10:56 AM
To: 'Dennis.Ahern@tevausa.com'; 'Diana.Landa@tevausa.com'
Cc: Chaudhry, Danyal; Laughner, Erik
Subject: Teva BLA STN 125294/0 (Neutroval/ (b) (4): CDRH Guidance Documents

Dennis and Diana -- please find below the links to the 2 discussed CDRH guidance documents at this morning's teleconference regarding relevant information for the review of a syringe.

(b) (4)

Please confirm receipt and also the name of the third individual on the call this morning.

Danyal.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: June 25, 2010

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 (b) (4) (Fifth Labeling Meeting)

Miscellaneous sections and items were discussed



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Center for Drug Evaluation and Research

Memorandum

Date: June 21, 2010

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 (b) (4) (IR from CDRH review communicated to (b) (4))

From: Laughner, Erik
Sent: Monday, June 21, 2010 1:54 PM
To: (b) (4)
Cc: Chaudhry, Danyal
Subject: Teva Neuroval BLA



052610 LOA.pdf
(413 KB)

Dear Ms. (b) (4)

Per our discussion, FDA has been authorized per a May 26, 2010 LOA, to contact (b) (4) concerning the syringe unit for Teva's BLA for Neuroval (see attached PDF). FDA would like a response to the following information requests that were communicated to Teva:

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)

(b) (4)

(b) (4) was cited in your submission but (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 (b) (4) or any other document, please provide the appropriate volumes and pertinent sections.

(b) (4)

If you could provide a confirmation of receipt and a response by this Thursday, I would appreciate.

Sincerely,

Erik S. Laughner, M.S., RAC (US)
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/cder/Offices/OODP/about.htm>

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and notify me immediately. Thank you.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Memorandum

Date: June 17, 2010

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 (b) (4) (Fourth Labeling Meeting)

Sections discussed:

-- Patient Counseling Information (section 17) and including the
PPI - Clinical, OSE/DRISK



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Memorandum

Date: June 14, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Third Labeling Meeting)

Sections discussed:

- Clinical Pharmacology - clin pharm
- Pharmacology Toxicology - pharm/tox & possibly MHT
- Clinical Studies- Clinical and stats



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Memorandum

Date: May 27, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Facilities Information Request)

From: Chaudhry, Danyal
Sent: Thursday, May 27, 2010 2:12 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: 'Diana.Landa@tevausa.com'; Laughner, Erik; Chaudhry, Danyal
Subject: Teva BLA STN 125294/0 (Neuroval (b) (4): Information Request (Facilities/Drug Substance))

Dennis -- please find attached a Facilities information request regarding your BLA 125294. We are requesting a response by Thursday, June 10.

Please confirm receipt.

Danyal



125294 request for
information...

1.  (b) (4)

2. For the microbial ingress test used to validate of the container closure integrity, please provide information on the sensitivity of the test (i.e., the leak size and volume).

3. In section 3.2.P.8.2 “Post-marketing stability protocol”, you indicated that sterility testing will be conducted at 0 and 36 month time points under the recommended storage conditions. This proposal should be revised to include sterility testing at the 12 and 24 month time points in addition to the initial and 36 month time point. We also recommend that a container closure integrity test be conducted on post-approval stability lots initially, annually and at expiry. This test may be conducted in lieu of a sterility test. Please revise your stability protocol or provide justification for an alternative approach. Also, please comment if you plan to develop a container closure integrity test method and include it in lieu of the sterility test in your stability program.

4.  (b) (4)

5. Provide the summary data for environmental monitoring during the two media fills performed in January and February of 2009.

6. Summary environmental monitoring data for the RABS was included in the submission. Provide a diagram showing the locations where microbial excursion were observed.

7. Provide the most recent requalification  (b) (4)

8. Submit details of the shipping/transport validation study (minimum and maximum loads, worst case conditions used, shock impact) and data to support shipping of

(b) (4) (XMO2) drug product in pre-filled syringes from Teva Pharmaceuticals, Kfar Saba, Israel to the US distribution site.

9. [Redacted] (b) (4)

10. [Redacted] (b) (4)

11. Submit summary data for the most recent (b) (4) study.



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Center for Drug Evaluation and Research

Memorandum

Date: May 25, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Facilities/Drug Substance Information Request)

From: Chaudhry, Danyal
Sent: Tuesday, May 25, 2010 1:41 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: 'Diana.Landa@tevausa.com'; Laughner, Erik; Chaudhry, Danyal
Subject: Teva BLA STN 125294/0 (Neuroval (b) (4)): Information Request (Facilities/Drug Substance)

Dennis -- below is an information request regarding your BLA 125294 and we are requesting a response by 6/15/10.

1. The microbial control strategy is not adequate for (b) (4) (b) (4) operations. Bioburden and endotoxin testing should be routinely monitored and used to demonstrate adequate process control based on a risk assessment.
 - a. Provide a risk assessment for routine testing of bioburden and bacterial endotoxins for the (b) (4) manufacturing process. Include monitoring locations, acceptance criteria and limits.
 - b. Bioburden and endotoxin test methods should be qualified appropriately for their intended use.
2. Provide results of method qualification studies for the bioburden and endotoxin test methods for all in-process steps tested to generate the data submitted to the BLA. The BLA submission includes only the method qualification reports for release testing of the (b) (4) drug substance.
3. Regarding endotoxin testing of the (b) (4) drug substance, please provide the following:
 - a. Explain why the SOP was revised recently so as not to pool samples for testing.
 - b. Clarify whether the method qualification study was conducted with pooled samples or not.

- c. Describe the impact of this change on the method qualification and the historical data generated using pooled samples.
4. Provide a more detailed description of the shipping validation studies submitted to the BLA.
 - a. Clarify whether conditions were simulated in a chamber or other controlled environment.
 - b. Provide the time points during shipping when the highest temperature readings were noted.
 - c. Provide additional detail regarding refrigeration of shipping containers during flight and custom delays. How will refrigeration be ensured and by whom?

Please acknowledge receipt.

Danyal



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: May 25, 2010

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 (b) (4) (Second Labeling Meeting)

Sections discussed:

- Warnings and Precautions - Clinical
- Adverse Reactions - Clinical



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Center for Drug Evaluation and Research

Memorandum

Date: May 24, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (information Request regarding the assessment of potential reproductive toxicity of Neutroval)

From: Chaudhry, Danyal
Sent: Monday, May 24, 2010 1:45 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: 'Diana.Landa@tevausa.com'; Laughner, Erik; Chaudhry, Danyal
Subject: Teva BLA STN 125294/0 (Neutroval/ (b) (4) Information Request (Reproductive Toxicity)

Dennis -- below is an information request regarding your BLA 125294 and we are requesting a response by 6/14/10.

"Provide an assessment of the potential reproductive toxicity of Neutroval as an amendment to the Biologics Licensing Application."

Please acknowledge receipt.

Danyal



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Memorandum

Date: May 21, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (First Labeling Meeting)

Sections discussed:

- Indications and Usage - Clinical
- Dosage and Administration - Clinical and CMC
- Dosage Forms and Strengths - CMC
- Contraindications - Clinical
- Drug Interactions - Clin Pharm
- Use in Specific Populations - Clin pharm, MFT/Peds
- Over dosage - Clinical
- How Supplied/ Storage and Handling - CMC



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Memorandum

Date: May 19, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (CMC Information Request)

From: Chaudhry, Danyal
Sent: Wednesday, May 19, 2010 4:46 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: 'Diana.Landa@tevausa.com'; Laughner, Erik; Chaudhry, Danyal
Subject: Teva BLA STN 125294/0 (Neurov (b) (4): CMC Information Request

Dennis -- please find attached a CMC information request for the Teva BLA STN 125294/0 (Neuroval (b) (4) The agency is requesting a response by 6/21/10.

Kindly confirm receipt.

Danyal



Teva rhGCSF
25294 CMC IR#3 2.

Shipping Validation:

1. In your shipping validation of the drug substance (DS) you focused only on the temperature component of the transportation and did not address the agitation issue. Please provide data that address the agitation issue during transportation of the DS from Vilnius to Kfar Saba.
2. In your section on drug product (DP) shipping you state that the distribution of the DP to warehouses/pharmacies is performed according to SOPs and in compliance with Good Distribution Practice (GDP). GDP does not address the effects of agitation and changes in barometric pressure on the DP in pre-filled syringes. Please provide data to support that transportation of the DP has no negative effect on the integrity, quality, and potency of the drug.

Container Closure Leachables and Extractables Study:

3. Please provide data on leachables for DP at the end-of-shelf life (36 months).
4. The current study for leachables for the DP container closure system was based on extraction study for the rubber stopper. Please provide data on potential extractables and leachables from the syringe barrel and the needle, which are also in contact with the DP.
5. The presence of (b) (4) in syringes as part of syringe manufacture is a concern as it may affect product quality. Please provide a description on how the syringes are qualified. Also, please provide a risk assessment of how (b) (4) may affect the integrity, quality, potency, and safety of your DP. If the DP is adversely affected by (b) (4), you should have procedures in place to control for (b) (4).

Release and Specifications:

6. The release specifications for DS and DP are based on commercial batch manufacturing history and supportive end-of-shelf-life stability data, e.g. the DP RP-HPLC for RRT (b) (4) release data show an average of (b) (4) (n=6) but the proposed acceptance criterion is (b) (4) to account for the amount observed at 36 month stability, which showed an average value of (b) (4) (n=6). You may set a separate stability specification if clinical safety and efficacy data are available to support the specification.
7. IE-HPLC acceptance criterion for the DP RRT (b) (4) peak was set as \leq (b) (4) which is outside of the validated range. Please revise the specification to be within the validated range.
8. Please provide a justification for basing the host cell protein specification as (b) (4) (b) (4)

9. The Polysorbate 80 control strategy response that you provided on April 30, 2010 is inadequate. The data on formulation development provided in the BLA demonstrates the importance of Polysorbate 80 as (b) (4) and the current Polysorbate 80 concentration in the DP is near the upper acceptable range (b) (4). Please include a release test to control for Polysorbate 80 quantity in the DP.

10. (b) (4)

Stability:

11. Please revise the time points for the filgratim DS post-approval stability protocol at storage temperature of (b) (4) as follows: 0, 3, 6, 9 and 12 months. When sufficient stability data will be available changes in time points can be considered.

12. Please revise the time points for the (b) (4) DP post-approval stability protocol at storage temperature of $5\pm 3^{\circ}\text{C}$ as follows: 0, 3, 6, 9, 12, 18, 24 and 36 months. When sufficient stability data will be available changes in time points can be considered.

13. Please include accelerated and stressed temperature stability testing for your DS and DP in your post-approval stability protocol.

14. If available, please provide updated stability data for Kfar Saba, Israel manufactured DP lots.

Reference Standard:

15. The Qualification Protocol for a New Reference Standard provided in the BLA is inadequate to control for possible drift in product quality over time. The acceptance criteria for the proposed tests for the qualification of future Reference Standards should reflect the actual results of the release tests of the past and current Reference Standards. Please tighten the acceptance criteria for the proposed qualification tests accordingly. Please revise the protocol to include additional characterization tests, such as a test to confirm (b) (4) and provide a description on how the new reference standard will be selected based on the analytical test results.

Drug Substance and Drug Product Process Validation Studies and Validation Studies for Impurities Clearance:

16. Please clarify how certain operational parameters were determined to be critical or non-critical. If the operational parameters are determined to be non-critical are you still monitoring and/or controlling them during the manufacturing process? For example, critical operational parameters for (b) (4) (Table 3.2.S.2.4-1) include (b) (4)

(b) (4) which were also studied as part of process development (MVP-LTR-02/02) were not considered as critical.

17. Please provide descriptions of methods used to measure (b) (4) impurities. In addition, please provide validation/qualification data for the methods used to measure (b) (4) impurities.

18. (b) (4)

19. Please address the following comments regarding (b) (4)

a. (b) (4)

b.

c.

Additional Comments:

20. (b) (4)

21. Polysorbate 80 is known to oxidize over time which may affect the product quality of your DS and DP. You provided in the Control of Excipients section that you are re-testing the Polysorbate 80 annually. Please justify your re-test dates for your Polysorbate 80. Additionally what steps would you take if a lot of DS or DP was produced with a failed lot of Polysorbate 80, determined by re-testing around the time of DS/DP manufacture?

BLANDA/PMA

~~Review Committee Assignment Memo~~

~~SUN:~~ 125294/0

<input checked="" type="checkbox"/> Initial Assignment
<input type="checkbox"/> Change

~~Applicant:~~ TEVA Pharmaceuticals USA

~~Product:~~ Neuroval/ (b) (4)

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
Danyal Chaudhry	Reg. Project Manager	Admin/Regulatory	Karen Jones	12/2/09
	Reviewer	Admin/Regulatory		
	Chairperson	Product*		
Jee Chung	Reviewer	Product*	Emily Shacter	12/2/09
Dov Pluznik	Reviewer	Product	Emily Shacter	12/2/09
	Chairperson	Clinical		
Thomas Herndon	Reviewer	Clinical	Patricia Keegan	12/2/09
Saran Schriber	Reviewer	Clinical Pharmacology	Hong Zhao	12/2/09
Mary Jane Masson-H	Reviewer	Pharm/Tox	Anne Pilaro	12/2/09
Hong (Laura) Lu	Reviewer	Biostatistics	Marc Kohnman	12/2/09
	Reviewer	BiMo		
	Reviewer	Safety Evaluator		
A. Lolas & K. Suvarn	Reviewer	CMC, Facility*	Patricia Hughes	12/2/09
Kimberly Rams	Reviewer: OBP/CMC	Labeling	--	12/2/09
		Other		
Erik Laughner	Senior RPM	Admin/Regulatory	Karen Jones	12/2/09
Laura Salazar-Fontana	Reviewer	Immunogenicity	Susan Kirshner	12/2/09

*add inspector, if applicable

Deletion of Committee Member

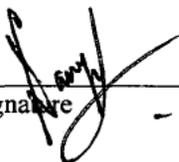
Name	Reviewer Type*	Job Type	Changed by	Date
			Chairperson	

*reviewer types: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Danyal Chaudhry

Name Printed


Signature

Chairperson

Date

MAY 14, 2010

Memo entered in RMS by: _____ Date: _____ QC by: _____ Date: _____



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: May 12, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (CDRH information request)

From: Chaudhry, Danyal
Sent: Wednesday, May 12, 2010 1:48 PM
To: 'Dennis.Ahern@tevausa.com'; Diana.Landa@tevausa.com
Cc: Chaudhry, Danyal; Laughner, Erik
Subject: Information Request: Teva BLA STN 125294/0 (Neuroval/ (b) (4))

Dennis -- please note below an information request regarding your application. We are requesting this information within 30 days (no later than Friday, June 11, 2010).

Please acknowledge receipt.

Danyal

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)



(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)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: May 12, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b)(4) (Clinical Pharmacology information request)

From: Chaudhry, Danyal
Sent: Wednesday, May 12, 2010 1:48 PM
To: 'Dennis.Ahern@tevausa.com'; Diana.Landa@tevausa.com
Cc: Chaudhry, Danyal; Laughner, Erik
Subject: Information Request, Clinical Pharmacology: Teva BLA STN 125294/0 (Neuroval, (b)(4))

Dennis -- please note the following information requests from the agency regarding your application. Each request is associated with a timeframe as indicated below.

Please acknowledge receipt.

Danyal

Clinical Pharmacology Information Request to Teva:

1. For trial XM02-05-DE, provide a summary of the XM02 pharmacokinetic and pharmacodynamic results by gender for each dose group. Submit this information to the BLA for FDA review by or before June 14, 2010.
2. Address the effect of renal impairment on the pharmacokinetics of Neuroval by conducting a renal impairment study. Submit a protocol to BLA 125294 for FDA review by or before June 30, 2010. The renal impairment protocol should be designed according to the principles described in the March 2010 Draft Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function" and can be found at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf>.

3. Address the effect of Neutroval on the QTc interval by conducting a thorough QT (TQT) study to assess the QTc prolongation risk. Submit a protocol to BLA 125294 for FDA review by or before June 30, 2010. The TQT protocol may be designed as a single-dose, cross-over study using the highest Neutroval SC dose studied. Refer to the guidance for industry entitled "E14 Clinical Evaluation of QT/QTc Interval Prolongation" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf> for more information.
4. Address comment #16 in the FDA-issued pre-BLA meeting minutes for the November 25, 2008 meeting. Submit a response with supporting data and *in vivo* study plans to BLA 125294 by or before June 30, 2010 for FDA review. The original comment and discussion that occurred during the meeting are included below for your reference. We also refer you to the recently published paper regarding therapeutic protein-drug interactions: Huang SM, et al. Therapeutic protein-drug interactions and implications for drug development. Clin Pharmacol Ther. 2010;87:497-503.

Following FDA review of the sponsor's responses to the information requests, post-marketing requirement determinations regarding items 2 through 4 will be made.

Excerpt from the November 25, 2008 FDA-issued pre-BLA meeting minutes:

16. FDA recommends that Teva conduct an *in vitro* drug-drug interaction screening study to assess any potential effects of XM02 on the activity of P450 metabolic enzymes. The results will determine whether further *in vivo* studies are necessary. For more information on designing *in vitro* drug-drug interaction studies, please see the Drug-Drug Interaction website and relevant guidance's at <http://www.fda.gov/cder/drug/drugInteractions/default.htm>.

DISCUSSION DURING THE MEETING: Teva questioned the utility of this drug-drug interaction study considering that XM02 was a large molecule with a well-known receptor mediated pharmacological action. FDA noted that experience with other biologic molecules demonstrated that potential effects on the activity of P450 pathway could occur at the DNA or transcriptional level. FDA restated the recommendation that Teva conduct an *in vitro* drug-drug interaction study. Additionally, FDA offered that Teva could perform a literature search regarding the drug-drug interaction history of filgrastim with P450 metabolic enzymes and provide justification to the FDA why an *in vitro* or *in vivo* study would not be relevant. If a literature review was not supportive to FDA's satisfaction, then *in vitro* and possibly *in vivo* follow-up studies would need to be conducted. Teva acknowledged FDA's position.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: May 10, 2010

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 (b) (4) (Mid Cycle Meeting)

Mid Cycle meeting was held 5/10/10. Participants were present from all disciplines including, clinical, statistics, clinical pharmacology, pharmacology-toxicology, product, immunogenicity and facilities.

A brief background including the regulatory history was presented by the clinical reviewer. The following sections were presented by the assigned reviewers in the indicated sequence: product, immunogenicity, facilities, pharmacology-toxicology, clinical pharmacology, statistics and clinical.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 30, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: FDA Information Requests; Teva BLA STN 125294/0 (b) (4). Stats information request

From: Chaudhry, Danyal
Sent: Friday, April 30, 2010 10:27 AM
To: 'Dennis.Ahern@tevausa.com'
Cc: 'Diana.Landa@tevausa.com'; Chaudhry, Danyal; Laughner, Erik
Subject: Request for Information (Stats): Teva BLA STN 125294/0 (Neutroval/ (b) (4))

Dennis -- we are requesting the following by close of business Thursday, May 6, 2010:

Subgroup analyses for DSN in Cycle 1 by country and adjuvant vs. metastatic therapy. The response can follow the format of Table 2 of submission SN08.

Please acknowledge receipt.

Danyal



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 30, 2010

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 (b) (4) (Second Team Meeting)

Team meeting was held 4/30/10. Participants were present from all disciplines including, clinical, statistics, clinical pharmacology, pharmacology-toxicology, product, immunogenicity and facilities. Team accessed the progress of the reviews and discussed issues that were identified during the course of the review. It was decided to have the next team meeting in June.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 21, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4): Request for define files as originally requested in the discussion between Clinical Review Team (Thomas Herndon (clinical reviewer) and Suzanne Demko (TL) and Teva regarding clinical data and analyses data sets

From: Herndon, Thomas
Sent: Wednesday, April 21, 2010 11:53 AM
To: 'Dennis.Ahern@tevausa.com'
Cc: Chaudhry, Danyal; Demko, Suzanne
Subject: RE: Teva BLA STN 125294/0 (Neuroval (b) (4) Follow-up to 4/15 e-mail request and 4/16 teleconference

Dennis,

These files are very helpful. As of now, we do not need to have an additional meeting.

We still do not have the revised define files that we requested. As has been mentioned before, the define files submitted in the BLA do not contain definitions for the column content for all of the data sets. We had asked TEVA to review the define files against the data sets and provide the missing information. When will we be receiving these?

Thanks.

Thomas

From: Dennis.Ahern@tevausa.com [mailto:Dennis.Ahern@tevausa.com]
Sent: Tuesday, April 20, 2010 11:28 AM
To: Chaudhry, Danyal
Cc: Debbie.Jaskot@tevausa.com; Diana.Landa@tevausa.com; Doug.Dobak@tevaneuro.com; Laughner, Erik; Steve.Barash@tevausa.com; Herndon, Thomas
Subject: Re: Teva BLA STN 125294/0 (Neuroval (b) (4)): Follow-up to 4/15 e-mail request and 4/16 teleconference

Dear Danyal,

Following up from our call this past Friday, please find attached to this e-mail the following:

- 1) SAS dataset consisting of the AEs for those patients/cycles where categorization of cycle-specific treatment actually given would differ from the "as randomized" category.
- 2) Listing (Word doc) of AEs for the relevant patients / cycle 1
- 2) Listing (Word doc) of SAEs for the relevant patients / cycle 1
- 3) Listing (pdf doc) for patient 50532-003 who had ambiguous categorization in cycle 4.
4. The categorization was presented in the MS Excel file entitled "Deviations from planned treatment 08Apr2010.xls" submitted to FDA by e-mail on April 12, 2010.

In addition to this e-mail, I will submit later this week an amendment to the BLA to include the information contained in this e-mail.

Finally, as we discussed on Friday, should you and Dr. Herndon want to have a brief discussion with Steve and I regarding the information submitted today as well as to map out possible next steps, we are available this week to discuss.

Please confirm receipt of this e-mail.

Kind regards,

Dennis

(See attached file: aae_sel.xpt)(See attached file: All SAEs for selected patients in cycle 1.doc)(See attached file: All AEs for selected patients in cycle 1.doc)(See attached file: 50532-003 All AEs.pdf)

Dennis E. Ahern
TEVA Branded Pharmaceutical Products R&D
Director, U.S. Regulatory Affairs
T - 215-293-6339
M - (b) (6)

Dennis Ahern/NWT/TEVA/IL

Dennis
Ahern/NW
T/TEVA/I
L

"Chaudhry, Danyal"
To <Danyal.Chaudhry@fda.hhs.gov>, "Herndon,
Thomas" <Thomas.Herndon@fda.hhs.gov>

04/16/2010
03:57 PM

Diana Landa/NOW/TEVA/IL@TEVANEW,
cc "Laughner, Erik"
<Erik.Laughner@fda.hhs.gov>, Steve
Barash/ROC/TEVA/IL, Doug
Dobak/NWT/TEVA/IL, Debbie
Jaskot/KUL/TEVA/IL

Re: Teva BLA STN 125294/0
Subject: (b) (4): Follow-up to 4/15 e-mail
request and 4/16 teleconference

Dear Thomas and Danyal,

Thank you very much for your time just now where Steve and I were able to clarify a few items relating to FDA's 4/15/10 request (e-mail below). The following is a response to the request as well as notes (*italic font*) from the teleconference between the four of us (which took place from 3:00 - 3:15):

Regarding FDA's statement "TEVA must submit the previously requested data sets (Safety Set and Per Protocol Set) that were used to perform the analyses described in 4.1.3 of the SAP for all three studies", we confirm that all analyses outlined in the submitted Safety Analysis Plan were performed and presented in the original CSRs and submitted with the original BLA. In particular, Section 4.1.3 of the SAP (for studies XM02-02, XM02-03, and XM02-04) defines the analysis populations, states that safety will be analyzed on the safety set, and describes patient disposition tables and listings that were included in the CSRs (Appendix Table 1.1, Listing 1.3).

Note from teleconference: Steve summarized and provided examples for FDA about how datasets at the study level were generated. The discussion evolved to a specific question around the AAE dataset for XM02-02-INT. Steve clarified that the AAE dataset contains flags identifying the population membership of each patient (FA, PP, PK, Safety), as documented in the submitted define files. Dr. Herndon agreed that these flags will be very helpful to review. I described for FDA that those flags can be found in the Analysis XM02-02-INT define.pdf file on pages 7, 10, and 11 of 53 pages.

respectively. Following the call with FDA, we realized that the define.pdf file that I presented was from S-0000 and that an updated define.pdf was requested by FDA and presented in S-0007. The corresponding page numbers for the FA, PP, PK, and Safety flags in that define.pdf are 8, 12, and 13 of 53 pages, respectively.

In the SAPs of the three cancer studies, treatment groups were defined solely in terms of overall treatment regimen across the entire duration of the study. However, in response to a recent request from FDA to consider treatment groups from a single-cycle-specific perspective, Teva has provided a spreadsheet (e-mail dated April 12, 2010) listing cases in which a cycle-specific treatment categorization for a patient would differ from the cycle-specific treatment to which the patient was randomized. To specifically address FDA's additional request from the 4/15/10 e-mail Teva will provide a separate listing of just the AEs occurring for those patients/cycles, as well as a SAS dataset that contains only the subset of the AAE dataset for those patients/cycles.

Note from teleconference: Teva described that (b) (4) has already been commissioned to perform the new analyses and that Teva will receive the information 4/19/10. Teva needs the balance of Monday to confirm that the analyses from (b) (4) are correct and proposed to send to FDA the subject analyses on 4/20/10. Teva then proposed a teleconference to take place on 4/21 or 4/22 between the same four individuals. The purpose of the call will be for Teva to orally present the findings (listings and dataset) to FDA as well as dialogue on the findings and agree on next steps (e.g., whether or not the finding warrant narration in the BLA).

On behalf of Teva, I again want to thank you for your time and look forward to our next interaction next week.

Kind regards,

Dennis

Dennis E. Ahern
TEVA Branded Pharmaceutical Products R&D
Director, U.S. Regulatory Affairs
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Dennis Ahern/NWT/TEVA/IL

Dennis
Ahern/NW
T/TEVA/I

"Chaudhry, Danyal"
To

L

<Danyal.Chaudhry@fda.hhs.gov>

04/15/2010

05:35 PM

Diana Landa/NOW/TEVA/IL@TEVANEW,
cc"Laughner, Erik"
<Erik.Laughner@fda.hhs.gov>

Re: Teva BLA STN 125294/0
Subject: (Neuroval/ (b)(4): Follow-up to 3/31 tcon,
3/26 question to FDA, & 3/24 stats question
response

Danyal,
Confirming receipt of your email and I will call you
tomorrow with an update on the proposed timeline.
Best regards
Dennis

----- Original Message -----

From: "Chaudhry, Danyal" [Danyal.Chaudhry@fda.hhs.gov]

Sent: 04/15/2010 04:55 PM AST

To: Dennis Ahern

Cc: Diana Landa; Laughner, Erik"

<Erik.Laughner@fda.hhs.gov>; Chaudhry, Danyal"

<Danyal.Chaudhry@fda.hhs.gov>

Subject: RE: Teva BLA STN 125294/0 (Neuroval/ (b)(4):
Follow-up to 3/31 tcon, 3/26 question to FDA, & 3/24 stats
question response

Dennis -- attached is the agency's response regarding the 4/13 communication
and the 3/31 teleconference (reanalysis of data).

The FDA agrees that the approach to analysis outlined in the submitted
Safety Analysis Plan appears reasonable. In addition to the data set of study
subjects who received a treatment different from the treatment group to
which they were randomized (for studies XM02-02, XM02-03, and XM02-
04), TEVA must submit the previously requested data sets (Safety Set and
Per Protocol Set) that were used to perform the analyses described in 4.1.3
of the SAP for all three studies. These should be accompanied by revised
define files that clearly describe the contents of all data sets. FDA requires

these by COB 18 April 2010. Amended Final Study Reports based on the analyses of these data sets are required by COB April 25, 2010.

Please confirm receipt and acknowledgement that you will submit this data in accordance with the above mentioned time points as a formal amendment to the BLA.

Danyal

From: Dennis.Ahern@tevausa.com [mailto:Dennis.Ahern@tevausa.com]
Sent: Wednesday, April 14, 2010 4:43 PM
To: Chaudhry, Danyal
Cc: Chaudhry, Danyal; Diana.Landa@tevausa.com; Laughner, Erik; Steve.Barash@tevausa.com
Subject: RE: Teva BLA STN 125294/0 (Neuroval/ (b) (4)): Follow-up to 3/31 tcon, 3/26 question to FDA, & 3/24 stats question response

Dear Danyal,

With this e-mail, Teva is providing a response to two open items as follows:

1. Response to the Agency's request to populate a clinical pharmacology table and submit to the BLA.

Response: The attached clinical pharmacology table has been populated, with the exception of four items that require further research. Teva submits this copy of the table as draft (four items requiring further research are highlighted in yellow) and will provide a final table with a formal submission to the BLA next week.

2. Response to the Agency's April 13, 2010 communication regarding the reanalysis of data from the 3/31/10 teleconference. The response was required by COB today.

Response:

The treatment codes given in the XM02-02-INT dataset AAE are the

treatment groups to which the patients were randomized (a copy of the relevant page from the XM02-02-INT SAP is attached) . In that study there were three treatment groups: XM02, Filgrastim, and Placebo/XM02. By design, these treatment groups define the overall treatment regimen for the entire duration of the study, and each patient can only be in one of these three groups. For every patient in the study, the vast majority of the treatments administered during the duration of the study were the correct treatment; no patient received a sufficient number of incorrect treatments to be reasonably re-categorized into a treatment group other than the group to which the patient was originally randomized. Accordingly, the "as randomized" and "as treated" groups coincided

In studies XM02-03-INT and XM02-04-INT, there were two treatment groups: XM02 and Filgrastim/XM02. Again, no patient received a sufficient number of incorrect treatments to be re-categorized into a treatment group other than the group to which the patient was originally randomized, and the "as randomized" and "as treated" groups coincided.

The page from the SAP attached in our email from 4/12/2010 was from the ISS SAP (copy attached for convenience). The ISS analyses were presented based on actual treatment given and combined the three studies and categorized the patients into four treatment groups: XM02, Filgrastim, Placebo/XM02 and Filgrastim/XM02. This provided the opportunity to categorize patients from XM02-02-INT who were randomized to Placebo/XM02 but incorrectly received some Filgrastim in cycle 1 to the category Filgrastim/XM02 for safety analysis purposes.

When Teva submits the clinical pharmacology table next week, we will also include the above response in the cover letter of that submission.

Kind regards,

Dennis

(See attached file: HighlightsofClinicalPharmacology 4-14-10.doc)(See attached file: AEs are analyzed as treated - ISS SAP.pdf)(See attached file: XM02-02 SAP. pdf.pdf)

Dennis E. Ahern
TEVA Branded Pharmaceutical Products R&D
Director, U.S. Regulatory Affairs
T - 215-293-6339
M - (b) (6)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 20, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (DMEPA/OSE request for samples of syringes)

From: Chaudhry, Danyal
Sent: Tuesday, April 20, 2010 3:18 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: Diana.Landa@tevausa.com; Laughner, Erik; Chaudhry, Danyal
Subject: Request for Information: Teva BLA STN 125294/0 (Neuroval (b) (4))

Dennis -- we are requesting the following:

"Working samples of the syringes, with and without the needle guard for BLA 125294 Neuroval".

The items can be sent using fed-ex with a tracking number to the following:

Sue Kang
Project Manager

Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22; Room 5185
10903 New Hampshire Avenue
Silver Spring, MD 20993

Tel: 301-796-4216
fax: 301-796-9895

Please confirm receipt.

Danyal



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 6, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (CMC Information Request)

From: Chaudhry, Danyal
Sent: Tuesday, April 06, 2010 9:08 AM
To: 'Dennis.Ahern@tevausa.com'
Cc: Diana.Landa@tevausa.com; Laughner, Erik; Chaudhry, Danyal
Subject: Teva BLA STN 125294/0 (Neuroval (b) (4)): CMC Information Request

Dennis -- please find attached a CMC information request for the Teva BLA STN 125294/0 (Neuroval (b) (4)). The agency is requesting a response by 5/7/10.

Kindly confirm receipt.

Danyal



Teva rhGCSF
25294 CMC IR 201.

BLA 125294 mGCSF Sponsor CMC IR Comments:

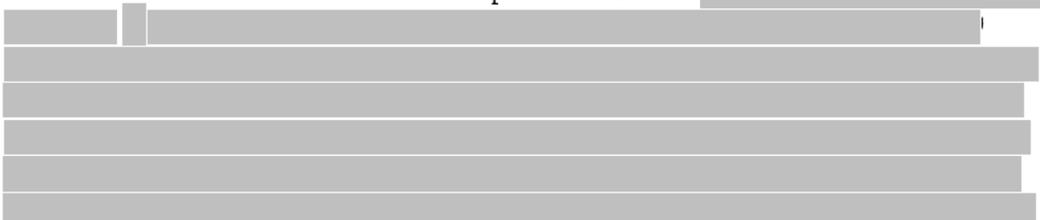
Cell Banks:

1.  (b) (4)
2. 
3.

Reference Standard:

1. Please clarify which reference standard is used for the bioactivity determinations performed as part of release and stability testing for XM02; e.g., do you use the WHO G-CSF standard or the primary in-house reference standard?

Method Validation:

1. The system suitability acceptance criterion for the retention time (RT) for the main peak in the RP-HPLC method (QCC-301 and QCC-302) allows a range of (b) (4) min. The historical data from 40 runs of the reference standard (RS) show that the RT of the main peak is between (b) (4) minutes (with most of the triplicate runs showing RTs of (b) (4) minutes). Please justify your system suitability acceptance criterion allowing a 10 minute range.
2. Your SOP for the RP-HPLC method specifies that the (b) (4)

Please justify allowing modification of (b) (4) used in the HPLC method and describe how you will ensure reliable results using this method.
3. In the current RP-HPLC method, the relative resolution calculation for system suitability is between the (b) (4)

However, this approach is not representative of the resolution of the method because the closest eluting impurities to [REDACTED] (b) (4). Please clarify how this method provides a reliable determination of purity of the G-CSF protein and quantification of product-related impurities.

4. Similar to comments #1 and #3 above for method validation, please justify your system suitability acceptance criteria for the IE-HPLC method (QCC-332 and QCC-333); e.g., the RT of the main peak in the reference standard and the calculation of the relative resolution between [REDACTED] (b) (4).
5. For the validation of the quantitative peptide mapping method used for release of the drug substance (DS) and drug product (DP), please justify the differences in the acceptance criteria for accuracy and precision. The acceptance criteria for % Recovery and CV are wider for DP than for DS.
6. Please include a staining/destaining control for your SDS-PAGE method in order to assure assay sensitivity (e.g., [REDACTED] (b) (4)).
7. When using the spectrophotometric method to quantify G-CSF protein, an experimentally-determined extinction coefficient for G-CSF should be employed to calculate protein concentration. The method should be validated using the experimentally-determined extinction coefficient.
8. Please update your SOPs to reflect the changes for all methods discussed above.

Drug Substance and Drug Product Characterization:

1. Table 3.2.S.3.1-19 provides data on the [REDACTED] (b) (4) in XM02. The residue numbers that were assigned for [REDACTED] (b) (4) do not appear to correspond correctly with to the sequence shown. Please clarify.

Additional Comments:

1. Regarding the peptide map analysis for the DS and DP, we note that the data for [REDACTED] (b) (4). Please provide an explanation for the differences observed between the DP and DS. In addition, please provide a justification [REDACTED] (b) (4) (acceptance limits) for the DP compared to the DS.
2. For the method (e.g. SEC) used to determine protein aggregation for release and stability testing of the DS and DP, please provide data using an orthogonal method to confirm that the chosen method is capable of detecting and quantifying all types of aggregates present in the DS and DP.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 5, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Clinical Pharmacology information request provided by the QT IRT Consult for the sponsor)

From: Chaudhry, Danyal
Sent: Monday, April 05, 2010 1:04 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: Diana.Landa@tevausa.com; Chaudhry, Danyal; Laughner, Erik
Subject: Information Request: Teva BLA STN 125294/0 (Neutroval/ (b) (4))

Dennis -- please complete the attached Clinical Pharmacology table and submit to the BLA.

Please also confirm receipt of this e-mail.

Danyal



HighlightsofClinicalP
harmacolo...

Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C _{max} and AUC
	Multiple Dose	Mean (%CV) C _{max} and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	T _{max}	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	V _d /F or V _d	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC
	Sex	Specify mean changes in C _{max} and AUC
	Race	Specify mean changes in C _{max} and AUC
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C _{max} and AUC
	Food Effects	Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical	Describe worst case scenario and expected fold-change in C _{max} and	

Exposure Scenario	AUC. The increase in exposure should be covered by the supra-therapeutic dose.
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: April 2, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Communication between FDA and Teva regarding Clinical, Stats and CMC issues)

From: Chaudhry, Danyal
Sent: Friday, April 02, 2010 3:16 PM
To: Chaudhry, Danyal; 'Dennis.Ahern@tevausa.com'
Cc: Laughner, Erik
Subject: RE: Teva BLA STN 125294/0 (Neuroval (b) (4)); Follow-up to 3/31 tcon, 3/26 question to FDA, & 3/24 stats question response

Dennis -- please note this update to my previous e-mail regarding the stats response:

3 -- Stats (follow up to 3/24 request for information from FDA Stats reviewer): your response is satisfactory.

Danyal

From: Chaudhry, Danyal
Sent: Friday, April 02, 2010 3:12 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: Laughner, Erik; Chaudhry, Danyal
Subject: RE: Teva BLA STN 125294/0 (Neuroval (b) (4)); Follow-up to 3/31 tcon, 3/26 question to FDA, & 3/24 stats question response

Hi Dennis -- I have the following responses regarding your e-mail below:

1 -- Clinical (follow up to 3/31 teleconference): Teva's proposal is not acceptable. TEVA must submit data sets that indicate a safety population (patients who actually received the study drug) and analysis of these data sets submitted as amendments to the clinical study reports for the 3 studies (XM02-02, XM02-03, and XM02-04). TEVA must clarify the content of the define files.

Appears this way on original

2 – CMC (follow up to 3/26 question for CMC reviewer): Your proposal to modify relevant sections in Module 3 containing to DS, DP, and reference standards is acceptable (i.e. no need to reformat tables in QOS).

3 -- Stats (follow up to 3/24 request for information from FDA Stats reviewer): Response from FDA stats reviewer still pending.

Danyal

From: Dennis.Ahern@tevausa.com [mailto:Dennis.Ahern@tevausa.com]
Sent: Thursday, April 01, 2010 5:38 PM
To: Chaudhry, Danyal
Subject: Teva BLA STN 125294/0 (Neuroval/ (b)(4)): Follow-up to 3/31 tcon, 3/26 question to FDA, & 3/24 stats question response

Hi Danyal,

With this e-mail, I am providing information regarding our teleconference on 3/31, following up to one question I asked FDA in a 3/26 e-mail, as well as providing a response to a question from the stats reviewer (3/24).

***** Follow-up to March 31, 2010
Teleconference between DBOP Clinical Reviewers and Teva:

Since our teleconference with the DBOP yesterday (3/31), Teva has worked to identify the scope of the problem by reviewing ISS listing 2.2. Based on what we found, Teva proposes to provide FDA with a tabular listing that identifies all patients that received a mismatch of drug, by cycle, across studies XM02-02, XM02-03, and XM02-04. We plan to submit this information next week. Also, Teva proposes to develop a listing of Adverse Events and Serious Adverse Events for those patients identified above. Once Teva provides FDA with this information (expected in the next few weeks), it will be helpful to receive correspondence from the division describing whether or not the original issue is resolved or whether additional information is needed.

***** Follow up to March 26, 2010
Question from Teva to DBOP CMC reviewer:

On 3/26, I asked the following question: "Also, we have a clarification question for the CMC reviewer. We were requested to reformat a lot of summary tables containing side-by-side data for the drug substance and the drug product, which we are in the process of addressing. Since most of these tables also appear in the QOS, our question is whether we need to reformat the QOS (Drug Substance section and Drug Product section) or would it be acceptable to resubmit only pertinent sections of Module 3?"

Reformatting of Module 2 would require additional time and may cause a delay in response. Since the data will be provided, as requested, in other sections of the application we would like to ask to not go back to reformat the QOS."

~~*****~~*****Follow-up to March 24, 2010

request from DBOP Statistical Reviewer:

On 3/24, you sent me the following comment and example code from the statistical reviewer: "The FDA reviewer can not verify the results of primary endpoint. Based on FDA reviewer's analysis, the least-square mean difference between tevagastim and placebo is 2.5 days instead of 2.7 days. The FDA reviewer's ASA program based on your datasets arandom and acycdsn is as following:

```
proc sort data=arandom;  
by patient;  
run;
```

```
proc sort data=acycdsn;  
by patient;  
run;
```

```
data temp;  
set acycdsn;  
where prueftag=1002;  
run;
```

```
data tevaeff;  
merge arandom temp;  
by patient;  
run;
```

```
proc glm data=tevaeff;  
where treat in (1,3) and fa=1;  
class country therapy treat;  
model ndsn = nancbase country therapy treat ;  
lsmeans treat ;  
estimate 'estimate' treat 1 -1;  
run;
```

```
proc glm data=tevaeff ;  
where treat in (1,2) and fa=1;  
class country therapy treat;  
model ndsn = nancbase country therapy treat ;  
lsmeans treat ;  
estimate 'estimate' treat 1 -1 ;
```

run;

Please explain the difference between FDA's results and your results by April 7, 2010."

Teva Response:

We have resolved this issue by consulting with our vendor (b) (4) and have confirmed that the result reported in the study report for XM02-02 is correct. It appears the FDA reviewer's code is missing a step that was specified in the SAP (highlighted below).

The XM02-02 SAP, page 19, states.

Special attention has to be given to placebo patients receiving therapeutic G-CSF (i.e. Filgrastim) in cycle 1. While administration of therapeutic G-CSF to patients of the placebo group in cycle 1 is a major protocol violation leading to exclusion of these patients from the PP set, they will be included in the FA set using two different methods: **for the main assay sensitivity analysis, the DSN of these patients will be replaced by the median DSN of all placebo patients without therapeutic G-CSF application** in cycle 1. In a second (sensitivity) analysis, the DSN values of these patients will be used as calculated, i.e. will not be replaced.

The FDA reviewer can check the programs that Teva provided to see the method of calculation, or can utilize the following code example from (b) (4) which shows the replacement of DSN with median DSN for the patients that were randomized to placebo but treated with G-CSF in cycle 1.

```
DATA cycdsn;

SET fdastat.acycdsn;

RUN;

PROC SORT DATA=cycdsn; BY PRUEFERN PATIENT PRUEFTAG; RUN;

/*Check if some observations in arandom but not in
acycdsn*/

data test;

merge fdastat.arandom(in=a) cycdsn(in=b);

by pruefern patient;

if a and not b then output;

run;

/*0 observations therefore no problem, all subjects in
arandom are also in acycdsn*/

DATA effAnco;

MERGE fdastat.arandom(IN=a) cycdsn;
```

```

BY PRUEFERN PATIENT ;

IF a; %*** preliminary data were inconsistent: less records
in random than in cycdsn ***;

RUN;

DATA effAnco;

SET effAnco;

BY PRUEFERN PATIENT ;

IF country=6 THEN countrypooled=6;

ELSE countrypooled=11;

nBase=nANCbase;

IF fa=1 THEN DO;

nPopu=1;

OUTPUT;

END;

IF pp=1 THEN DO;

nPopu=2;

OUTPUT;

END;

RUN;

%*** G-CSF patients of the Placebo group has to replaced by
the Medians of the remaining Placebos ***;

PROC SORT DATA=effAnco; BY nPopu treat PRUEFTAG PRUEFERN
PATIENT ; RUN;

PROC UNIVARIATE DATA=effAnco(WHERE=(treat=3 AND bGCSF1=0
AND PRUEFTAG=1002)) NOPRINT;

VAR nDSN;

BY nPopu treat PRUEFTAG;

OUTPUT OUT=uniEff MEDIAN=nDSNmedian;

RUN;

```

Please note that we will send the ~~statistical~~ response outlined here as an official correspondence to the BLA.

Kind regards,

Dennis

Dennis E. Ahern
TEVA Branded Pharmaceutical Products R&D
Director, U.S. Regulatory Affairs
T - 215-293-6339
M - (b) (6)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: March 31, 2010

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 (b) (4) Discussion between Clinical Review Team (Thomas Herndon (clinical reviewer) and Suzanne Demko (TL) and Teva regarding clinical data and analyses data sets

FDA: Data and analyses tables regarding safety studies 02, 03, and 04 will need to be reanalyzed based on the actual treatment that patients received rather than on intent to treat. As confirmed by Teva, currently the analysis data provided (AAE tables) reflect analyses based on the treatment to which patients were randomized.

FDA also requested that the define file contents are clarified to make sure that data columns containing numbers indicative of specific data are defined.

TEVA: agreed to reanalyze the data and provide amended clinical study reports for studies 02, 03, and 04. After consulting with their vendor (b) (4), Teva will let the agency know when the data will be resubmitted .

FDA Participants:

Suzanne Demko: Clinical Team Leader

Thomas Herndon: Clinical Reviewer

Danyal Chaudhry: Regulatory Project Manager

TEVA Participants:

Yao Yao -- Regulatory Affairs Manager, TEVA Branded Pharmaceutical Products R&D

Steve Barash -- Associate Director, Biostatistics; TEVA Branded Pharmaceutical Products R&D

(b) (4) -- Independent Clinical Consultant

Dennis Ahern -- Director, U.S. Regulatory Affairs



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: March 26, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Request to provide paste friendly version of "Study Report Body" under Section 5.3.3.1.3)

From: Chaudhry, Danyal
Sent: Friday, March 26, 2010 2:36 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: Chaudhry, Danyal
Subject: Request for Paste Friendly Version of Study Report

Dear Dennis -- am following up on the request (from yesterday's phone conversation) for a past friendly version of the "Study Report Body" under Section 5.3.3.1.3 of the original BLA submission.

Danyal



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: March 24, 2010

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 (b) (4) (Information Request from Clinical and Stats)

From: Chaudhry, Danyal
Sent: Wednesday, March 24, 2010 2:08 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: Diana.Landa@tevausa.com; Laughner, Erik; Chaudhry, Danyal
Subject: Information Request: Teva BLA STN 125294/0 (Neuroval (b) (4))

Dennis -- please find below two information request items from the clinical and statistical disciplines:

Clinical: (response requested by 7/12/10)

Your proposal for a timeline to submit a Pediatric Plan is not acceptable. Provide the following information by July 12, 2010.

Drug information:

- Route of administration:
- Formulation:
- Dosage: Regimen:

Types of studies/ Study Design:

Age group and population in which study will be performed:

Entry criteria:

Clinical endpoints:

Timing of assessments:

Statistical information (statistical analyses of the data to be performed):

Timeframe for submitting reports of the studies:

Discussion on specific drug safety issues that should be addressed:

Statistical: (response requested by 4/7/10)

The FDA reviewer can not verify the results of primary endpoint. Based on FDA reviewer's analysis, the least-square mean difference between tevagastim and placebo is 2.5 days instead of 2.7 days. The FDA reviewer's ASA program based on your datasets arandom and acycdsn is as following:

```
proc sort data=arandom;  
by patient;  
run;
```

```
proc sort data=acycdsn;  
by patient;  
run;
```

```
data temp;  
set acycdsn;  
where prueftag=1002;  
run;
```

```
data tevaeff;  
merge arandom temp;  
by patient;  
run;
```

```
proc glm data=tevaeff;  
where treat in (1,3) and fa=1;  
class country therapy treat ;  
model ndsn = nancbase country therapy treat ;  
lsmeans treat ;  
estimate 'estimate' treat 1 -1;  
run;
```

```
proc glm data=tevaeff ;  
where treat in (1,2) and fa=1;  
class country therapy treat ;  
model ndsn = nancbase country therapy treat ;  
lsmeans treat ;  
estimate 'estimate' treat 1 -1 ;  
run;
```

Please explain the difference between FDA's results and your results by April 7, 2010.

Kindly acknowledge receipt of this e-mail.

Danyal



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: March 22, 2010

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 (b) (4) (Communication between Dr. Herndon (clinical reviewer) and TEVA regarding randomization of patients)

From: Dennis.Ahern@tevausa.com [mailto:Dennis.Ahern@tevausa.com]
Sent: Monday, March 22, 2010 10:09 PM
To: Herndon, Thomas
Cc: Chaudhry, Danyal
Subject: RE: BLA 125,294 -- Response to your question

Dear Dr. Herndon,

The variables TREAT and TREATX specify the treatment to which the patient was randomized, not the treatment the patient was actually given (if the two differ).

My statistician and I confirmed this by checking patient 50-532-07, who was listed as having a protocol violation of receiving the wrong treatment throughout cycle 1. The patient was randomized to XM02 but was treated with filgrastim in cycle 1. In AAE, TREATX=XM02 for this patient (for an AE occurring during cycle 1).

Kind regards,

Dennis E. Ahern
TEVA Branded Pharmaceutical Products R&D
Director, U.S. Regulatory Affairs

T - 215-293-6339

M - (b) (6)

"Herndon, Thomas" <Thomas.Herndon@fda.hhs.gov>

"Herndon,
Thomas"
<Thomas.
Herndon@
fda.hhs.gov
>

<Dennis.Ahern@tevausa.com>
To

"Chaudhry, Danyal"
cc<Danyal.Chaudhry@fda.hhs.gov>

03/22/2010
09:58 AM

RE: BLA 125,294 -- Response to your question
Subject

Dennis,

Thanks for the information, but this is not what I was asking about. I understand that they are randomized patients, but is the treatment listed under this heading, the treatment they were randomized to or the treatment that they received? Please feel free to call if you need further clarification.

Thomas Herndon, MD
Medical Officer, Division of Biologic Oncology Products
Food and Drug Administration; Silver Spring MD
thomas.herndon@fda.hhs.gov

From: Dennis.Ahern@tevausa.com [mailto:Dennis.Ahern@tevausa.com]
Sent: Friday, March 19, 2010 4:16 PM
To: Herndon, Thomas
Cc: Chaudhry, Danyal
Subject: BLA 125,294 -- Response to your question

Dear Dr. Herndon,

Following up from our call earlier today, I am confirming that patients in the AAE dataset, under variable "TREAT" or "TREATX" are randomized patients.

Please let me know if you have further questions.

Have a nice weekend.

Dennis

Dennis E. Ahern
TEVA Branded Pharmaceutical Products R&D
Director, U.S. Regulatory Affairs
T - 215-293-6339
M - (b) (6)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: March 19, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b)(4) (Comment regarding labeling: route of administration)

From: Chaudhry, Danyal
Sent: Friday, March 19, 2010 10:36 AM
To: 'Diana.Landa@tevausa.com'; 'Dennis.Ahern@tevausa.com'
Cc: Laughner, Erik; Chaudhry, Danyal
Subject: RE: Response to 74 Day Letter Communication: Teva BLA STN 125294/0 (Neuroval/ (b)(4))

Dear Dennis -- please note the following comment regarding labeling for your BLA:

In the proposed label FDA provided to you as "tracked changes" on February 19, 2010,

(b)(4)
In addition, under Section 2 of the FPI, please add back in the subcutaneous route.

Kindly confirm receipt.

Danyal

From: Chaudhry, Danyal
Sent: Thursday, March 18, 2010 4:08 PM
To: 'Diana.Landa@tevausa.com'; 'Dennis.Ahern@tevausa.com'
Cc: Laughner, Erik; Chaudhry, Danyal
Subject: Response to 74 Day Letter Communication: Teva BLA STN 125294/0 (Neuroval/ (b)(4))

Dear Dennis -- this is to acknowledge that we expect to receive your response to the 74 day letter issued 2/19/10 by Friday, March 26, 2010. This response is to include the revised label incorporating the suggested changes in the version of the label provided with the 74 day letter.

Please acknowledge receipt of this note.

Danyal



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: March 12, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (First Team Meeting)

Team meeting was held 3/12/10. Participants were present from all disciplines including, clinical, statistics, clinical pharmacology, pharmacology-toxicology, product, immunogenicity and facilities. Team accessed the progress of the reviews and discussed issues that were identified during the course of the review. It was decided to have the next team meeting in April.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: February 19, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b)(4) (74 Day Letter with Label Embedded Comments)

From: Chaudhry, Danyal
Sent: Friday, February 19, 2010 2:50 PM
To: 'Dennis.Ahern@tevausa.com'
Cc: Diana.Landa@tevausa.com; Laughner, Erik; Chaudhry, Danyal
Subject: 74 Day Letter Communication: Teva BLA STN 125294/0 (Neuroval/ (b)(4))

Dennis -- find attached the 74 day letter communication regarding your BLA. Please confirm receipt.

Danyal



74 Day
ar-Teva-125294Scar



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125294/0

FILING ISSUES

February 19, 2010

Teva Pharmaceuticals U.S.A.
Attention: Deborah A. Jaskot, M.S., R.A.C.
Vice-President, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Ms. Jaskot:

Please refer to your biologics license application (BLA) dated November 30, 2009, received November 30, 2009, submitted under section 351 of the Public Health Service Act for Neutroval (b) (4). Also refer to our information request letter of January 15, 2010 and our filing letter dated January 29, 2010. While conducting our filing review we identified the following additional potential review issues:

Chemistry, Manufacturing & Controls

1. The current proposed release and stability specifications lack a test to monitor protein aggregates, i.e. higher molecular weight species, as well as dimers, trimers etc. A test to monitor protein aggregates is necessary to control the product in the event of unforeseen changes to the manufacture and stability of the product. Please provide a validated method, which includes the determination of assay robustness criteria, to measure protein aggregates for the drug substance (DS) and drug product (DP) release and stability specifications and provide justification for the proposed acceptance criterion.
2. You have provided your lot release and comparability data in tables that make lot-to-lot comparisons difficult to assess. Please reformat the tables that compare lots so that the lot numbers are listed across the top of the table (top row) and the release and characterization assays are listed down the first column, with the results for each assay listed down each lot column.
3. Analysis of method robustness should be part of method validation in order to gauge a method's reliability during normal use. Please provide any data that you have that demonstrate robustness for the validated methods used for release and stability testing of the DS and DP.

4. Please provide release data or the Certificates of Analysis for all lots of DS and DP used in your clinical studies. A comparison table formatted as described in point 2 above would also facilitate review of the data.
5. Please provide a comparability study report for the DS lots manufactured at the (b) (4) scales. Please include side-by-side tabular data as well as high quality representative raw data (e.g., (b) (4) for the lots manufactured with the (b) (4).
6. Please provide representative high quality raw data (e.g., (b) (4) for the results obtained with the lots used in your DP comparability study.
7. Please provide the release data for all of the primary and secondary in-house reference standards used during product development. Please arrange the results in a single table as described in point 2 above.
8. Please describe your control strategy for sorbitol and polysorbate 80 content in the DP if the tests to monitor the concentrations of these excipients will be removed from DP release testing.
9. The plasmid copy number for the End-of-Production Cells (EPC) and the Master, and Working Cell Banks show a high degree of variability. Please provide in-process control test data (b) (4).
(b) (4) to verify the consistency of the manufacturing process. In addition, please provide a control strategy for maintaining plasmid stability.
10. Please quantify the levels of sub-visible particulates in the DP in the size range between (b) (4). The levels should be quantified at the time of product release and during stability testing. Due to the ability of protein particles to increase the immunogenicity of proteins, please provide a risk assessment and risk mitigation strategy for sub-visible particulates in your product. In addition, please provide a description of the method used to measure the (b) (4) sub-visible particulates.

Immunogenicity

11. Please provide the standard operating procedures (SOPs) for the listed assays used for the assessment of anti-XM02 (Neuroval) antibodies: Western blot confirmatory assay (CIR040413D); immunoassay using xMAP technology (CIR050608); antibody binding assessed by BIAcore methodology (CIR041913) and the neutralizing antibody assay (CIR040920).
12. Regarding the ELISA screening assay for the detection of anti-XM02 antibodies in human serum:

- a. Please provide information about the specificity of the positive control antibody preparation used in the screening assay. In particular, does the preparation recognize the modified N-terminus of XM02, native G-CSF, or both?
- b. Please provide information demonstrating the specificity of the ELISA screening assay.
- c. We recommend the determination of the screening assay sensitivity in mass units of antibody detectable/mL matrix. Please provide a value, with supporting data, for the sensitivity of the validated ELISA assay for the detection of anti-XM02 antibodies.
- d. Please provide a statistically based justification for your method of determining the screening assay cut point. (b) (4)

[REDACTED]

We recommend the calculation of a cut point based on a 95% confidence interval that allows the inclusion of 5% of false positives, there by precluding a failure to detect patient samples with low antibody titers. Please address these issues.

13. Regarding the xMAP anti-XM02 (Luminex) screening assay:

- a. Please provide a statistically based justification for your method of determining the Luminex screening assay cut point. (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]. We recommend the calculation of a cut point based on a 95% confidence interval that allows the inclusion of 5% of false positives, thereby precluding a failure to detect patient samples with low antibody titers. Please address these issues.
- b. Please provide information demonstrating the specificity of the Luminex screening assay.
- c. We recommend the determination of the screening assay sensitivity in mass units of antibody detectable/mL of matrix. Please provide a value for the sensitivity, with supporting data, of the validated Luminex method for the detection of anti-XM02 antibodies.

14. You do not include a positive control for the anti-IgG secondary reagent in the Confirmatory Western Blot anti-XM02 assay. Therefore, the status of IgG negative samples is questionable. Please address this concern.
15. Regarding the BIAcore anti-XM02 assay:
 - a. Please provide a statistically based rationale for your method of determining the BIAcore cut point value.
 - b. Please provide an explanation for the broad range of variability observed between BIAcore assays runs at different times. You show an inter-assay % CV between 18% and 35%, suggesting that the confirmatory BIAcore assay platform may be unable to fully confirm the low positive patient serum samples due to high inter-assay variability. Please address this concern.
16. Regarding the neutralizing assay:
 - a. You have validated a neutralizing assay that consists of measuring the decline in viability of the (b) (4) The parental cell line (b) (4) is dependent on IL-3 for viability and the related cell line (b) (4) responds well to IL-3 and weakly to G-CSF (Nakoinz I, et al. J. Immunol. 145: 860-864, 1990 and ATCC catalog). Please provide information about the effect of IL-3 on the (b) (4) cell line viability to ensure specificity of the assay.
 - b. Please provide the proliferative dose response curve of (b) (4) cell line to the product, XM02, in order to ensure optimal response concentration and maximal sensitivity of the neutralizing assay.
 - c. Please provide information about the optimal passage number of (b) (4) cells required to achieve maximal response of the assay to XM02 and/or G-CSF in order to ensure reproducibility of the assay.
 - d. The dilutional linearity data indicate that the assay has dilutional linearity over a limited dynamic range. This suggests that the assay may not be accurate for high and low titer patient sera. Please address this concern.

Clinical

17. In our January 15, 2010, letter listing deficiencies identified during the initial administrative review of Teva's BLA, you were notified that if the active control was not the U.S.-licensed product, you would need to provide adequate data characterizing the treatment effect of the active control if you intend to rely on non-inferiority comparisons as part of the evidence to support product approval.

Your response to item 5 of our January 15, 2010, letter references your response to item #4 of that same letter, which states, in part, that " (b) (4)

This information is relevant to assessing compliance with good manufacturing practices, but does not address the Division's request for data that would permit FDA to draw a scientifically valid conclusion regarding preservation of the treatment effect between your product and the non-U.S.-licensed product.

Statistical

18. For Study XM02, subgroup analyses should be conducted for age (<65 and ≥65 years) and race (Caucasian, Black, Hispanic and other). Analysis results should include the mean in each treatment group, mean differences (tevagastim vs. placebo, tevagastim vs. filgrastim, filgrastim vs. placebo), and standard errors for the mean differences. We acknowledge that subgroup analyses may not be powered to demonstrated efficacy, but these are necessary for assessing consistency among different patient populations.

Regulatory

19. The nonproprietary name for your proposed r-metHuG-CSF product will be a review issue. FDA designates the proper name of a biological product at the time of approval of a biologics license application (BLA) (see section 351(a) of the Public Health Service Act (PHS Act); 42 U.S.C. 262(a)).
20. Your submission notes that XM02 was developed in accordance with the European Union guidelines for "biosimilars" and contains certain data that is described by terminology that is not recognized under the current statute and regulations for BLAs (for example, "bioequivalence to the reference medicinal product" (module 2.7.1)). As we have previously stated, there is no abbreviated approval pathway analogous to that in section 505(b)(2) or 505(j) of the Federal Food, Drug, and Cosmetic Act (FFD&C Act, 21 U.S.C. 355) for protein products licensed as biological products under section 351 of the PHS Act. Such a pathway for the approval or licensure of "follow-on biologics" under the PHS Act would require new legislation. Your BLA is being reviewed as a "stand-alone" application in accordance with current laws and regulations.

Proposed Labeling

21. We have completed a preliminary review of the proposed labeling submitted in this application and provide, as an attachment to this letter, a preliminary revision that contains comments based on 21 CFR Parts 201.56 and 201.57, the preamble to the Final Rule, and FDA Guidance documents. Please address the identified deficiencies/issues and re-submit labeling in clean and red-line MS WORD versions as an amendment to

your application by March 19, 2010. This revised labeling will be used for further labeling discussions.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we will advise you in writing of any action we have taken and request additional information if needed.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, contact Danyal Chaudhry, Regulatory Project Manager at (301) 796-3813 or Erik Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

A handwritten signature in black ink that reads "Summers" with a stylized flourish above it.

/Jeffrey Summers/

Jeffrey Summers, M.D.

Deputy Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

Enclosure: FDA preliminary labeling with comments



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: February 12, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Clinical Pharmacology Response)

From: Chaudhry, Danyal
Sent: Friday, February 12, 2010 11:14 AM
To: 'Dennis.Ahern@tevausa.com'
Cc: Dennis.Ahern@tevaneuro.com; Diana.Landa@tevausa.com; Laughner, Erik; Chaudhry, Danyal
Subject: RE: Information Request: Teva BLA STN 125294/0 (Neuroval (b) (4))

Dennis -- attached is the response from clinical pharmacology regarding your query to question 14 of the FDA letter dated 1/15.

Danyal

From: Dennis.Ahern@tevausa.com [mailto:Dennis.Ahern@tevausa.com]
Sent: Wednesday, February 03, 2010 11:27 PM
To: Chaudhry, Danyal
Cc: Chaudhry, Danyal; Dennis.Ahern@tevaneuro.com; Diana.Landa@tevausa.com; Laughner, Erik
Subject: Re: Information Request: Teva BLA STN 125294/0 (Neuroval (b) (4))

Hi Danyal,

My team and I are working to address the balance of questions from the January 15th letter and have the following question related to item #14 as follows:

14. Provide a tabular listing of patients with renal or hepatic impairment included in the BLA submission, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation, LFT, T.Bil, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.

Teva would like clarification on what level of renal or hepatic impairment should be examined to address FDA's question. The clinical trial in each of the oncology studies had inclusion criteria regarding renal and hepatic function and these are listed below. In order to evaluate the effect of XM02 in patients with renal or hepatic impairment we would like clarification on the criteria to use to define these patients consistently across the studies.

	Study XM02-02	Study XM02-03	Study XM02-04
Inclusion criteria: renal function	Adequate renal function, i.e., creatinine <1.5 x ULN.	Adequate hepatic, cardiac and renal function for the chosen CTX regimen.	Creatinine <2 x ULN.
Inclusion criteria: hepatic function	Adequate hepatic function i.e., alanine and aspartate aminotransferases (ALT/AST) <2.5 x upper limit of normal (ULN), alkaline phosphatase (AP) <5 x ULN, bilirubin <ULN	Adequate hepatic, cardiac and renal function for the chosen CTX regimen.	Alanine and aspartate aminotransferases (ALT/AST) <3 x upper limit of normal (ULN), bilirubin <2 x ULN

Dennis E. Ahern
 TEVA Branded Pharmaceutical Products R&D
 Director, U.S. Regulatory Affairs
 T - 215-293-6339
 M [REDACTED] (b) (6)

"Chaudhry, Danyal" <Danyal.Chaudhry@fda.hhs.gov>

**"Chaudhry,
 Danyal"
 <Danyal.Ch
 audhry@fd
 a.hhs.gov>**

To<Dennis.Ahern@tevaneuro.com>

cc<Diana.Landa@tevausa.com>, "Laughner,

01/15/2010
04:54 PM

Erik" <Erik.Laughner@fda.hhs.gov>,
"Chaudhry, Danyal"
<Danyal.Chaudhry@fda.hhs.gov>

Subject: Information Request: Teva BLA STN 125294/0
(Neuroval/i (b) (4))

Dennis -- please find attached an Information Request letter regarding the Teva BLA STN 125294/0 (Neuroval/i (b) (4)). Please note that responses to items 1 through 8 of this letter are required by 1/22/10 and should be submitted as a formal amendment to the BLA.

Kindly confirm receipt of this e-mail.

Danyal

<<IR Letter_BL 125294_TEVAScanDoc.PDF>> (See attached file: IR Letter_BL 125294_TEVAScanDoc.PDF)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: February 3, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Product/ Immunogenicity Information Request)

From: Chaudhry, Danyal
Sent: Wednesday, February 03, 2010 11:25 AM
To: 'Dennis.Ahern@tevausa.com'
Cc: Diana.Landa@tevausa.com; Laughner, Erik; Chaudhry, Danyal
Subject: Product/ Immunogenicity Information Request: Teva BLA STN 125294/0 (Neurova) (b) (4)

Hello Dennis: our Product/ Immunogenicity reviewers have the following request for information:

Please provide the results for the validation method used to detect antibodies against endogenous or native G-CSF (anti-G-CSF) in human samples.

Danyal



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125294/0

FILING COMMUNICATION
January 29, 2010

Teva Pharmaceuticals U.S.A.
Attention: Deborah A. Jaskot, M.S., R.A.C.
Vice-President, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Ms. Jaskot:

Please refer to your biologics license application (BLA) dated November 30, 2009, received November 30, 2009, submitted under section 351 of the Public Health Service Act for Neutroval (b)(4). We also refer to your additional amendments dated December 8, 2009, December 21, 2009, December 23, 2009, January 11, 2010, and January 22, 2010, which provided responses to FDA requests for additional information.

We have completed an initial review of your application to determine its acceptability for filing. Under 21 CFR 601.2(a) we have filed your application today. The review classification for this application is Standard. Therefore, the user fee goal date is September 30, 2010. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

In addition to the specific deficiencies and information requests outlined in our January 15, 2010, letter, we have identified additional potential review issues and will be communicating them to you on or before February 12, 2010.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 12, 2010.

REQUIRED PEDIATRIC ASSESSMENTS

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application for all pediatric patients under age 18.

If you have any questions, contact Danyal Chaudhry, Regulatory Project Manager at (301) 796-3813 or Erik Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,



/Patricia Keegan/

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: January 29, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: Filing Letter Communication: Teva BLA STN 125294/0 (Neuroval/ (b) (4))

From: Chaudhry, Danyal
Sent: Friday, January 29, 2010 9:36 AM
To: 'Dennis.Ahern@tevaneuro.com'
Cc: 'Diana.Landa@tevausa.com'; Laughner, Erik; Chaudhry, Danyal
Subject: Filing Communication: Teva BLA STN 125294/0 (Neuroval/ (b) (4))

Dennis -- attached find the filing communication regarding the Teva BLA STN 125294/0 (Neuroval/ (b) (4)).

Please acknowledge receipt.

Danyal



FilingLetter_BLA125
294_TEVASca...



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: January 29, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (SOP request/ immunogenicity data)

From: Chaudhry, Danyal
Sent: Friday, January 29, 2010 9:21 AM
To: 'Dennis.Ahern@tevaneuro.com'
Cc: 'Diana.Landa@tevausa.com'; Laughner, Erik; Chaudhry, Danyal
Subject: FW: Teva BLA STN 125294/0 (Neuroval (b) (4))

Dear Dennis -- we are following up with respect to the information request below regarding the SOPs that guided the analysis of the clinical samples that are the source of the immunogenicity data for the BLA. Please let me know when we can expect to have this information and if already submitted where it resides in the file.

Danyal

From: Laughner, Erik
Sent: Monday, January 11, 2010 11:45 AM
To: 'Dennis.Ahern@tevaneuro.com'
Cc: Chaudhry, Danyal
Subject: RE: Teva BLA STN 125294/0 (Neuroval, (b) (4))

Hello Dennis,

The FDA team has clarified to me that they want the SOPs that were followed for analysis of the clinical samples that are the source of immunogenicity data for this BLA.

Erik Laughner

From: Dennis.Ahern@tevaneuro.com [mailto:Dennis.Ahern@tevaneuro.com]
Sent: Sunday, January 10, 2010 11:46 AM

To: Laughner, Erik

Subject: Re: Teva BLA STN 125294/0 (Neuroval/ (b) (4))

Hi Erik,

I've been traveling since Friday and just getting to my emails now....

Just to be clear, clinical immunogenicity studies per se were not formally conducted ; though blood samples from patients that participated in the clinical studies were analyzed according to the algorithm noted in Module 2.7 Clinical Summary of Safety, section 5.2.1 and provided as a screen shot at the end of this e-mail. Since the algorithmic approach was used, there are a total of five different assays which are associated with one document each that contains a protocol, validation report, and results. Two of the assays list an SOP; however, the other three utilize a statement of compliance describing that "applicable SOPs were used..." without listing specific SOPs.

ELISA --> CIR040413 --> SOP IMM030821-1

Luminex --> CIR050608 --> SOP IMM050816-1

Western Blot --> CIR040413D --> no specific SOP listed

Neutralizing Ab --> CIR040920 --> no specific SOP listed

Biosensor --> CIR041913 --> no specific SOP listed.

I've requested from the owner of the XM02 data (b) (4) to secure from the vendor (b) (4) a copy of both SOPs listed above and expect to receive them this week.

Please confirm that I am securing the correct SOPs for you or if you have an additional request relating to SOPs.

Best regards,

Dennis

Dennis E. Ahern

TEVA Branded Pharmaceutical Products R&D

Director, U.S. Regulatory Affairs

T - 215-293-6339

M - (b) (6)

"Laughner, Erik" <Erik.Laughner@fda.hhs.gov>

**"Laughner,
Erik"
<Erik.Laug
hner@fda.
hhs.gov>**

To<Dennis.Ahern@tevaneuro.com>

cc

01/08/2010
11:10 AM

SubjectTeva BLA STN 125294/0
(Neuroval (b) (4))

Dennis,

Can you provide a location of the SOPs for the human immunogenicity studies in the submission?

Thank you very much,

Erik Laughner, RPM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: January 22, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Sponsor Clarification)

From: Laughner, Erik
Sent: Friday, January 22, 2010 8:50 AM
To: Dennis.Ahern@tevausa.com
Cc: Chaudhry, Danyal; Diana.Landa@tevausa.com
Subject: RE: Information Request: Teva BLA STN 125294/0 (Neuroval/ (b) (4))

Hi Dennis,

See responses in blue below.

Thanks,

Erik Laughner, RPM

From: Dennis.Ahern@tevausa.com [mailto:Dennis.Ahern@tevausa.com]
Sent: Thursday, January 21, 2010 4:59 PM
To: Chaudhry, Danyal
Cc: Chaudhry, Danyal; Diana.Landa@tevausa.com; Laughner, Erik
Subject: RE: Information Request: Teva BLA STN 125294/0 (Neuroval/ (b) (4))

Hi again,

I want to provide you both a status update, seek confirmation on our submission plan regarding the actual carton, package and syringe for the comparator product, and determine Dr. Keegan's availability for a brief call this or next week to discuss options related to a potential RTF.

We will submit our response as requested tomorrow as S-0005 as a full e-CTD. Regarding the actual carton, package and syringe I propose to send as a desk copy (with an electronic copy contained within S-0005 under M1.14.4.2). Do you agree with this approach?

This is fine.

The actual carton, package, and syringe were sent by [REDACTED] (b)(4) and we have just received them on-site here in Horsham. Will it be acceptable to provide the actual samples Monday morning or will you require them tomorrow -- the electronic copy will be sent tomorrow and contained in the eCTD ? I can certainly have the samples couriered tomorrow, if needed.

Monday is fine.

Finally, I am interested in a brief call (10 minutes) this or next week with Dr. Keegan as the division considers the adequacy of the response and assessment for RTF. I want to assure that we have good communication over this time-period and that neither of us are surprised.

I will share this request with Dr. Keegan.

Best regards,

Dennis

Dennis E. Ahern
TEVA Branded Pharmaceutical Products R&D
Director, U.S. Regulatory Affairs
T - 215-293-6339

[REDACTED] (b)(6)

"Chaudhry, Danyal" <Danyal.Chaudhry@fda.hhs.gov>

"Chaudhry,
Danyal"
<Danyal.Ch
audhry@fd
a.hhs.gov>

01/20/2010
09:19 AM

<Dennis.Ahern@tevaneuro.com>
To

<Diana.Landa@tevausa.com>, "Laughner,
Erik" <Erik.Laughner@fda.hhs.gov>,
"Chaudhry, Danyal"
<Danyal.Chaudhry@fda.hhs.gov>

RE: Information Request: Teva BLA STN
Subject: 125294/0 (Neuroval/1 (b) (4))

Dennis -- We are looking for you to provide the actual carton, package and syringe.

Danyal

From: Dennis.Ahern@tevaneuro.com [mailto:Dennis.Ahern@tevaneuro.com]
Sent: Wednesday, January 20, 2010 8:06 AM
To: Chaudhry, Danyal
Cc: Chaudhry, Danyal; Diana.Landa@tevausa.com; Laughner, Erik
Subject: Re: Information Request: Teva BLA STN 125294/0
(Neuroval (b) (4))

Hi Danyal and Erik,

Regarding the attached letter, I've got one clarification and one question where I need clarification. For #4, it reads "Provide a representative sample of the package and carton and vial for the active comparator used in Study XM02-02." For clarification, Study 02 utilized pre-filled syringes. The question I have is will a scanned image be sufficient for Friday or will you require the actual package, carton, and syringe?

I have physical samples on the way from Germany; however, we may experience delays with customs.

Have a good day...

Dennis

Dennis E. Ahern
TEVA Branded Pharmaceutical Products R&D

Director, U.S. Regulatory Affairs

T - 215-293-6339

M - [REDACTED] (b) (6)

"Chaudhry, Danyal" <Danyal.Chaudhry@fda.hhs.gov>

**"Chaudhry,
Danyal"
<Danyal.Ch
audhry@fd
a.hhs.gov>**

01/15/2010
04:54 PM

To <Dennis.Ahern@tevan

<Diana.Landa@tevaus
cc"Laughner, Erik"
<Erik.Laughner@fda.h
"Chaudhry, Danyal"
<Danyal.Chaudhry@fc

Information Request: T
Subject: STN 125294/0
(Neuroval/[REDACTED] (b) (4))

Dennis -- please find attached an Information Request letter regarding the Teva BLA STN 125294/0 (Neuroval/[REDACTED] (b) (4)). Please note that responses to items 1 through 8 of this letter are required by 1/22/10 and should be submitted as a formal amendment to the BLA.

Kindly confirm receipt of this e-mail.

Danyal

<<IR Letter_ BL 125294_TEVAScanDoc.PDF>> (See attached file: IR Letter_ BL 125294_TEVAScanDoc.PDF)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL [125294/0]

January 15, 2010

Teva Pharmaceuticals U.S.A.
Attention: Deborah A. Jaskot, M.S., R.A.C.
Vice-President, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Ms. Jaskot:

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Neutroval (b)(4). We have identified the deficiencies listed below during our initial administrative review of your BLA. Unless you address these deficiencies during our filing review, sufficient grounds may exist for a refusal to file (RTF) decision. Submit this information as soon as possible, but no later than January 22, 2010.

The specific deficiencies are as follows:

Statistical

1. Provide results of subgroup analyses for the primary endpoint by gender, age and race.
2. Provide detailed documentation, such as a define.pdf file, for the programs used in deriving analysis datasets.
3. Provide a summary for the extent of missing absolute neutrophil count (ANC) data including percent of missing data for each study day of Cycle 1 and percent of patients missing at least 20%, 40%, 60%, 80% and 100% of ANC measurement in Cycle 1 of the protocol-required ANC measurements in Cycle 1.

Clinical

4. Provide the source of the Neupogen (U.S.-licensed or EMEA approved) that was used for the active control in Study XM02-02. Provide documentation regarding where the drug product and drug substance were manufactured and filled. Provide a representative sample of the package and carton and vial for the active comparator used in Study XM02-02.

5. The single study intended to be the primary support for efficacy in your BLA includes a non-inferiority comparison. If the study did not use an active control that is FDA-approved and manufactured in an FDA-licensed facility, then you must provide adequate data and information to demonstrate that it would be scientifically appropriate to use EU licensed filgrastim as an active control in a non-inferiority trial intended to support BLA approval.
6. The financial disclosure information provided in the BLA was incomplete. Provide this information in a dataset that lists investigators by site who declared no conflict of interest, a conflict of interest, or for whom no data is available. You must provide information that supports your efforts regarding due diligence in attempting to collect financial disclosure information from the investigators who did not provide this information. This due diligence would typically consist of a minimum of two documented attempts of contacting the investigator specifically for collection of financial disclosure information.

Facility

7. Provide the following information for the drug substance manufacturing site SICOR Biotech UAB in Vilnius, Lithuania (DUNS number 565487722):
 - a. A tentative production table/chart indicating (b) (4) operations for the manufacture of drug substance for the April 15 – June 15 timeframe.
 - b. A statement that the facility is ready for inspection. Please also provide the FEI number assigned by FDA.
 - c. A list of products manufactured at the Vilnius site. Indicate if these products are produced by cell culture or microbial fermentation.
8. Provide the following information for the drug product manufacturing site Teva Pharmaceutical, Kfar Saba, Israel (FEI no 3002721084):
 - a. A production schedule for manufacture of drug product.
 - b. A statement that the facility is ready for inspection.
 - c. A list of drug products manufactured at the Kfar Saba site.

In addition, we have the following requests for information that should be submitted as a formal amendment to your BLA no later than February 12, 2010.

Clinical

9. Provide datasets that contain metadata that accurately and completely describe the data for each variable in every dataset or provide this information in the dataset define files.
10. The “primary” efficacy and “analysis” efficacy datasets contain more subjects than were randomized. This is highly irregular for datasets contained in a BLA. Although this irregularity was noted in the study report and the non-randomized patients’ data, or lack thereof, was not used in determining the results or conclusion drawn from the study data, we are concerned that other irregularities may be present in the datasets provided in the BLA. Provide detailed information regarding the steps that were used to ensure quality control of the datasets.
11. The final study report for a clinical study should have a single data cutoff point and the results, analyses, and conclusions drawn from the study data should be complete. Multiple additional addendums to a final study report are not acceptable and do not facilitate a functional review. Submit a complete final study report.
12. Provide justification of the proposed non-inferiority margin; the fraction of the treatment effect for the active control that is to be established for XM02 should be sufficient to confer a clinical benefit. Such evidence is required to support a claim of clinical benefit (reduction in incidence of febrile neutropenia) based on the surrogate of reduction in DSN.

Clinical Pharmacology

13. Conduct the following analyses described in 13a-d below and propose revised package insert language describing the clinically relevant findings, as appropriate, to replace the currently proposed language summarizing healthy volunteer results (i.e. Label Sections 12.2 and 12.3).
 - a. Directly compare the Neutroval pharmacodynamic (PD) results (e.g. ANC, CD34+) from each of the three trials, Study XM02-02-INT, Study XM02-03-INT, and Study XM02-04-INT, and provide a description of similarities and/or differences observed between the three patient populations. Additionally, compare these data to the two Phase 1 healthy volunteer trial (XM02-01-LT and XM02-05-DE) PD results.
 - b. Combine the Neutroval PD data from these three phase 3 trials as and provide a summary of PD results for the oncology patient population as a whole. Present the data as geometric mean with standard deviation and median with range as appropriate for individual PD parameters. Include the data file(s) used to generate the results.

- c. Combine the Neutroval pharmacokinetic (PK) data from these three phase 3 trials and provide a summary of PK results for the oncology patient population as a whole. Present the data as geometric mean with coefficient of variation and median with range as appropriate for individual PK parameters. Include the data file(s) used to generate the results.
 - d. Evaluate the effect of neutrophil count and other potential contributing factors, on Neutroval PK (e.g., the relationship between neutrophil count and plasma clearance) in each of the 3 oncology patient populations separately, as well as combined, and provide a summary of the findings.
14. Provide a tabular listing of patients with renal or hepatic impairment included in the BLA submission, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation, LFT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.

If you have any questions, contact Danyal Chaudhry, Regulatory Project Manager at (301) 796-3813 or Erik Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

/Patricia Keegan/
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: January 15, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: Information Request: Teva BLA STN 125294/0 (Neuroval/ (b) (4))

From: Chaudhry, Danyal
Sent: Friday, January 15, 2010 4:54 PM
To: 'Dennis.Ahern@tevaneuro.com'
Cc: Diana.Landa@tevausa.com; Laughner, Erik; Chaudhry, Danyal
Subject: Information Request: Teva BLA STN 125294/0 (Neuroval/ (b) (4))

Dennis -- please find attached an Information Request letter regarding the Teva BLA STN 125294/0 (Neuroval (b) (4)). Please note that responses to items 1 through 8 of this letter are required by 1/22/10 and should be submitted as a formal amendment to the BLA.

Kindly confirm receipt of this e-mail.

Danyal



IR Letter_BL
25294_TEVAScanD.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: January 12, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Information regarding the Syringe)

From: Laughner, Erik
Sent: Tuesday, January 12, 2010 2:33 PM
To: Dennis.Ahern@tevaneuro.com; Diana.Landa@tevausa.com
Cc: Chaudhry, Danyal
Subject: RE: FDA Information Requests; Teva BLA STN 125294/0 (b) (4)

Hi Dennis:

Regarding the syringe as presented in the submitted BLA, can you confirm that this is a 510K approved syringe? If so, is that information provided in the BLA?

Sincerely,

Erik Laughner, RPM



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE of DECISION: January 12, 2010

FROM: Patricia Keegan, M.D.
Director
Division of Biological Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Designation of BLA application review status
Sponsor: TEVA Pharmaceuticals USA
Product: Neutroval (b) (4)

TO: BLA file STN 125294/0

The review status of this file submitted as a BLA application is designated to be:

Standard (10 Months)

Priority (6 Months)

Patricia Keegan, M.D.: Patricia Keegan Date: 1-12-2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: January 11, 2010
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Immuno Assay Response)

From: Laughner, Erik
Sent: Monday, January 11, 2010 11:45 AM
To: 'Dennis.Ahern@tevaneuro.com'
Cc: Chaudhry, Danyal
Subject: RE: Teva BLA STN 125294/0 (Neuroval/ (b) (4))

Hello Dennis,

The FDA team has clarified to me that they want the SOPs that were followed for analysis of the clinical samples that are the source of immunogenicity data for this BLA.

Erik Laughner

From: Dennis.Ahern@tevaneuro.com [mailto:Dennis.Ahern@tevaneuro.com]
Sent: Sunday, January 10, 2010 11:46 AM
To: Laughner, Erik
Subject: Re: Teva BLA STN 125294/0 (Neuroval (b) (4))

Hi Erik,

I've been traveling since Friday and just getting to my emails now....

Just to be clear, clinical immunogenicity studies per se were not formally conducted ; though blood samples from patients that participated in the clinical studies were analyzed according to the algorithm noted in Module 2.7 Clinical Summary of Safety, section 5.2.1 and provided as a screen shot at the end of this e-mail. Since the algorithmic approach was used, there are a total of five different assays which are associated with one document each that contains a protocol, validation report, and results. Two of the assays

list an SOP; however, the other three utilize a statement of compliance describing that "applicable SOPs were used..." without listing specific SOPs.

ELISA --> CIR040413 --> SOP IMM030821-1

Luminex --> CIR050608 --> SOP IMM050816-1

Western Blot --> CIR040413D --> no specific SOP listed

Neutralizing Ab --> CIR040920 --> no specific SOP listed

Biosensor --> CIR041913 --> no specific SOP listed.

I've requested from the owner of the XM02 data (b)(4) to secure from the vendor (b)(4) a copy of both SOPs listed above and expect to receive them this week.

Please confirm that I am securing the correct SOPs for you or if you have an additional request relating to SOPs.

Best regards,

Dennis

Dennis E. Ahern
TEVA Branded Pharmaceutical Products R&D
Director, U.S. Regulatory Affairs
T - 215-293-6339

(b)(6)

"Laughner, Erik" <Erik.Laughner@fda.hhs.gov>

**"Laughner,
Erik"
<Erik.Laug
hner@fda.
hhs.gov>**

To <Dennis.Ahern@tevaneuro.com>

cc

01/08/2010
11:10 AM

Subject Teva BLA STN 125294/0
(Neuroval (b) (4))

Dennis,

Can you provide a location of the SOPs for the human immunogenicity studies in the submission?

Thank you very much,

Erik Laughner, RPM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: November 20, 2009
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b)(4) (Quality Assessment)

From: Laughner, Erik
Sent: Friday, November 20, 2009 2:40 PM
To: Dennis.Ahern@tevaneuro.com
Cc: Chaudhry, Danyal
Subject: RE: (b)(4) BLA 125,294

Hi Dennis,

This appears to be a go on 01/15/09. I will provide logistics later on.

As part of our new GRMP review process for BLA/NDA submissions, I have also enclosed a quality assessment form that both FDA and the Sponsor can complete for possible post-action feedback discussions.

In addition, please note that Mr. Danyal Chaudhry will also be an RPM working with me on this file.

Tx,

Erik Laughner, RPM

From: Dennis.Ahern@tevaneuro.com [mailto:Dennis.Ahern@tevaneuro.com]
Sent: Thursday, November 19, 2009 5:13 PM
To: Laughner, Erik
Subject: RE: (b) (4) BLA 125,294

Hi Erik,

Yes, 1/15/10 is fine.

thanks,

Dennis

Dennis E. Ahern
Teva Neuroscience
Director, U.S. Regulatory Affairs
T - 215-293-6339
M - (b) (6)

"Laughner, Erik" <Erik.Laughner@fda.hhs.gov>

"Laughner,
Erik"
<Erik.Laug
hner@fda.
hhs.gov>

To <Dennis.Ahern@tevaneuro.com>

11/19/2009
04:45 PM

cc

Subject RE: (b) (4) BLA 125,294

Dennis,

Between yesterday and today, the 01/08/10 date got overbooked....

Would 01/15/10 be acceptable for you?

Tx,

Erik

From: Dennis.Ahern@tevaneuro.com
[mailto:Dennis.Ahern@tevaneuro.com]
Sent: Thursday, November 19, 2009 10:54 AM
To: Laughner, Erik
Subject: RE: (b) (4) BLA 125,294

Hi again Erik,

One quick question, who from FDA will be part of the meeting?

Best regards,

Dennis

Dennis E. Ahern
Teva Neuroscience
Director, U.S. Regulatory Affairs
T - 215-293-6339
M - (b) (6)
Dennis Ahern/NWT/TEVA/IL

**Dennis
Ahern/NW
T/TEVA/I
L**

To: "Laughn
<Erik.La

11/19/2009
10:38 AM

cc Yao.Yac

Subject RE: (b) (4)

Hi Erik,

Confirming receipt of your e-mails regarding an applicant orientation meeting.

Thank you for offering us one of these meetings, most divisions do not take the time to hold these meetings; however, I understand that they can be very helpful in assuring an

efficient regulatory review.

With this e-mail I am accepting the invitation for January 8th. Please let me know what the overall preference is for planning and conducting the meeting. For instance, when will you need a list of attendees? Also, how much time and is there a preferred format for presentation to the OODP? Any recommendations for the meeting will help me and my team prepare so that the meeting is most productive.

Thanks again!

Dennis

Dennis E. Ahern
Teva Neuroscience
Director, U.S. Regulatory Affairs
T - 215-293-6339
M - [REDACTED] (b) (6)

"Laughner, Erik" <Erik.Laughner@fda.hhs.gov>

**"Laughner,
Erik"
<Erik.Laug
hner@fda.
hhs.gov>**

To <Dennis

<Yao.Yi
cc

11/18/2009
02:21 PM

Subject RE: [REDACTED] (b) (4)

Update: Will 01/08/09 in the afternoon work for you (face-to-face meeting)?

Please let me know by Friday if possible.

Thanks,

Erik

From: Laughner, Erik
Sent: Wednesday, November 18, 2009 1:51 PM
To: Dennis.Ahern@tevaneuro.com
Cc: Yao.Yao@tevaneuro.com
Subject: RE: [REDACTED] (b) (4) BLA 125,294

Hello Dennis and Yao:

As a heads up, OODP will likely request that Teva come in for an "Applicant Orientation Meeting" to provide a slide presentation overview of your BLA submission. These are generally scheduled within 45 days of submission of the BLA/NDA. My guess is we are looking for sometime in early Jan 2010. We try to schedule these during our office Friday afternoon clinical rounds.

We do not require a briefing document for this informal meeting, just a slide deck to "guide" the FDA review team through the contents of the BLA submission. I will try to coordinate some dates in Jan and let you know what we are thinking.

Sincerely,

Erik

From: Dennis.Ahern@tevaneuro.com
[mailto:Dennis.Ahern@tevaneuro.com]
Sent: Thursday, November 12, 2009 11:40 AM
To: Laughner, Erik
Cc: Diana.Landa@tevausa.com; Yao.Yao@tevaneuro.com
Subject: RE: [REDACTED] (b) (4) BLA 125,294 (filing delay)

Dear Eric,

As discussed on the phone just now, I want to again offer my sincere apologies that we are only able to inform you today; however, we learned this morning that we will need an additional two weeks to complete the overall eCTD build of our BLA. Therefore, the file will not be sent tomorrow and we are targeting submission for Monday, November 30th.

I will update you late next week or early the following week to confirm the filing status.

Kind regards,

Dennis

Dennis E. Ahern
Teva Neuroscience
Director, U.S. Regulatory Affairs
T – 215-293-6339
M – (b) (6)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: December 31, 2009
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 Neutroval Request for Proprietary Name Review

From: Simon, Sarah
Sent: Thursday, December 31, 2009 1:20 PM
To: 'Dennis.Ahern@tevaneuro.com'; 'Diana.Landa@tevausa.com'
Cc: Laughner, Erik; Chaudhry, Danyal
Subject: BLA 125294 Neutroval Request for Proprietary Name Review

Hello Dennis and Diana,

FDA has received your submission "Request for Proprietary Name Review" dated December 23, 2009. In the attached cover letter, it states "For consistency of review, TEVA submits herewith the identical information as contained in the July 10, 2009, request for proprietary name review submission." DMEPA would like to confirm that none of the product characteristics as stated in the original IND proprietary name request dated July 10, 2009 (which TEVA is requesting be used for the BLA name review) have changed. Please respond at your earliest convenience, as this information is necessary to ascertain before DMEPA can begin their review.

Thank you for your prompt attention to this matter.

Happy Holidays,

Sarah Simon, PharmD
LT, United States Public Health Service
Project Manager
Office of Surveillance and Epidemiology
FDA CDER Bldg 22, Room 3491
10903 New Hampshire Avenue
Silver Spring, MD 20993
301-796-5205



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: December 17, 2009
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Manufacturing Query)

From: Lolos, Anastasia
Sent: Thursday, December 17, 2009 12:26 PM
To: 'diana.landa@tevausa.com'
Cc: Chaudhry, Danyal
Subject: BLA 125294 (b) (4)

Dear Ms. Landa,

I'm in the Biotech Manufacturing Team in the Office of Compliance and I have been assigned BLA 125294 (b) (4). I cannot find in the application a manufacturing schedule for the Vilnius, Lithuania drug substance manufacturing site. If you haven't submitted one, please do so by the filing date. The schedule should indicate when (b) (4) activities are planned to facilitate the planning of the pre-approval inspection for the site. Please submit the manufacturing schedule as an amendment to the BLA prior to January 14, 2010.

Regards,

Anastasia G. Lolos, M.S.
Microbiologist
Biotech Manufacturing Team/MAPCB/DMPQ
Office of Compliance, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Bldg 51, Room 4216
Silver Spring, MD 20993-0002

Phone: 301-796-1566
Fax: 301-847-8742
E-mail: anastasia.lolos@fda.hhs.gov



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: December 16, 2009

From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER

Subject: BLA 125294 (b) (4) (First Committee Meeting)

First Committee meeting was held 12/16/09. Participants were present from all disciplines including, clinical, statistics, clinical pharmacology, pharmacology-toxicology, product, immunogenicity and facilities. Initial application content and structure were discussed along with consult requests and over all timelines. Team was also made aware of the scheduled filing meeting.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: December 14, 2009
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: BLA 125294 (b) (4) (Acknowledgement Letter)

From: Chaudhry, Danyal
Sent: Monday, December 14, 2009 1:00 PM
To: 'Dennis.Ahern@tevaneuro.com'
Cc: Diana.Landa@tevausa.com; Laughner, Erik; Chaudhry, Danyal
Subject: RE: FDA Information Requests; Teva BLA STN 125294/0 (b) (4)

Dennis -- please find attached the Acknowledgement Letter regarding your submission.

Danyal

From: Dennis.Ahern@tevaneuro.com [mailto:Dennis.Ahern@tevaneuro.com]
Sent: Friday, December 11, 2009 2:49 PM
To: Chaudhry, Danyal
Cc: Chaudhry, Danyal; Diana.Landa@tevausa.com; Laughner, Erik
Subject: RE: FDA Information Requests; Teva BLA STN 125294/0 (b) (4)

Hi Danyal,

Yes, an electronic confirmation is acceptable.

Best regards,

Dennis

Dennis E. Ahern
Teva Neuroscience
Director, U.S. Regulatory Affairs
T - 215-293-6339
M - [REDACTED] (b) (6)

"Chaudhry, Danyal" <Danyal.Chaudhry@fda.hhs.gov>

"Chaudhry,
Danyal"
<Danyal.Chaudhry@fda.hhs.gov>

12/11/2009
01:18 PM

<Dennis.Ahern@tevaneuro.com>
To

<Diana.Landa@tevausa.com>, "Chaudhry,
ccDanyal" <Danyal.Chaudhry@fda.hhs.gov>,
"Laughner, Erik"
<Erik.Laughner@fda.hhs.gov>

RE: FDA Information Requests; Teva BLA
Subject: STN 125294/0 [REDACTED] (b) (4)

Dennis -- please confirm if I can electronically communicate a copy of the Acknowledgement Letter for your application.

Danyal

From: Dennis.Ahern@tevaneuro.com [<mailto:Dennis.Ahern@tevaneuro.com>]
Sent: Wednesday, December 09, 2009 11:41 AM
To: Laughner, Erik
Cc: Chaudhry, Danyal; Diana.Landa@tevausa.com
Subject: RE: FDA Information Requests; Teva BLA STN 125294/0 [REDACTED] (b) (4)

Dear Erik,

Confirming receipt of your e-mail and will correct 1.12.14 accordingly.

Kind regards,

Dennis

Dennis E. Ahern
Teva Neuroscience
Director, U.S. Regulatory Affairs
T - 215-293-6339

M - [REDACTED] (b) (6)

"Laughner, Erik" <Erik.Laughner@fda.hhs.gov>

**"Laughner,
Erik"
<Erik.Laug
hner@fda.
hhs.gov>**

12/09/2009
11:25 AM

To <Dennis.Ahern@teva
<Diana.Landa@tevaus

"Chaudhry, Danyal"
cc <Danyal.Chaudhry@fd

Subject RE: FDA Information I
Teva BLA STN 12529

[REDACTED] (b) (4)

Dear Dennis:

Please submit a revised 1.12.14 Environmental analysis as an amendment to your BLA. You must submit either a request for environmental assessment or a request of categorical exclusion from preparation of an environmental assessment for Neutroval [REDACTED] (b) (4). Compliance with the categorical exclusion criteria is made pursuant to 21 CFR Part 25, Subpart C, Categorical Exclusions, Section 25.31 (b), Human drugs and biologics.

See:

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm088977.htm>

Please confirm receipt of this email.

Sincerley,

Erik Laughner, RPM

From: Dennis.Ahern@tevaneuro.com
[mailto:Dennis.Ahern@tevaneuro.com]
Sent: Friday, December 04, 2009 3:26 PM
To: Laughner, Erik; Diana.Landa@tevausa.com
Cc: Chaudhry, Danyal
Subject: Re: FDA Information Requests; Teva BLA STN 125294/0

(b) (4)

Hi Erik,

Confirming receipt of your email. Thank you for the email and have a nice weekend.

Dennis

----- Original Message -----

From: "Laughner, Erik" [Erik.Laughner@fda.hhs.gov]
Sent: 12/04/2009 03:18 PM EST
To: Dennis Ahern; Diana Landa
Cc: Chaudhry, Danyal" <Danyal.Chaudhry@fda.hhs.gov>
Subject: FDA Information Requests; Teva BLA STN 125294/0

(b) (4)

Hello Dennis and Diana:

During a cursory quick administrative review of the newly submitted BLA (b) (4) the following items need correction:

1. The 356h form should be revised to include all the establishment information on the form, not just referencing where found in the BLA application (this information can be "attached" to the 356h form).

2. The debarment certificate that was provided did not use the proper language for an NDA/BLA (note: this is not a generic). Please refer to suggested debarment language: *Debarment Certification should use wording in FD&C Act section 306(k)(1) 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."*

Also See:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080584.pdf>

3. Review of proposed proprietary names is managed by OSE. FDA did approve the proposed tradename under pre-IND 103188 on 12/2/09 (see copy of letter). This tradename will also have to be re-reviewed for the BLA under a separate internal review clock.

See:

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM182730.pdf>

FDA therefore requests that you submit a re-review request for the proposed tradename as a separate stand-alone amendment to the BLA file. If you have any questions on the contents of this re-request submission, please contact the OSE RPM, Sarah Simon, as noted in the letter below.

<<Teva Prop Name Review pre-IND 103188.pdf>>

In Summary, items 1 and 2 can come in as one combined amendment (with 356h). Item 3 should be a stand-alone amendment (with 356h).

If you have any questions regarding this email, please contact me.

Please confirm receipt.

Thanks,

Erik

Erik S. Laughner, M.S.
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393

erik.laughner@fda.hhs.gov

<http://www.fda.gov/cder/Offices/OODP/about.htm>

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and notify me immediately. Thank you.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125294/0

BLA ACKNOWLEDGEMENT

December 10, 2009

Teva Pharmaceuticals U.S.A.
Attention: Deborah A. Jaskot, M.S., R.A.C.
Vice-President, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Ms. Jaskot:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Neutroval (b) (4)

Date of Application: November 30, 2009

Date of Receipt: November 30, 2009

Our Submission Tracking Number (STN): BL 125294/0

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

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of revised 21 CFR 201.56-57.

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

BL 125294/0

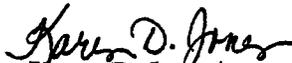
Page 2

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call, me at (301) 796-3813 or Mr. Erik Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,



Karen D. Jones

Karen D. Jones, on behalf of Patricia Keegan
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: December 9, 2009
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: FDA Information Requests; Teva BLA STN 125294/0 (b) (4)

From: Laughner, Erik
Sent: Wednesday, December 09, 2009 11:25 AM
To: Dennis.Ahern@tevaneuro.com; Diana.Landa@tevausa.com
Cc: Chaudhry, Danyal
Subject: RE: FDA Information Requests; Teva BLA STN 125294/0 (b) (4)

Dear Dennis:

Please submit a revised 1.12.14 Environmental analysis as an amendment to your BLA. You must submit either a request for environmental assessment or a request of categorical exclusion from preparation of an environmental assessment for Neuroval (b) (4). Compliance with the categorical exclusion criteria is made pursuant to 21 CFR Part 25, Subpart C, Categorical Exclusions, Section 25.31 (b), Human drugs and biologics.

See:

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm088977.htm>

Please confirm receipt of this email.

Sincerley,

Erik Laughner, RPM

From: Dennis.Ahern@tevaneuro.com [mailto:Dennis.Ahern@tevaneuro.com]
Sent: Friday, December 04, 2009 3:26 PM
To: Laughner, Erik; Diana.Landa@tevausa.com
Cc: Chaudhry, Danyal
Subject: Re: FDA Information Requests; Teva BLA STN 125294/0 (b) (4)

Hi Erik,

Confirming receipt of your email. Thank you for the email and have a nice weekend.

Dennis

----- Original Message -----

From: "Laughner, Erik" [Erik.Laughner@fda.hhs.gov]
Sent: 12/04/2009 03:18 PM EST
To: Dennis Ahern; Diana Landa
Cc: Chaudhry, Danyal" <Danyal.Chaudhry@fda.hhs.gov>
Subject: FDA Information Requests; Teva BLA STN 125294/0 (b) (4)

Hello Dennis and Diana:

During a cursory quick administrative review of the newly submitted BLA for (b) (4), the following items need correction:

1. The 356h form should be revised to include all the establishment information on the form, not just referencing where found in the BLA application (this information can be "attached" to the 356h form).
2. The debarment certificate that was provided did not use the proper language for an NDA/BLA (note: this is not a generic). Please refer to suggested debarment language: *Debarment Certification should use wording in FD&C Act section 306(k)(1) 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."*

Also See:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080584.pdf>

3. Review of proposed proprietary names is managed by OSE. FDA did approve the proposed tradename under pre-IND 103188 on 12/2/09 (see copy of letter). This tradename will also have to be re-reviewed for the BLA under a separate internal review clock.

See:

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM182730.pdf>

FDA therefore requests that you submit a re-review request for the proposed tradename as a separate stand-alone amendment to the BLA file. If you have any questions on the contents of this re-request submission, please contact the OSE RPM, Sarah Simon, as noted in the letter below.

<<*Teva Prop Name Review pre-IND 103188.pdf*>>

In Summary, items 1 and 2 can come in as one combined amendment (with 356h). Item 3 should be a stand-alone amendment (with 356h).

If you have any questions regarding this email, please contact me.

Please confirm receipt.

Thanks,

Erik

Erik S. Laughner, M.S.
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/cder/Offices/OODP/about.htm>

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and notify me immediately. Thank you.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: December 4, 2009
From: Danyal Chaudhry, M.P.H., DBOP/OODP/CDER
Subject: FDA Information Requests; Teva BLA STN 125294/0 (b) (4)

From: Laughner, Erik
Sent: Friday, December 04, 2009 3:18 PM
To: Dennis.Ahern@tevaneuro.com; Diana.Landa@tevausa.com
Cc: Chaudhry, Danyal
Subject: FDA Information Requests; Teva BLA STN 125294/0 (b) (4)

Hello Dennis and Diana:

During a cursory quick administrative review of the newly submitted BLA (b) (4), the following items need correction:

1. The 356h form should be revised to include all the establishment information on the form, not just referencing where found in the BLA application (this information can be "attached" to the 356h form).
2. The debarment certificate that was provided did not use the proper language for an NDA/BLA (note: this is not a generic). Please refer to suggested debarment language: *Debarment Certification should use wording in FD&C Act section 306(k)(1) 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."*

Also See:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080584.pdf>

3. Review of proposed proprietary names is managed by OSE. FDA did approve the proposed tradename under pre-IND 103188 on 12/2/09 (see copy of letter). This tradename will also have to be re-reviewed for the BLA under a separate internal review clock.

See:

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM182730.pdf>

FDA therefore requests that you submit a re-review request for the proposed tradename as a separate stand-alone amendment to the BLA file. If you have any questions on the contents of this re-request submission, please contact the OSE RPM, Sarah Simon, as noted in the letter below.



Teva Prop Name
Review pre-IND ...

In Summary, items 1 and 2 can come in as one combined amendment (with 356h). Item 3 should be a stand-alone amendment (with 356h).

If you have any questions regarding this email, please contact me.

Please confirm receipt.

Thanks,

Erik

Erik S. Laughner, M.S.
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-1393
erik.laughner@fda.hhs.gov
<http://www.fda.gov/cder/Offices/OODP/about.htm>

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and notify me immediately. Thank you.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, Maryland 20993

IND 103188

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Teva Neuroscience, Inc.
901 E. 104th Street, Suite 900
Kansas City, Missouri 64131

ATTENTION: Carol Childers, PharmD
Senior Manager

Dear Dr. Childers:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) Injection, 300 mcg/0.5 mL and 480 mcg/0.8 mL.

We also refer to your July 10, 2009, correspondence, received July 13, 2009, requesting a review of your proposed proprietary name, Neuroval. We have completed our review of the proposed proprietary name, Neuroval, and have concluded that it is acceptable.

A request for proprietary name review for Neuroval should be submitted once the Biologic License Application (BLA) is submitted.

If **any** of the proposed product characteristics as stated in your July 10, 2009, submission are altered prior to submission of the BLA, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Simon, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5205. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Erik Laughner, at (301) 796-2320.

Sincerely,
{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-103188

ORIG-1

Teva
Pharmaceuticals,
USA

Recombinant N-methionyl human
granulocyte colony-stimulating
factor (rmetHuG-CSF)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL A HOLQUIST
12/02/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration
Rockville, MD 20857

Pre-IND 103188

Teva Pharmaceuticals, USA
Attention: Yao Yao, PhD, RAC, CQA
Manager, US Regulatory Affairs
PO Box 1005
425 Privet Road
Horsham, PA 19044

Dear Dr. Yao,

We refer to your Pre-Investigational New Drug Application (Pre-IND) for “Recombinant N-methionyl human granulocyte colony-stimulating factor (rmetHuG-CSF) (b) (4)”. We also refer to the meeting held on November 25, 2008, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1393.

Sincerely,

{See appended electronic signature page}

Erik S. Laughner
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures: FDA Minutes

MEMORANDUM OF MEETING MINUTES

SPONSOR: Teva Pharmaceuticals, USA [Teva]
MEETING DATE: November 25, 2008
TIME: 11:00 a.m. E.T.
LOCATION: White Oak Building 22, Conference Room: 1313
DRUG NAME: Recombinant N-methionyl human granulocyte colony-stimulating factor (rmetHuG-CSF) [TevaGrastim, XM02, filgrastim]
TYPE OF MEETING: Pre-IND/Pre-BLA
MEETING CHAIR: Dr. Patricia Keegan
MEETING RECORDER: Erik Laughner

FDA ATTENDEES:

Patricia Keegan, M.D.	Director, DBOP/OODP
Jeff Summers, M.D.	Clinical Team Leader, DBOP/OODP
Thomas Herndon, M.D.	Clinical Reviewer, DBOP/OODP
William Pierce, Pharm D.	Clinical Reviewer, DBOP/OODP
Sandra Casak, M.D.	Clinical Reviewer, DBOP/OODP
Erik Laughner, M.S.	Regulatory Project Manager, DBOP/OODP
Anne Pilaro, Ph.D.	Supervisory Toxicologist, DBOP/OODP
Andrew McDougal, Ph.D.	Toxicology Reviewer, DBOP/OODP
Mary Jane Masson, Ph.D.	Toxicology Reviewer, DBOP/OODP
Hong (Laura) Lu, Ph.D.	Statistical Reviewer, DV5/OB
Mark Rothmann, Ph.D.	Statistical Team Leader, DV5/OB
Jee Chung, Ph.D.	Product Reviewer, DTP/OBP
Emily Shacter, Ph.D.	CMC Supervisor, DTP/OBP
Bo Chi, Ph.D.	Facilities Reviewer, DMPQ/OC
Mary Farbman, Ph.D.	Facilities Reviewer, DMPQ/OC
Maan Abduldayem, M.B.A.	Facilities Reviewer, DMPQ/OC
Sarah Schrieber, Ph.D.	Clinical Pharmacology Reviewer, DCP5/OC
Hong Zhao, Ph.D.	Clinical Pharmacology Team Leader, DCP5/OC
Janice Weiner, J.D., M.P.H.	Regulatory Counsel, DRPII/ORP

TEVA ATTENDEES:

Ram Petter, PhD, MBA	VP, Biotechnology Resources, Global Generic Resources
Yafit Stark, PhD	VP, Chief Clinical Officer, IR&D
Ivan Cohen-Tanugi, MD, MBA	VP, Global BioGenerics, Teva Pharma AG Switzerland
Debbie Jaskot	VP, Regulatory Affairs, Teva Pharmaceuticals USA
Diana Landa	Sr. Manager, Regulatory Affairs, Teva Pharmaceuticals USA
Mike Nicholas, PhD	Sr. Director, Strategic Regulatory Affairs & Post-Marketing Labeling/Compliance, Teva Neuroscience
Dennis Ahern	Director, Regulatory Affairs, Teva Neuroscience
Yao Yao, PhD	Manager, Regulatory Affairs, Teva Neuroscience
(b) (4)	CMC consultant
(b) (4)	Preclinical consultant
(b) (4)	Clinical consultant

Background and Meeting Purpose: On July 29, 2008, Teva requested a pre-IND/pre-BLA meeting to discuss their intent to submit by the end of Q4 2008 or early Q1 2009, an eCTD, Biologics License Application (BLA) for a recombinant N-methionyl human granulocyte colony-stimulating factor (rmetHuG-CSF, *E. coli*) [TevaGrastim, XM02, filgrastim]. Teva has noted that this product was developed in accordance with EU regulations and EMEA guidance as a biosimilar product to the product Neupogen (filgrastim) manufactured by Amgen Inc. TevaGrastim was granted EU Marketing Authorization by EMEA on Sept 15, 2008, on the basis of safety and efficacy studies conducted outside the U.S. during 2003-2006. **Teva would like to obtain FDA's advice and concurrence on the clinical, preclinical, and CMC data requirements to support the submission of a BLA.**

The completed clinical program as described by Teva is composed of five studies:

Two Phase I studies in a total of 200 healthy volunteers

1. **XM02-01-LT, titled "Comparative study of pharmacodynamic and pharmacokinetic parameters of XM02 and Neupogen when formulations are given to healthy volunteers"**
2. **XM02-05-DE, titled "Study on the bioequivalence of 5 µg/kg or 10 µg/kg of XM02 and Neupogen, each after intravenous or subcutaneous administration, in healthy female and male subjects. A multi-center, randomized, single dose, single-blind, two-way crossover design"**

One study designed to investigate efficacy and safety in 348 patients and two additional safety studies in 329 patients randomized 2:1 to XM02 versus Neupogen.

3. **XM02-02-INT, titled "Efficacy and safety of XM02 compared to Neupogen in patients with breast cancer receiving chemotherapy. A multinational,**

multi-center, randomized, controlled study”.

4. XM02-03-INT, titled “Safety and efficacy of XM02 in patients with small cell or non-small-cell lung cancer receiving platinum-based chemotherapy. A multi-national multi-center, randomized, controlled study”,
5. XM02-04-INT, titled “Safety and efficacy of XM02 in patients with Non-Hodgkin’s-Lymphoma receiving chemotherapy. A multi-national, multicenter, randomized, controlled study”

These studies are further summarized in a table as provided by Teva in their meeting briefing document:

Type of Study	Study Code; Status; Type of Report	Objective(s) of the Study	Healthy Subjects or Diagnosis of Patients	Study design	Test Product(s); Dosage Regimen; Route of Admin.	Number of Subjects	Duration of Treatment
PK (PK/PD)	XM02-01-LT complete full	Comparison of PK-and PD parameters	Healthy male	Cross over, 2 arms with 2 periods	T: XM02 vs. R: Neupogen, Single dose A: 5 µg/kg s.c. B: 10 µg/kg s.c.	56 (2x28 random.) completed: A: 24 B: 26	single dose 96-hour periods 2-week wash-out
BE (PK/PD)	XM02-05-DE complete full	Demonstration of equivalence of PK and PD parameters	Healthy female or male	Cross over, 4 groups with 2 periods	T: XM02 vs. R: Neupogen, Single dose of 1: 5 µg/kg i.v. 2: 10 µg/kg i.v. 3: 5 µg/kg s.c. 4: 10 µg/kg s.c.	144 (4x36 random.) completed: (PK) 1: 36 2: 35 3: 35 4: 34	single dose 16-day periods 3-week wash-out
Efficacy	XM02-02- INT complete full	Demonstration of equivalence in efficacy (DSN) - Safety - PK (subgroup)	Breast cancer with chemotherapy (CTX)	Randomised, placebo- and active- controlled	T: XM02 vs. R: Neupogen P: Placebo (CTX Cycle 1) then switch to XM02 5 µg/kg s.c.	ITT/PP T: 140/133 R: 136/129 P: 72/58	per CTX-cycle: 5-14 days (until ANC ≥ 10x10 ⁹ /l) up to 4 CTX cycles
Safety	XM02-03-INT complete full	Safety - Efficacy (DSN) - PK (subgroup)	Lung cancer with CTX (platinum-based)	Randomised, active controlled (first cycle)	T: XM02 vs. R: Neupogen (CTX Cycle 1) then switch to XM02 5 µg/kg s.c.	Safety/PP T: 158/148 R: 79/ 77	per CTX-cycle: 5-14 days (until ANC ≥ 10x10 ⁹ /l) up to 6 CTX cycles
Safety	XM02-04-INT complete full	Safety - Efficacy (DSN) - PK (subgroup)	Non-Hodgkin lymphoma with CTX (CHOP)	Randomised, active controlled (first cycle)	T: XM02 vs. R: Neupogen (CTX Cycle 1) then switch to XM02 5 µg/kg s.c.	Safety/PP T: 63/55 R: 29/29	per CTX-cycle: 5-14 days (until ANC ≥ 10x10 ⁹ /l) up to 6 CTX cycles

Teva intends to seek U.S. marketing approval for XM02

(b) (4)

• [Redacted]

(b) (4)

-  (b) (4)
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The primary meeting briefing packages were received on October 23, 2008. On November 4, 2008, additional CMC and clinical study details were provided in a subsequent briefing document. FDA preliminary comments were provided to Teva on November 24, 2008.

FDA PREAMBLE:

A recombinant N-methionyl human granulocyte colony-stimulating factor would be licensed under section 351 of the Public Health Service Act (PHS Act, 42 U.S.C. 262), rather than approved pursuant to a New Drug Application under section 505 of the Federal Food, Drug, and Cosmetic Act (FFD&C Act, 21 U.S.C. 355). There is no abbreviated approval pathway analogous to that in section 505(b)(2) or 505(j) of the FFD&C Act for protein products licensed as biological products under section 351 of the PHS Act. Such a pathway for the approval or licensure of follow-on protein products under the PHS Act would require new legislation.

POST-MEETING NOTE: Our comments on your development program, including the circumstances under which Neupogen may be used as an active control in clinical studies, reflect current law and regulations for submission of a BLA. To the extent that your meeting information package suggests that aspects of your development program are intended to support submission of an application through an abbreviated approval pathway, should such a pathway be established by legislation in the future, please note that we cannot speculate on whether any such proposals would or would not be acceptable given the current absence of an abbreviated approval pathway. In particular, we cannot comment on whether comparisons to products (or components thereof) that have not been licensed in the United States (including but not limited to non-U.S. versions of a U.S.-licensed product) would be acceptable, to any extent, should an abbreviated approval pathway be established by legislation in the future.

Sponsor Submitted Questions and FDA Response:

DISCUSSION DURING THE MEETING: Teva acknowledged all of FDA's preliminary comments received on November 24, 2008. Teva gave a brief presentation (see powerpoint slides attached at end of FDA minutes) and noted that no further discussion was needed with

FDA except for Clinical Pharmacology questions 14 and 16 (See **FDA Additional Comments** section below for those minutes). FDA noted that an INN name of (b) (4) may likely be acceptable based on current thinking, but advised that this would be a review issue. FDA also noted that Teva should provide several proposed proprietary names for consideration in their original BLA. FDA advised Teva that as an additional CMC comment the HPLC method for measuring total protein is not recommended due to potential issues with protein recovery.

Teva inquired how proposed legislation, if enacted, to establish an abbreviated approval pathway under the PHS Act would affect a pending BLA submission. FDA would not speculate on this issue, as it would depend on whether legislation was enacted and the content of any such legislation. FDA reiterated that there is no abbreviated approval pathway under the PHS Act, and advised that Teva's proposed BLA would need to meet current statutory and regulatory requirements for a BLA submission.

CMC

1. Based on the data of Drug Substance filgrastim and Drug Product XM02, Teva considers that the available CMC information – including production strain and cell banks, product characterization, manufacturing controls, and specifications at release and the end of shelf life – is sufficient to support an application for marketing approval. Does the Agency concur?

FDA RESPONSE: At this time, the limited data and descriptions provided in the meeting package are insufficient for FDA to definitely determine the adequacy of Teva's CMC program to support a BLA. However, FDA has identified the following preliminary list of deficiencies that Teva must address in the BLA submission:

- a. Demonstration of the complete (100%) amino acid sequence of the protein product (drug substance, DS).
- b. Detailed information on the assays and data used to assess the immunogenicity of the product, including:
 - 1) cut-point determination, sensitivity, specificity, linearity, and reproducibility;
 - 2) a description and raw data from the assay(s) used to determine G-CSF neutralizing activity of sera that test positive for anti-product antibodies;
 - 3) a description and full justification of the criteria and methods used for eliminating positive test samples from the calculation of product immunogenicity.
- c. A description of the methods employed to assess the stability and degradation pathways for the protein. Data from additional stability assessments such as

photostability testing, and the identification of stability-indicating assays should be part of the license application.

- d. Information and test results from End-of-Production Cell characterization for gene sequence, plasmid copy number and stability, purity, and viability.
- e. Information regarding in-process controls and tests for DS and drug product (DP).
- f. A complete description of manufacturing process validation and demonstration of consistency of manufacture for DS and DP.
- g. A comparison of the proposed commercial manufacturing process to the process(es) used to manufacture product for the non-clinical and clinical studies.
- h. Side-by-side lot release data for the DS and DP used in the non-clinical and clinical studies.
- i. A definitive identity test for release of the DP, such as peptide mapping, N-terminal sequencing, or an anti-G-CSF immunoassay.
- j. An assay to measure sub-visible particulates [REDACTED] (b) (4) in the DP (for release and stability testing).
- k. A quantitative analysis of the peptide analysis used for the release of the DS; *i.e.*, visual, qualitative analysis of the peptide map compared to a reference standard does not provide sufficient control over product microheterogeneity
- l. Justification for any differences in the release and end-of-shelf life specifications for the drug substance and the drug product e.g. the specification for peptide mapping is qualitative rather than quantitative.

Pre-Clinical

- 2. Teva has completed multiple pre-clinical studies on [REDACTED] (b) (4) in the following section. In light of the pre-clinical data, it is Teva USA's **opinion that the** preclinical studies performed on [REDACTED] (b) (4) are sufficient to support the safety of the drug substance and drug product. Does the Agency concur?

FDA RESPONSE: FDA anticipates that the nonclinical data for XM02 will be sufficient to support the indication related to the Phase 3 clinical trial; however, this question cannot be definitively answered now and would be a review issue.

The summary of the nonclinical information (c.f. pp 25-29) does not indicate that the pharmacological relevance of the animal test species was demonstrated, or that information is available from which to extrapolate pharmacodynamic differences between the animal models and humans. For example, the Pharmacology summary (c.f. p 25) reports that XM02 and Neupogen binding to the human G-CSF receptor were measured to demonstrate specificity, but the summary does not mention testing of XM02 binding to rodent or monkey G-CSF receptor. If additional relevant data are available, they should be included in the BLA.

Clinical

3. Teva has conducted 3 confirmatory Phase III studies and 2 Phase I studies as described in the following section, demonstrating superiority over placebo as well as comparability to Neupogen in both: PK, PD, safety tolerability, immunogenicity and efficacy. All studies were multinational. The Clinical development has included patients with 3 different major indications as well as multiple chemo cycles, covering broad range of patients under different conditions. The clinical development program (b) (4) was performed in accord with the ICH S7, S8, and EMEA guidances. In light of the data from the clinical study program, it is Teva USA's opinion that the clinical studies (b) (4) are sufficient to support the submission of BLA. Does the Agency concur?

FDA RESPONSE: Teva has completed two studies designed to look at safety (XM02-03-INT, XM02-04-INT) and a single study designed to look at efficacy (XM02-02-INT). The only efficacy endpoint that incorporated appropriate alpha adjustment was the duration of severe neutropenia endpoint (DSN) in Study XM02-02-INT. All other efficacy endpoints in the three studies were exploratory analyses.

The study design and statistical analysis plan were not discussed with FDA prior to initiation. We have the following comments that would need to be addressed in order to file the proposed license application:

- a. Based on historical information, a clinically important incidence of febrile neutropenia is present only when the duration of severe neutropenia is 5 or more days in the absence of prophylactic antibiotics. The application should provide evidence that the clinical setting (average DSN in the placebo arm for the same patient population/chemotherapy regimen) in which XM02 was evaluated is one that requires growth factor support to avoid a clinically important risk of febrile neutropenia. Such evidence is necessary to support the proposed claim of a clinical benefit (reduction in incidence of febrile neutropenia) based on the surrogate of reduction in DSN.
- b. Replication of the treatment effect in multiple trials. Ordinarily, a minimum of two adequate and well-controlled trials are required.

- c. For comparisons to an active control (Neupogen) to be considered, the following information should be provided in the BLA
 - 1) Data establishing the treatment effect size (i.e., difference in DSN between the placebo and Neupogen) in this clinical setting defined by the patient population and background chemotherapy regimen. Ordinarily, such evidence should be replicated across multiple studies.
 - 2) Justification of the proposed non-inferiority margin; the fraction of the treatment effect for the active control that is to be established for XM02 should be sufficient to confer a clinical benefit.
 - 3) The comparisons should be performed in both the intent-to-treat and the per-protocol populations. A definition for the per-protocol population should be included in the statistical analysis plan. If substantial differences are observed between the two populations, this may be indicative of poor study conduct.

- d. In light of the absence of an abbreviated approval pathway under section 351 of the PHS Act, this study will not support claims based on comparability to Neupogen nor will it support claims based on extrapolation to other indications for which Neupogen is approved.

Additional FDA Comments:

Statistical

If a BLA is submitted, please provide the following for Study XM02-02 INT:

- 4. The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the sBLA submission.
- 5. Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will be appearing in the label.

Facilities

- 6. All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include a complete list of manufacturing and testing sites with their corresponding FEI numbers in the BLA. A preliminary manufacturing schedule for both the drug

substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspection.

7. The facility diagrams in the briefing package are inadequate as it is difficult to determine the adequacy of room air classification and product and personnel flow without the knowledge of where different manufacturing stages take place. In the BLA, facility diagrams with higher resolution should be provided.
8. The CMC Drug Product part of the BLA should contain validation summary data to support the (b) (4) processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 “FDA Guidance of the Submission Documentation for Sterilization Process Validation for Human and Veterinary Products”. Please submit methods and validation information and data for the container closure integrity test under Section 3.2.P.2.5.
9. Provide the following summary validation data and information under 3.2.P.3.5:
 - a. (b) (4)
 - b. (b) (4)
 - c. in-process hold times;
 - d. summaries from three media fill runs, including summary environmental monitoring data obtained during the media fills and a description of the environmental monitoring program.
10. FDA recommends container closure integrity test in lieu of sterility test on stability samples initially, annually, and at expiry.

Pre-clinical

11. The briefing information package uses the terminology (b) (4) and XM02 to describe the nonclinical test materials. It is not clear which material was tested and how it relates to product intended for commercialization. If a BLA is submitted, please include a listing of each nonclinical lot tested, which product corresponds with which lot number, the comparability among the nonclinical lots of the different products used in the safety testing, and the comparability between the nonclinical lots and the clinical lots of XM02. If the XM02 test article used in the pivotal nonclinical studies is not comparable to the commercial product, additional studies might be needed to support the BLA.
12. Table 12 of the pre-BLA briefing information package provides a succinct listing of the nonclinical studies. In addition to providing each of these studies to the BLA, please also submit all other available relevant nonclinical data.

13. Please be aware that FDA has not made a determination regarding [REDACTED] (b) (4)

[REDACTED] The BLA (and any future BLA) should address the potential developmental and reproductive toxicity of XM02. If nonclinical developmental and reproductive toxicity data are not provided as part of the initial registration package, their absence should be scientifically justified. Please be aware that Teva cannot rely upon proprietary nonclinical data submitted to another BLA to support the safety of XM02 without written authorization from the license holder of that BLA. FDA advises that if a BLA is submitted for an indication that would include treatment of patients at risk for reproductive or developmental toxicity, and if the BLA lacks sufficient information regarding developmental and reproductive toxicity following exposure to XM02, then full nonclinical reproductive and developmental toxicity testing in pharmacologically responsive species will be required..

Clinical Pharmacology

14. In the BLA submission, pharmacokinetics study reports should also include an evaluation of the effects of covariates such as age, weight, gender, race, etc. on the pharmacokinetics of XM02.

DISCUSSION DURING THE MEETING: Teva requested clarification on the utility of covariate analysis when a homogenous population was used. FDA noted that this was a standard request for all products. FDA acknowledged the issue of a homogenous population but requested that Teva provide any available data and justify in the BLA why such special population evaluations were not necessary. Teva agreed to provide any available analyses.

15. The potential effects of XM02 on the QT interval needs to be evaluated through ECG monitoring in clinical studies following the principles discussed in the ICH-E14 guidance document (www.fda.gov/cder/guidance/6922f1.htm). Please provide all available ECG data from XM02 studies and a summary of findings in the BLA submission. The results will determine whether further QT evaluation is warranted.
16. FDA recommends that Teva conduct an *in vitro* drug-drug interaction screening study to assess any potential effects of XM02 on the activity of P450 metabolic enzymes. The results will determine whether further *in vivo* studies are necessary. For more information on designing *in vitro* drug-drug interaction studies, please see the Drug-Drug Interaction website and relevant guidance's at <http://www.fda.gov/cder/drug/drugInteractions/default.htm>.

DISCUSSION DURING THE MEETING: Teva questioned the utility of a drug-drug interaction study considering that XM02 was a large molecule with a well-known

receptor mediated pharmacological action. FDA noted that experience with other biologic molecules demonstrated that potential effects on the activity of P450 pathway could occur at the DNA or transcriptional level. FDA restated the recommendation that Teva conduct an *in vitro* drug-drug interaction study. Additionally, FDA offered that Teva could perform a literature search regarding the drug-drug interaction history of cytokines with P450 metabolic enzymes and provide justification to the FDA why an *in vitro* or *in vivo* study would not be relevant. If a literature review was not **supportive to FDA's satisfaction, then *in vitro* and possibly *in vivo* follow-up studies would need to be conducted. Teva acknowledged FDA's position.**

Clinical/Administrative

17. Please see the following attachment for general advice on BLA submissions.

General Clinical Comments Regarding the BLA Application

The BLA should contain the following:

1. Clinical study report(s) following the ICH E3 Structure and Content of Clinical Study Reports guidance (<http://www.ich.org/LOB/media/MEDIA479.pdf>).
2. Preparation of integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance document “Cancer Drug and Biological Products-Clinical Data and Marketing Applications” (<http://www.fda.gov/cder/guidance/4332fml.pdf>).
3. Assessment of safety as per the Guidance for Industry: Pre-marketing Risk Assessment <http://www.ich.org/LOB/media/MEDIA479.pdf>. Additional guidance on a good safety review can be found on the following web link: www.fda.gov/cder/guidance/3580fml.pdf
4. **Safety Analysis Plan**
In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. At a minimum the Safety Analysis Plan should address the following components:
 - a. Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/CDER/guidance/6357fml.pdf>).
 - b. Safety endpoints for Adverse Events of Special Interest (AERI)
 - c. Definition of Treatment Emergent Adverse Event (TEAE)
 - d. Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter))
 - e. Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
 - f. Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
 - g. When unanticipated safety issues are identified the QSAP may be amended.
5. Provide detailed information, including a narrative, for all patients terminating study drug/participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision.
6. Narrative summaries should contain the following components:
 - a. subject age and gender
 - b. signs and symptoms related to the adverse event being discussed
 - c. an assessment of the relationship of exposure duration to the development of the adverse event
 - d. pertinent medical history

- e. concomitant medications with start dates relative to the adverse event
 - f. pertinent physical exam findings
 - g. pertinent test results (for example: lab data, ECG data, biopsy data)
 - h. discussion of the diagnosis as supported by available clinical data
 - i. a list of the differential diagnoses, for events without a definitive diagnosis
 - j. treatment provided
 - k. re-challenge results (if performed)
 - l. outcomes and follow-up information
 - m. an informed discussion of the case, allowing a better understanding of what the subject experienced.
7. Provide complete CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs upon request.
 8. For patients listed as discontinued due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

The BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: <http://www.fda.gov/cder/mapp/6010.3.pdf>.

To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

9. Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
10. Exposure-Response Relationships - important exposure-response assessments.
11. Less common adverse events (between 0.1% and 1%).
12. Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
13. Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
14. Marked outliers and dropouts for laboratory abnormalities.
15. Analysis of vital signs focused on measures of central tendencies.
16. Analysis of vital signs focused on outliers or shifts from normal to abnormal.
17. Marked outliers for vital signs and dropouts for vital sign abnormalities.

18. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value
19. Overview of ECG testing in the development program, including a brief review of the nonclinical results.
20. Standard analyses and explorations of ECG data.
21. Overdose experience.
22. Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
23. Explorations for
 - a. Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
 - b. Dose dependency for adverse findings.
 - i. Provide summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
 - c. Time dependency for adverse finding
 - i. Provide data summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
 - d. Drug-demographic interactions
 - e. Drug-disease interactions.
 - f. Drug-drug interactions.
24. Dosing considerations for important drug-drug interactions.
25. Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

CDISC Data Requests to Sponsors

The agency strongly encourages that data be supplied in CDISC format in order to facilitate a timely review.

The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org) .

Study Data Tabulation Model (SDTM) Issues

1. The current published SDTM and SDTM Implementation Guide (SDTMIG) should be followed carefully. Refer to the SDTMIG section on Conformance (3.2.3)
2. Domains
 - a. There are additional domains listed below that are not included in the current DTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.
 - (DV) Protocol deviations
 - (DA) Drug Accountability
 - (PC, PP) Pharmacokinetics
 - (MB, MS) Microbiology
 - (CF) Clinical Findings
 - b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.
 - Tumor information
 - Imaging Data
 - Complex Inclusion/Exclusion Criteria
3. Variables
 - a. All required variables are to be included.
 - b. All expected variables should be included in all SDTM datasets.
 - c. Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.
 - d. A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.
 - e. A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.
 - f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.
4. Specific issues of note:
 - a. SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets.

- b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy should be placed in the SUPPQUAL dataset or an ADaM dataset.
- c. These issues can be addressed through the request for ADaM datasets

Analysis Data Model (ADaM) Issues

1. Specify which ADaM datasets you intend to submit.
2. Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
3. Discuss the structure of the datasets with the reviewing division and specify in the QSAP.
4. Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.
5. Indicate which core variables will be replicated across the different datasets, if any.
6. SDTM and ADaM datasets should use the unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.

General Items

1. Controlled terminology issue
 - a. Use a single version of MedDRA for a submission. Does not have to be the most recent version
 - b. We recommend that the WHO drug dictionary be used for concomitant medications.
 - c. Refer to the CDISC terminology for lab test names.
 - d. Issues regarding ranges for laboratory measurements should be addressed.

Non-CDISC Data Sets

The division requests the following for the submitted datasets:

1. All datasets should contain the following variables/fields (in the same format and coding)
 - a. Each subject should have one unique ID across the entire NDA
 - b. Study number
 - c. Treatment assignment
 - d. Demographic characteristics (age, race, gender, etc.)
2. The safety dataset that should include the following fields/variables:
 - a. A unique patient identifier
 - b. Study/protocol number
 - c. **Patient's treatment assignment**
 - d. Demographic characteristics, including gender, chronological age (not date of birth), and race
 - e. Dosing at time of adverse event
 - f. Dosing prior to event (if different)

- g. Start and stop dates for adverse events
 - h. Days on study drug at time of event
 - i. Outcome of event (e.g. ongoing, resolved, led to discontinuation)
 - j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
 - k. Marker for serious adverse events
 - l. Verbatim term
3. The adverse event dataset should include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset should also include the Verbatim term taken from the case report form. Ensure that mapping of a preferred term to the primary MSSO defined SOC level is not changed.
 4. See the attached mock adverse event data set in [figure 1](#) that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables should appear and does not address other content that is usually contained in the adverse event data set.
 5. In the adverse event data set, please provide a variable that gives the numeric MedDRA code for each lower level term.
 6. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire BLA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
 7. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.
 8. The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
 9. The concomitant medication dataset should use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
 10. Ensure that laboratory data are organized in the data sets in a standardized manner with consistent units and a single reference range for each laboratory variable. Include a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result should be in numeric format. Define the range(s), with supporting documentation, that are used to identify severe toxicity.

11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. In every dataset, all dates should be formatted as ISO date format.
13. Across all datasets, the same coding should be used for common variables, e.g. “PBO” for the placebo group. Datasets should not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable should be included in the datasets.

Common PLR Labeling Deficiencies

Highlights

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. **The drug name must be followed by the drug’s dosage form, route of administration, and controlled substance symbol.** [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must **have the verbatim statement “See full prescribing information for complete boxed warning.” Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).**
6. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line (“margin mark”) on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
7. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:
“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”
8. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
9. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).

10. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].
11. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights.
12. The Patient Counseling Information statement must appear in Highlights and must read “See 17 for PATIENT COUNSELING INFORMATION.” [See 21 CFR 201.57(a)(14)]
13. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
14. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Contents (Table of Contents)

1. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
2. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
3. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
4. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
5. When a subsection is omitted, the numbering does not change.
[See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
6. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:
 - “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

1. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).

2. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
3. **Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.**
4. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not *See Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
5. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
6. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
7. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
8. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
9. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
10. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
11. **If the “Rx only” statement appears at the end of the labeling, delete it.** This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
12. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.

13. Refer to the Institute of Safe Medication Practices' website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

Specific Electronic Common Technical Document Issues

Relating Sequences Properly

Relating sequences properly allows reviewers to easily navigate the application's original and supplemental submissions. By relating sequences correctly a reviewer can focus on the data at hand without wondering "what is missing" or "what are the reasons for this disorganized submission?" Delays in your review are also avoided.

1. First-level submission types should not use related sequence
 - a. First-level submission types are
 - i. "original-application"
 - ii. "annual-report"
 - iii. "efficacy-supplement"
 - iv. "labeling-supplement"
 - v. "chemistry-manufacturing-controls-supplement"
 - vi. "other"
2. Second-level submission types should use a single related sequence
 - a. The related sequence should always be a first-level submission type
 - b. Second-level submission types are:
 - i. "amendment"
 - ii. "resubmission"
 - c. Related Sequences are indicated in the us-regional.xml file

Submission Type	Level	Related Sequence
Original	Primary	NO
Annual Report	Primary	NO
Efficacy Supplement	Primary	NO
Labeling Supplement	Primary	NO
CMC Supplement	Primary	NO
Other	Primary	NO
Amendment	Secondary	YES
Resubmission	Secondary	YES

Code snippet examples of correct usregional.xml file submissions

An usregional.xml file for a First Level Submission

NOTE because this is a primary submission type there is NO related sequence:

```
<?xml version="1.0" standalone="no"?>
<?xml-stylesheet type="text/xsl" href="../../../util/style/us-regional.xsl" ?>
<!DOCTYPE fda-regional:fda-regional SYSTEM "../../../util/dtd/us-regional-v2-01.dtd">
<fda-regional:fda-regional xmlns:fda-regional="http://www.ich.org/fda"
xmlns:xlink="http://www.w3c.org/1999/xlink" dtd-version="2.01">
```

```
<admin>
  <applicant-info>
    <company-name> Pharma USA</company-name>
    <date-of-submission>
      <date format="yyyymmdd">20080601</date>
    </date-of-submission>
  </applicant-info>
  <product-description>
    <application-number>999999</application-number>
    <prod-name type="established">Fixitol</prod-name>
  </product-description>
  <application-information application-type="nda">
    <submission submission-type="labeling supplement">
      <sequence-number>0010</sequence-number>
    </submission>
  </application-information>
</admin>
```

In the example above the sponsor is sending in a labeling supplement and it will not have a related sequence.

In the example below the sponsor has been asked to provide some additional data to support their labeling supplement. Because it is an amendment it will need to designate a related sequence.

```
<?xml version="1.0" standalone="no"?>
<?xml-stylesheet type="text/xsl" href="../../util/style/us-regional.xsl" ?>
<!DOCTYPE fda-regional:fda-regional SYSTEM "../../util/dtd/us-regional-v2-01.dtd">
<fda-regional:fda-regional xmlns:fda-regional="http://www.ich.org/fda"
xmlns:xlink="http://www.w3c.org/1999/xlink" dtd-version="2.01">
  <admin>
    <applicant-info>
      <company-name> Pharma USA</company-name>
      <date-of-submission>
        <date format="yyyymmdd">20080705</date>
      </date-of-submission>
    </applicant-info>
    <product-description>
      <application-number>999999</application-number>
      <prod-name type="established">Fixitol</prod-name>
    </product-description>
    <application-information application-type="nda">
      <submission submission-type="amendment">
        <sequence-number>0012</sequence-number>
        <related-sequence-number>0010</related-sequence-number>
      </submission>
    </application-information>
  </admin>
```

Figure 1

Please note that the HLG T and HLT level terms in this table are from the primary MedDRA mapping only. There is no need to provide HLT or HLG T terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data that is typically found in an adverse event data set.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

MEETING ATTENDANCE LIST

Meeting between Teva Pharmaceuticals, USA and
the Center for Drug Evaluation and Research.

DATE: NOV 25, 2008 TIME: 11:00AM ET ROOM: W022 1313

NAME - Please print	AFFILIATION
Erik Laurinier	FDA
	(b) (4) CONSULTING FOR TEVA
	(b) (4) Consulting for TEVA
	(b) (4) for TEVA
Dennis Abern	Teva Neuroscience
Yafut Stark	TEVA Corporate
Ram Petter	Teva Corporate
Debbie Jaskot	TEVA USA
MIKE NICHOLAS	TEVA NeuroScience
Ivan COHEN-TANUGI	Teva Corporate
Diana Landa	TEVA USA
Yao Yao	Teva Neuroscience
Patricia Keegan	FDA/CDER/OODP/DBOP
Thomas Herndon	FDA/CDER/OODP/DBOP
Jeff Summers	" "
Anne Pizaro	FDA/CDER/OODP/DBOP/PTB
ANDREW MCDUGAL	FDA/CDER/OODP
Mary Jane Masson	FDA
Bob Chi	FDA
MaryFarbman	FDA/CDER/OC
MAAN ABDULDAYEM	FDA/CDER/OC
SANDRA J. CAROL	FDA/CDER/OODP/DBOP
Laura Lei	FDA/CDER/OTS/OB/DBV
Jeanice Weiner	FDA/CDER/ORP
Mark Rothmann	FDA/CDER/OTS/OB/DBV
William Pierce	FDA/CDER/OODP/DBOP
Jee Chung	FDA/CDER/OBP/DTP
Hong Zhao	FDA/CDER/OTS/OC/DCPS
Sarah Schriber	FDA/CDER/OTS/OC/DCPS
Emily Shacter	FDA/DTP



Teva Attendees

Dennis Ahern	Director, Regulatory Affairs, Teva Neuroscience
(b) (4)	Preclinical consultant
Ivan Cohen-Tanugi, MD, MBA	Vice President Portfolio Management, Teva
(b) (4)	Clinical consultant
(b) (4)	CMC consultant
Debbie Jaskot	Vice President, Regulatory Affairs, Teva Pharmaceuticals USA
Diana Landa	Senior Manager, Regulatory Affairs, Teva Pharmaceuticals USA
Mike Nicholas, Ph.D.	Senior Director, Strategic Regulatory Affairs & Post-Marketing Labeling/ Compliance, Teva Neuroscience
Ram Petter, Ph.D., MBA	Vice President, Biotechnology Resources, Teva
Yafit Stark, Ph.D.	Vice President, Chief Clinical Officer, Innovative R&D, Teva
Yao Yao, Ph.D.	Manager, Regulatory Affairs, Teva Neuroscience

Linked Applications

Sponsor Name

Drug Name / Subject

IND 103188

Teva Pharmaceuticals,
USA

Recombinant N-methionyl human
granulocyte colony-stimulating factor
(rmetHuG-CSF)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIK S LAUGHNER
12/19/2008