

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-311

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-311

SUPPL #

HFD # 150

Trade Name Mozobil™

Generic Name plerixafor

Applicant Name Genzyme

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, **EXPLAIN** why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====
Name of person completing form: Susan Jenney
Title: Project Manager
Date: December 4, 2008

Name of Office/Division Director signing form: Robert Justice
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Robert Justice
12/15/2008 02:44:09 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-311 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____
Division Name: Division of Drug Oncology Products PDUFA Goal Date: _____ Stamp Date: 6/16/2008
December 16, 2008

Proprietary Name: Mozobil
Established/Generic Name: plerixafor
Dosage Form: for Injection
Applicant/Sponsor: Genzyme

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(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: Enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma.

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	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 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)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Susan Jenney
8/25/2008 12:18:19 PM



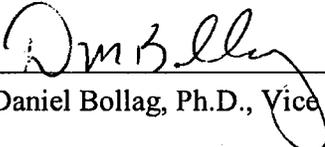
Mozobil (plerixafor)
Module 1: Administrative and Prescribing Information
US Food and Drug Administration

1.3.3 Debarment Certification

Pursuant to Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act:

Genzyme Corporation 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.

Genzyme Corporation



Daniel Bollag, Ph.D., Vice President Regulatory Affairs

17 April 2008
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-311 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Mozobil™ Established/Proper Name: plerixafor Dosage Form: Solution for Injection, 20 mg/mL		Applicant: Genzyme Corporation Agent for Applicant (if applicable):
RPM: Susan Jenney		Division: Division of Oncology Drug Products
<p>NDAs: NDA Application Type: <input checked="" 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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</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> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		December 16, 2008 December 15, 2008
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		<input checked="" type="checkbox"/> None
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed (<i>indicate dates of reviews</i>)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

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.

❖ Application ² Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 1 <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 checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) 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 <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments:	
❖ Application Integrity Policy (AIP) http://www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• If yes, exception for review granted (<i>file Center Director's memo in Administrative/Regulatory Documents section, with Administrative Reviews</i>)	<input type="checkbox"/> Yes
• If yes, OC clearance for approval (<i>file communication in Administrative/Regulatory Documents section with Administrative Reviews</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: <input checked="" type="checkbox"/>	Orphan Designation
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• 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 checked="" type="checkbox"/> Other Burst

² All questions in all sections pertain 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)? 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. 	<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? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<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? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<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? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<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)? (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.) 	<input checked="" 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 checked="" 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). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)). 	<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	
❖ Copy of this Action Package Checklist ³	December 17, 2008
Officer/Employee List	
❖ 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>)	<input checked="" type="checkbox"/> Included
Documentation of consent/nonconsent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval - December 15, 2008
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	December 15, 2008
❖ Original applicant-proposed labeling	June 16, 2008
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

³ Fill in blanks with dates of reviews, letters, etc.

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
❖ Original applicant-proposed labeling	
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	
❖ Most recent applicant-proposed labeling	December 12, 2008
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP October 31, 2008 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC November 7, 2008 and December 5, 2008 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	August 29, 2008
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If approval action, OC clearance for approval 	<input checked="" type="checkbox"/> Not on AIP
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	<input checked="" type="checkbox"/> Included
❖ 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
❖ Postmarketing Requirement (PMR) Studies <ul style="list-style-type: none"> • Outgoing communications (<i>if located elsewhere in package, state where located</i>) • Incoming submissions/communications 	<input type="checkbox"/> None Not Applicable Not Applicable
❖ Postmarketing Commitment (PMC) Studies <ul style="list-style-type: none"> • Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) • Incoming submission documenting commitment 	<input type="checkbox"/> None November 17, 2008 November 21, 2008 December 10, 2008 December 11, 2008
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	October 31, 2008 December 10, 2008 December 15, 2008
❖ Minutes of Meetings <ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) • Regulatory Briefing (<i>indicate date</i>) • Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input type="checkbox"/> Not applicable November 25, 2008 <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> No mtg October 1, 2007

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.

<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg September 10, 2004 November 17, 2004
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	
❖ 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 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None December 15, 2008
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None December 13, 2008
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None December 12, 2008
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	Concurred with review dated November 24, 2008
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	November 24, 2008 December 10, 2008 December 12, 2008
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	See Clinical Review dated November 24, 2008
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See Clinical Review dated November 24, 2008
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ REMS <ul style="list-style-type: none"> REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) Review(s) and recommendations (including those by OSE and CSS) (<i>indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None November 25, 2008
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
<ul style="list-style-type: none"> Clinical Studies 	November 13, 2008
<ul style="list-style-type: none"> Bioequivalence Studies 	
<ul style="list-style-type: none"> Clinical Pharmacology Studies 	
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 checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.

Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Concluded with review dated November 12, 2008
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None November 12, 2008
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Concluded with review dated November 17, 2008
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Concluded with review dated November 17, 2008, and December 5, 2008
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None November 17, 2008 December 5, 2008
❖ DSI Clinical Pharmacology Inspection Review Summary	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None December 3, 2008
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None December 3, 2008
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None November 14, 2008
❖ 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 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None December 8, 2008
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None December 12, 2008
• CMC/product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None December 2, 2008
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	November 12, 2008 <input type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC Review dated December 2, 2008
<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	

<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i> 	<p>Date completed:</p> <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ➤ TBP-EER ➤ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i> 	<p>Date completed:</p> <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <p>Date completed:</p> <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
<ul style="list-style-type: none"> ❖ NDAs: Methods Validation 	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

Appendix A 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/

Susan Jenney

12/17/2008 03:37:44 PM

Jenney, Susan

From: Sattarzadeh, Sherwin [Sherwin.Sattarzadeh@genzyme.com]
Sent: Thursday, December 11, 2008 6:19 PM
To: Jenney, Susan
Cc: Mondano, Laura
Subject: RE: NDA 22-311
Attachments: NDA 22311 PMC to sponsor (Genzyme's Response - Version 3).doc

Hi Susan,

Based on our last discussion this evening, please find attached an updated PMC document. As Dr. Farrell requested, we agree to amend the 3101-LTF and 3102-LTF protocols to include all patients enrolled in the 3101 and 3102 studies.

Thank you,

Sherwin
T: 617-252-7593
M: 508-202-8021

From: Sattarzadeh, Sherwin
Sent: Thursday, December 11, 2008 5:31 PM
To: 'Jenney, Susan'
Cc: Mondano, Laura
Subject: RE: NDA 22-311

Hi Susan,

Per our telephone discussion with Ann Farrell earlier this evening, please find Genzyme's updated response to the PMCs.

Thank you,

Sherwin
T: 617-252-7593
M: 508-202-8021

From: Sattarzadeh, Sherwin
Sent: Thursday, December 11, 2008 4:00 PM
To: Jenney, Susan
Cc: Mondano, Laura
Subject: RE: NDA 22-311

Hi Susan,

Please find attached Genzyme's response to the 5 PMCs. We have proposed slight revisions to the wording for PMC 1 and 2. There are currently 2 ongoing long-term follow-up studies (AMD3100-3101-LTF and AMD3100-3102-LTF). The objective of both LTF studies is to assess progression-free survival and overall survival in transplanted NHL (3101) and MM (3102) patients for a period of 4 years following the initial 12-month post-transplantation follow-up of the investigational studies. Genzyme agrees to amend these protocols to follow patients for a period of 4 years, for a total of 5 years follow-up post-transplantation as requested by the FDA. The other wording change to PMC 1 and 2 involves changing "disease-free" to (b) (4) for consistency with the ongoing LTF protocols. We propose to include the 3101-LTF and 3102-LTF status reports as part of the annual progress report for post marketing commitments. Per the regulations the first annual report will be submitted within 60 days of the first anniversary of the marketing approval (i.e. by 13 February 2010). Updated progress reports will be submitted annually thereafter until study completion.

In regards to PMC 5 (lower weight NHL dosing study), the provided dates are Genzyme's best estimates. Both the study start date and study completion date are dependent on study design, patient population, and enrollment rate.

Please confirm that you have received this email and feel free to contact me if you have any questions or comments.

12/15/2008

Sherwin
T: 617-252-7593
M: 508-202-8021

From: Jenney, Susan [mailto:susan.jenney@fda.hhs.gov]
Sent: Wednesday, December 10, 2008 2:30 PM
To: Sattarzadeh, Sherwin
Cc: Mondano, Laura
Subject: NDA 22-311

Good afternoon:

Please refer to your NDA 22-311 (Mozobil) submitted on June 16, 2008. The attached file has the PMCs for your application. Note that the numbering has been changed for the PMCs.

(b) (4)

Please provide specific dates for all 5 of the PMC timelines (for example: January 1, 2009). Please let me know when you will be able to respond.

In regards to your e-mail sent on December 5, 2008, you may use the numbers you have proposed for the safety section. Let me know if you still want to have the meeting today. The meeting was set up as requested in your November 24, 2008, e-mail to discuss the PMCs.

Contact me if you have any comments or questions. Please confirm you have received this e-mail.

Thank you,
Susan

<<NDA 22311 PMC to sponsor.doc>>

Susan Jenney, MS
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-0062
301-796-9845 (FAX)
Susan.Jenney@fda.hhs.gov

2 Page(s) Withheld after this page as B4 (CCI/TS)

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/s/

Susan Jenney
12/15/2008 11:16:59 AM
CSO

Jenney, Susan

From: Jenney, Susan
Sent: Friday, December 12, 2008 6:04 PM
To: 'Sattarzadeh, Sherwin'
Cc: Mondano, Laura; Jenney, Susan
Subject: NDA 22-311 labeling changes

Attachments: NDA 22311 label FDA changes 12dec2008.doc

Dear Sherwin:

We have reviewed your label for NDA 22-311 submitted earlier today and have some changes (see the attached file). Please let me know your response to the changes.

Contact me if you have any comments or questions. Please confirm you have received this e-mail.

Thank you,
Susan



NDA 22311 label
FDA changes 12...

Susan Jenney, MS
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-0062
301-796-9845 (FAX)
Susan.Jenney@fda.hhs.gov

**14 Page(s) of Draft Labeling are Withheld after this
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/s/

Susan Jenney
12/15/2008 11:11:06 AM

MEMORANDUM

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

DATE: December 12, 2008

TO: NDA #22-311

FROM: Michael Brave, M.D.
Medical Officer, OND/DDOP

SUBJECT: Mozobil (plerixafor) post-marketing safety meeting

ATTENDEES: Kendra Worthy, OSE/DRISK
Corrinne Kulick, OSE/DAEA II
Cathy Miller, OSE/DMEDP
Sandra Griffith, OSE
JuWon Lee, OMP/DDMAC
Robert Boucher, OND/DPAP
Ann Farrell, M.D., OND/DDOP
Michael Brave, M.D., OND/DDOP
Kun He, Ph.D., OTS/OB/DBV
Shwu-Luan Lee, Ph.D., OND/DDOP
Amy Tilley, OND/DDOP
Alice Kacuba, OND/DDOP

Representatives from DDOP and the Office of Surveillance and Epidemiology met on November 25, 2008 to discuss potential toxicities of Mozobil (plerixafor) that will require post-marketing pharmacovigilance. The theoretical possibility that Mozobil may mobilize tumor cell would best be addressed by long-term follow-up of patients enrolled in the randomized studies 3101 and 3102. The Applicant has agreed as a post-marketing commitment to follow patients in 3101 and 3102 for relapse rate and mortality for five years, and to submit a final study report to the FDA when complete. OSE will monitor closely for other potential toxicities following approval, including thrombocytopenia, splenomegaly and splenic rupture, cardiovascular ischemia, systemic reactions (i.e. hypersensitivity), and peripheral neuropathy.

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/s/

Michael Brave
12/12/2008 10:03:31 AM
MEDICAL OFFICER

Ann Farrell
12/12/2008 12:09:37 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE:

December 15, 2008

APPLICATION NUMBER: NDA 22-311, Mozobil (plerixafor injection)

BETWEEN:

Name: Sherwin Sattarzadeh
Phone: 617-252-7596
Representing: Genzyme

AND

Name: Susan Jenney
Division of Drug Oncology Products, HFD-150

SUBJECT: Confirmation of sponsor receipt of action letter for NDA 22-311.

A copy of the official action letter was e-mailed to Sherwin Sattarzadeh and Laura Mondano on December 15, 2008 at 4:37 PM. On December 15, 2008, at 4:40 PM, Sherwin Sattarzadeh called to confirm the receipt of the action letter.

{See appended electronic signature page}

Susan Jenney
Project Manager

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/s/

Susan Jenney
12/15/2008 04:48:34 PM
CSO

MEMORANDUM OF TELECON

DATE: December 10, 2008

APPLICATION NUMBER: NDA 22-311

BETWEEN:

Name: Frank Hsu (Sr Medical Director, Clinical Research)
Pat Fraser (Medical Director, Pharmacovigilance)
Jennifer Angell (Director, Biostatistics)
Marjie Hard (Principal Pharmacokinetics Analyst)
Sara Saltzman (Principal Associate, Reg Affairs)
Laura Mondano (Director, Reg Affairs)
Dan Bollag (Vice President, Reg Affairs)
Sherwin Sattarzadeh (Principal Associate, Reg Affairs)
Tammara Lewis (Director, Regulatory Affairs)
Phone: 1-866-617-3597 code 8782673
Representing: Genzyme

AND

Name: Robert Justice, Division Director
Ann Farrell, Deputy Division Director
Michael Brave, Medical Officer
Susan Jenney, Project Manager
Division of Drug Oncology Products, HFD-150

SUBJECT: Discussion concerning e-mail dated December 5, 2008

NDA 22-311 (Mozobil) was submitted on June 16, 2008, for enhancing mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma. During the review of the submission, several PMCs were identified. A teleconference was scheduled to discuss outstanding labeling and PMC issues.

PMC issues discussed include the timing of the submission of the completed thorough TQT study and the Agency's request to receive 5 years of additional follow-up information on Studies 3101 and 3102. The sponsor plans to submit the final study report and data from the completed thorough TQT study in January 2009. The sponsor noted that previously the two protocols have been amended to collect 2 additional years of follow-up information and did not think the requirement to provide a total of five additional years would be problematic. The sponsor agreed to provide 5 additional years of follow-up information regarding disease status (including relapse and death).

Labeling issues discussed included whether the information on G-CSF can be added to the section under Warnings and Precautions regarding the Potential for Tumor Cell Mobilization, the appropriate denominators for the label's safety tables, whether a general statement regarding engraftment and graft durability could be placed in the label and whether the recent revisions to the carton and container labeling were acceptable.

{See appended electronic signature page}

Ann Farrell
Deputy Division Director

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/s/

Susan Jenney
12/12/2008 09:30:21 AM
CSO

Ann Farrell
12/12/2008 12:08:55 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: October 31, 2008

APPLICATION NUMBER: NDA 22-311

BETWEEN:

Name: Laura Mondano, Director, Regulatory Affairs

Phone: 1-866-818-1634 passcode 7576266#

Representing: Genzyme

Other Genzyme attendees:

Frank Hsu (Sr Medical Director, Clinical Research)

Pat Fraser (Medical Director, Pharmacovigilance)

Jennifer Angell (Director, Biostatistics)

Marjie Hard (Principal Pharmacokinetics Analyst)

Sara Saltzman (Principal Associate, Reg Affairs)

Dan Bollag (Vice President, Reg Affairs)

Sherwin Sattarzadeh (Principal Associate, Reg Affairs)

Gary Calandra (Clinical Research)

AND

Name:

Jeanne Fourie, Clinical Pharmacology Reviewer

Brian Booth, Ph.D., Deputy Director, Division of Clinical Pharmacology 5

Christoffer Tornoe, Pharmacometrics Reviewer

Yaning Wang, Ph.D., Team Leader Pharmacometrics

Michael Brave, M.D., Medical Officer, DDOP

Anne Farrell, M.D., Deputy Director, Division of Drug Oncology Products

Susan Jenney, M.S., Regulatory Health Project Manager

SUBJECT: Discuss responses to the Office of Clinical Pharmacology recommendations.

NDA 22-311 for Mozobil (plerixafor) Injection was received on June 16, 2008. During the review of the submission, Clinical Pharmacology recommended an alternative dosing regimen. An information request was sent on October 8, 2008, and the Sponsor responded on October 21, 2008. After reviewing the response, Clinical Pharmacology requested a teleconference with the Sponsor to discuss the dose adjustment in patients that weigh < 85 kg and patients with severe and moderate renal impairment.

The sponsor discussed their rationale for not adjusting the dose in patients less than 85 kg. The FDA discussed the results from their population PK analysis indicating that patients with low body weight have a decreased exposure which could contribute to a lower response compared to patients weighing more than 85 kg.

The FDA discussed the results from the renal impairment study indicating that patients with moderate impairment have a higher exposure than those with normal function. The increase is equal to that of severe patients. Therefore, the dose reduction to match exposure to that of normal patients should be done in patients with severe and moderate impairment. The FDA also stated that matching the exposure was the basis for the proposed dose adjustment in patients less than 85 kg.

The Sponsor will send the following items in one week:

- The results from their ANCOVA (for high low body weight effect on response rate) in which they correct for differences in baseline CD34+.
- The rationale and details (background) for the argument that the fold increase from the baseline CD34+ count is the factor limiting response (total CD34+ count per kg).

{See appended electronic signature page}

Brian Booth, Ph.D.
Deputy Director, Division of Clinical Pharmacology 5

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/s/

Susan Jenney
11/3/2008 01:03:13 PM
CSO

Brian Booth
11/4/2008 07:23:01 AM
BIOPHARMACEUTICS

Jenney, Susan

From: Jenney, Susan
Sent: Friday, December 05, 2008 3:58 PM
To: Jenney, Susan; 'Sattarzadeh, Sherwin'
Cc: 'Mondano, Laura'
Subject: RE: NDA 22-311 - label 2

Good afternoon:

We have another correction for the label. Please list vomiting in the sentence starting with "The most common adverse reactions" found under section 6.1 (Adverse Events - Clinical Trial Experience). The table states vomiting as 10% but vomiting is not listed in the sentence mentioned above.

Thank you,
Susan

From: Jenney, Susan
Sent: Friday, December 05, 2008 9:10 AM
To: 'Sattarzadeh, Sherwin'
Cc: Mondano, Laura
Subject: NDA 22-311 - label 2

Good morning Sherwin and Laura:

We have a response concerning the prominence of the tradename and our responses to the package insert. This label does not yet reflect input from all management levels. The package insert is attached and the comments for the tradename are below.

2 Page(s) Withheld after this page as B4 (CCI/TS)



We will need your responses in order to continue with our review. Let me know when you will be able to respond.

Contact me if you have any comments or questions. Please confirm you have received this e-mail.

12/5/2008

Thank you,
Susan

Susan Jenney, MS
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-0062
301-796-9845 (FAX)
Susan.Jenney@fda.hhs.gov

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/s/

Susan Jenney
12/8/2008 01:54:24 PM

Jenney, Susan

From: Jenney, Susan
Sent: Thursday, December 04, 2008 11:19 AM
To: 'Sattarzadeh, Sherwin'
Cc: Mondano, Laura
Subject: RE: NDA 22-311 - label

Good morning Sherwin:

We have been reviewing the label and have requests and responses below. Please revise section 8.5 and get back to me ASAP. Let me know when you would be able to send your amended language.

We are still working on the post marketing commitments and will contact you later concerning your request for a teleconference.

Thank you,
Susan

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

From: Sattarzadeh, Sherwin [mailto:Sherwin.Sattarzadeh@genzyme.com]
Sent: Tuesday, December 02, 2008 1:41 PM
To: Jenney, Susan
Cc: Mondano, Laura; Kacuba, Alice
Subject: RE: NDA 22-311 - label

Hi Susan,

12/4/2008

Please find attached Genzyme's comments on Sections 7 and 12.3 of the label. I hope this facilitates the Agency review team's meeting later this afternoon. For ease of review, we accepted all text changes from FDA and worked from the clean FDA version. Please feel free to contact either myself or Laura Mondano (617-591-5994) if you have any questions.

Alice had asked me last Friday to submit to the electronic document room Genzyme's Nov. 26th responses back to the FDA's initial label comments. Unless you have any objections, we will consolidate our initial response with the one attached here so that we may submit one revised label to the EDR tomorrow.

Thank you,

Sherwin
T: 617-252-7593
M: 508-202-8021

From: Jenney, Susan [mailto:susan.jenney@fda.hhs.gov]
Sent: Monday, December 01, 2008 6:14 PM
To: Sattarzadeh, Sherwin
Cc: Mondano, Laura; Kacuba, Alice
Subject: RE: NDA 22-311 - label

Hi Sherwin:

Thank you for your updated labeling for NDA 22-311 (Mozobil) in the e-mail below. During the review of your updated label, the Clinical Pharmacology reviewer has the following response to your clarification concerning the 40 mg/day limit:

In the phase 3 clinical trials, the recommended Mozobil dose (0.24 mg/kg) was administered to patients with body weight up to 160 kg. The mg/kg based dosage calculation would result in administration of a 40 mg dose to a 160 kg patient. The 40 mg/day dose is the highest absolute dose and exposure studied in the phase 3 trials.

We have also completed our comments for Sections 7 and 12.3 in the label. The file containing only those 2 sections is attached. To make it easier, I have deleted the sections that were sent to you on Nov. 21, 2008. The file only contains sections 7 and 12.3.

Please send your responses as soon as possible. Let me know if you are able to respond by 2 PM tomorrow. You can also send me any comments about our clarification to the 40 mg/day limit.

Contact me if you have any comments or questions. Please confirm you have received this e-mail.

Thank you,
Susan

From: Sattarzadeh, Sherwin [mailto:Sherwin.Sattarzadeh@genzyme.com]
Sent: Wednesday, November 26, 2008 3:22 PM
To: Jenney, Susan; Kacuba, Alice
Cc: Mondano, Laura
Subject: RE: NDA 22-311 - label

Hi Susan and Alice,

Attached is Genzyme's proposed Mozobil labeling text based on FDA comments received 21 November 2008. For ease of review, we accepted all text changes from FDA and worked from the clean FDA version. Please feel free to contact either myself or Laura Mondano (617-591-5994) if you have any questions.

Thank you,

Sherwin
T: 617-252-7593
M: 508-202-8021

From: Jenney, Susan [mailto:susan.jenney@fda.hhs.gov]
Sent: Friday, November 21, 2008 5:14 PM
To: Sattarzadeh, Sherwin
Cc: Mondano, Laura; Kacuba, Alice
Subject: RE: NDA 22-311 - label

Good afternoon Sherwin and Laura:

Please refer to your NDA 22-311 for Mozobil submitted on June 16, 2008. The attached file is our revisions to the label. Sections 7 and 12.3 are still under discussion and have been deleted from the file. We are having meetings to discuss sections 7 and 12.3 and our revisions will be communicated to you when our revisions are complete. We request your response by Monday, December 1, 2008, at 9 AM. Please confirm you received this e-mail. If you have any questions you can contact me or Alice Kacuba at 301-796-1381.

Thank you,
Susan

Susan Jenney, MS
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-0062
301-796-9845 (FAX)
Susan.Jenney@fda.hhs.gov

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/s/

Susan Jenney
12/8/2008 02:01:36 PM

Jenney, Susan

From: Jenney, Susan
Sent: Friday, November 21, 2008 11:54 AM
To: 'Sattarzadeh, Sherwin'
Cc: Mondano, Laura
Subject: RE: NDA 22-311 - post marketing commitments

Good morning Sherwin and Laura:

(b) (4)

Protocol submission Date:
Study Start Date:
Study Completion Date:
Date for Study Report and Data Submission to the Agency:

Please fill in the time line for this commitment and let me know the timeline you have proposed. Please confirm you have received this e-mail. Contact me if you have any comments or questions.

Thank you,
Susan

From: Jenney, Susan [mailto:susan.jenney@fda.hhs.gov]
Sent: Monday, November 17, 2008 4:00 PM
To: Sattarzadeh, Sherwin
Cc: Mondano, Laura
Subject: NDA 22-311 - post marketing commitments

Good afternoon:

Please refer to your NDA 22-311 for Mozobil submitted on June 16, 2008. During our review of your submission, we have 3 post marketing commitments (listed below). Please fill in the time line for the commitments and let me know the timelines you have proposed.

1. Genzyme agrees to screen plerixafor in vitro to assess whether it is a substrate and inhibitor of P-glycoprotein. Depending on the results of this study, an in vivo drug-drug interaction study may be needed.
Study Start:
Final Report Submission:
2. Genzyme agrees to submit the final study report and data from the thorough QT/QTc study report upon its completion.
Protocol Submission:
Study Start:
Final Report Submission:

(b) (4)

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The redaction covers the top portion of the page, starting below the header and extending across most of the width. The text "(b) (4)" is visible in the top-left corner of this redacted area.

Contact me if you have any comments or questions. Please confirm you have received this e-mail.

Thank you,
Susan

Susan Jenney, MS
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-0062
301-796-9845 (FAX)
Susan.Jenney@fda.hhs.gov

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/s/

Susan Jenney
11/21/2008 12:03:19 PM

Jenney, Susan

From: Jenney, Susan
Sent: Friday, November 14, 2008 4:22 PM
To: 'Sattarzadeh, Sherwin'
Cc: Mondano, Laura
Subject: NDA 22-311

Good afternoon Sherwin:

Please refer to your NDA 22-311 (Mozobil). During the review of your submission, we have the following comments:

(b) (4)



If you have any comments or questions, contact me. We need responses in order for us to continue our review. We request a response as soon as possible. Please confirm you have received this e-mail.

Thank you,
Susan

Susan Jenney, MS
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-0062
301-796-9845 (FAX)
Susan.Jenney@fda.hhs.gov

Jenney, Susan

From: Sattarzadeh, Sherwin [Sherwin.Sattarzadeh@genzyme.com]
Sent: Wednesday, November 12, 2008 12:47 PM
To: Jenney, Susan
Cc: Mondano, Laura
Subject: RE: NDA 22-311 question

Hi Susan,

In the plerixafor program, investigation of lymphoma and multiple myeloma tumor cell mobilization has been conducted in four Phase 2 studies (AMD3100-2101, 2102, 2103, and EU21) and one Phase 3 study (AMD3100-3101). Investigation of leukemia tumor cell mobilization has been conducted in the compassionate use program (AMD3100-CUP001) and one Phase 2 study (AMD3100-2112). The following reports summarizing these investigations are included in Module 5, Section 5.3.5.4 of the NDA:

amd3100-2102-tcm
amd3100-2103-tcm
amd3100-eu21-tcm
amd3100-2101-amd3100-3101-tcm
amd3100-cup001-amd3100-2112-aml-tcm

Please also refer to the Integrated Summary of Safety Section 9.4.5 for a summary and discussion of the results from each of these studies. Note that protocols 2102, 2103, EU21, and 2112 prospectively included tumor cell analysis whereas studies 2101, 3101 and the CUP did not. Available blood samples from several patients who participated in studies 2101, 3101 and the CUP were retrospectively tested for tumor cell contamination.

As we discussed earlier today, please don't hesitate to call Laura or I if there is anything we can do to facilitate your review on this topic.

Thank you,

Sherwin
T: 617-252-7593
M: 508-202-8021

From: Jenney, Susan [mailto:susan.jenney@fda.hhs.gov]
Sent: Monday, November 10, 2008 4:53 PM
To: Sattarzadeh, Sherwin
Subject: RE: NDA 22-311 question

Thank you!

From: Sattarzadeh, Sherwin [mailto:Sherwin.Sattarzadeh@genzyme.com]
Sent: Monday, November 10, 2008 4:52 PM
To: Jenney, Susan; Mondano, Laura
Subject: RE: NDA 22-311 question

Hi Susan,

We have received your email and are working to reply this week.

Thank you,

Sherwin
T: 617-252-7593
M: 508-202-8021

From: Jenney, Susan [mailto:susan.jenney@fda.hhs.gov]
Sent: Monday, November 10, 2008 12:20 PM
To: Mondano, Laura

11/13/2008

Cc: Sattarzadeh, Sherwin
Subject: NDA 22-311 question

Good afternoon, Laura:

Please refer to your NDA 22-311 (Mozobil) submitted on June 16, 2008. During the review of your submission, we have the following information request:

What studies did you conduct to specifically ascertain whether or not tumor cells are mobilized?

Please confirm receipt of this e-mail and when you will be able to reply. Contact me if you have any comments or questions.

Thank you,
Susan

Susan Jenney, MS
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-0062
301-796-9845 (FAX)
Susan.Jenney@fda.hhs.gov

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/s/

Susan Jenney
11/13/2008 03:36:46 PM
CSO

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/s/

Susan Jenney
11/17/2008 05:10:52 PM

CLINICAL INSPECTION SUMMARY

DATE: November 13, 2008

TO: Susan Jenney, Regulatory Project Manager
Michael Brave, Medical Officer
Division of Drug Oncology Products

FROM: Robert Young
Good Clinical Practice Branch 2
Division of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22 311

APPLICANT: Genzyme Corporation

DRUG: Mozobil (plerixafor)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: Enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma.

CONSULTATION REQUEST DATE: 17 July 2008

DIVISION ACTION GOAL DATE: 16 Dec 2008

PDUFA DATE: 16 Dec 2008

I. BACKGROUND:

Genzyme submitted this NDA for the use of the new molecular entity, plerixafor, to facilitate the collection of hematopoietic stem cells by patients with non-Hodgkin’s lymphoma or multiple myeloma undergoing autologous stem cell transplantation. This application is supported by two adequate and well controlled studies, AMD3100-3101 and AMD3100-3002, which were conducted at 40 centers in the United States.

Three academic sites were selected for audit: Washington University of Medicine (Dr. DiPersio), University of Pennsylvania (Dr. Stadtmauer), and Mayo Clinic (Dr. Micallef). The reviewing division reports the DiPersio site enrolled the largest number of subjects and reported the second largest number of protocol violations 460 in all and the largest number of major protocol violations 40 in all. The Stadtmauer site enrolled the third largest number of subjects and had the largest number of total protocol violations 638 in all and the second largest number of major protocol violations 30 in all. The Micallef site had 351 total protocol violations.

The protocols inspected include:

AMD 3100-3101 – “A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Comparative Trial of AMD3100 (240 µg/kg) Plus G-CSF (10 µg/kg) Versus G-CSF (10 µg/kg) Plus Placebo to Mobilize and Collect $\geq 5 \times 10^6$ CD34+ cells/kg in Non-Hodgkin’s Lymphoma Patients for Autologous Transplantation”

AMD 3100-3102 – “A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Comparative Trial of AMD3100 (240 µg/kg) Plus G-CSF (10 µg/kg) Versus G-CSF (10 µg/kg) Plus Placebo to Mobilize and Collect $\geq 6 \times 10^6$ CD34+ cells/kg in Multiple Myeloma Patients for Autologous Transplantation”

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
Edward Stadtmauer Philadelphia	AMD 3100-3102 33 subjects	Closed 27 Oct 2008	Pending Interim classification: VAI
Ivana Micallef Rochester, MN	AMD 3100-3101 36 subjects	23 – 26 Sept 2008	Pending Interim classification: NAI
John DiPersio St. Louis	AMD 3100-3101 34 subjects AMD 3100-3102 34 subjects	23-30 Sept 2008	Pending Interim classification: NAI
Genzyme Corp. Cambridge, MA	AMD 3100-3101 AMD 3100-3102	6-20 October 2008	Pending Interim classification: VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.

1. Edward Stadtmauer
University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104

Note: Observations noted below are based on the Form FDA 483 and communications with the field investigator, an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** At this site 33 subjects were enrolled. Records of 11 subjects were inspected. There were no limitations to the inspection.
 - b. **General observations/commentary:** The CD 34+ levels for 9 of the 11 subjects records reviewed were not fully documented and for 5 of the 11 subject records reviewed SAEs were not timely reported to the sponsor. A 483 was issued with these observations. There was no evidence of underreporting of AEs and the primary efficacy endpoint data could be verified.
 - c. **Assessment of data integrity:** The data appears to be acceptable in support of the pending application
2. Ivana Micallef
Mayo Clinic Rochester
200 First St.
Rochester, MN 55905

Note: this assessment is based on the EIR.

- a. **What was inspected:** In this study 36 subjects were enrolled. The records of 12 subjects were reviewed. There were no limitations to the inspection.
- b. **General observations/commentary:** There were no significant findings and no Form FDA 483 was issued. There was no evidence of underreporting of adverse events or enrollment of ineligible subjects.
- c. **Assessment of data integrity:** The data from this site is acceptable in support of the pending application

3. John DiPersio
Washington University
School of Medicine
660 S. Euclid Avenue
St. Louis, MO 63110

Note: this assessment is based on a review of the EIR.

- c. **What was inspected:** For protocol AMD 3100-3101, 34 subjects were enrolled and the records of 20 were reviewed. For protocol AMD 3100-3102, 34 subjects were enrolled and the records of 15 were reviewed. There were no limitations to the inspection.
- d. **General observations/commentary:** There were no significant findings and no 483 was issued. There was no evidence of underreporting of adverse events and all subjects appeared to meet the eligibility requirements.
- c. **Assessment of data integrity:** The data are acceptable in support of the pending application

4. Genzyme
500 Kendall Street
Cambridge, MA 02142

Note: Observations noted below are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- a. **What was inspected:** For AMD 3100-3101, nine subject records from site 03 and seven subject records from site 05 were reviewed. For AMD 3100-3102, seven subject records from site 03 and twelve subject records from site 18 were reviewed. The records appeared to be in order. There were no limitations to the inspection.
- b. **General observations/commentary:** The sponsor did not promptly bring investigators into compliance with their signed agreement among other things failing to submit AEs in a timely manner, using the most current informed consent, etc. The sponsor failed to implement its own monitor plan allowing some sites to initiate the study without having attended the investigator's meeting or having a site initiation visit. Each of these observations was the subject of the issued 483.

The applicant of this NDA was not the sponsor of the IND study, which was sponsored by AnorMED. AnorMED was acquired by Genzyme after the IND

study had been initiated and was well underway. When Genzyme purchased AnorMED it brought AnorMED's product line, but not necessarily AnorMED regulatory failures. AnorMED has since folded (Dec 2007). July 2006 - enrollment closed for AMD 3100-3102, and Oct 2006 for AMD 3100-3101. Genzyme acquired AnorMED in Nov 2006.

- c. **Assessment of data integrity:** The data are acceptable in support of the pending application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites, and the applicant were inspected as part of the data audit for this application. Data appears to be valid and may be used in evaluating this NDA.

Note that for Dr. Stadtmauer's and Genzyme's site audits, observations are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

Robert Young
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

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/s/

Robert Young
11/13/2008 08:46:53 AM
MEDICAL OFFICER

Tejashri Purohit-Sheth
11/13/2008 04:03:02 PM
MEDICAL OFFICER



NDA 22-311

Genzyme Corporation
Attention: Laura Mondano
Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Mondano:

Please refer to your new drug application (NDA) submitted on June 16, 2008, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mozobil™ (plerixafor injection).

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Tighten the acceptance criteria for (b) (4) in the proposed drug substance specification based on the capability of the proposed drug substance manufacturing process.
2. Use appropriate decimal places for the acceptance criteria for impurities in the drug substance and drug product, in accordance with ICH Q3A and Q3B. For example, ICH Q3A specifies that two decimal places (e.g., 0.06 percent, 0.13 percent) be used for impurities below 1.0 percent. Therefore, revise the acceptance criterion for “any other single unspecified impurity” from the currently proposed (b) (4) in the drug substance specification. Revise the acceptance criteria for all other impurities accordingly.
3. Provide data to show whether starting material (b) (4) is genotoxic. Test and appropriate acceptance criteria for residual (b) (4) should be included in the specification for intermediate (b) (4). Provide data to show that (b) (4) is controlled below the threshold of toxicological concern (TCC) of 1.5 µg/day in the drug substance if data is not provided to show that it is not potentially genotoxic.
4. The weight of desiccant used in the stability samples for the drug substance stability studies (b) (4) is proportionally more than that used in the proposed storage conditions for the drug substance (b) (4) of drug substance). Please provide justification.

5. The proposed range for osmolality (b) (4)) appears to be wider than the \pm (b) (4) range obtained from the batch and stability data. Tighten the acceptance criteria for osmolality in the drug product specification based on the batch data and the physiological osmolality.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope, Ph.D.
Branch Chief (Acting)
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Sarah Pope
11/6/2008 11:29:34 AM

Jenney, Susan

From: Jenney, Susan
Sent: Wednesday, November 05, 2008 8:17 AM
To: 'Mondano, Laura'
Cc: Sattarzadeh, Sherwin; Jenney, Susan
Subject: NDA 22-311 - Clarification request

Good morning:

Please refer to your NDA 22-311 (Mozobil) submitted on June 16, 2008. We have a clarification request unrelated to your recent e-mail for the statistician. The Pharm/Tox reviewer has requested the following clarification:

- According to Table 2.4-2 and Table 2.4-3 (Module 2.4, nonclinical overview), the batch used in most of the toxicology studies was # 93802. However, in the individual studies, the batch number of test drug (plerixafor (b) (4) was #Y021 0294. Please provide comparative batch data for these two batches.

Please provide the information as soon as possible in order for us to continue our review. Contact me if you have any comments or questions. Please confirm you have received this e-mail and a timeline when you would be able to provide this information.

Thank you,
Susan

Susan Jenney, MS
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-0062
301-796-9845 (FAX)
Susan.Jenney@fda.hhs.gov

11/5/2008

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/s/

Susan Jenney
11/5/2008 08:22:17 AM



INFORMATION REQUEST LETTER

NDA 22-311

Genzyme Corporation
Attention: Laura Mondano
Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Mondano:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mozobil (plerixafor) Injection.

We are reviewing your submission and have the following labeling comments from the CMC Reviewers. We request a prompt written response in order to continue our evaluation of your NDA.

1. The following comments pertain to the container labels:

- (a) Inconsistencies have been noted in the presentation of the proprietary name and established name. They are presented as (b) (4) in the package insert, but as “Mozobil (plerixafor injection)” in the container label and carton labeling. Please be consistent in the presentation of the drug name. If the proprietary name “Mozobil” is meant for the injection only, use “Mozobil (plerixafor injection)” for the package insert and the following presentation for container label and carton labeling:

Mozobil
(plerixafor injection)

Use the following presentation for the package insert, container label, and carton labeling if the proprietary name “Mozobil” may be used for other dosage forms in addition to the injection:

(b) (4)

- (b) Unit-dose injectables should be labeled primarily in terms of total amount (with prominent expression in bold characters), followed immediately by contents per mL enclosed by parentheses. Refer to USP<1> Injections. Therefore, revise the presentation of the strength and content from the current “20 mg/mL solution, Delivers: 1.2 mL” to the following:

24 mg/1.2 mL
(20 mg/mL)

- (c) Increase the prominence of the nonproprietary name to at least half that of the proprietary name. Please note that prominence includes a combination of font shape, size, font color, and overall visual appeal.
- (d) (b) (4) 
- (e) Please economize on the area used for the lot number and expiration date and create more space to accommodate better prominence for drug name, total amount and strength, and other important information.

2. The following comments pertain to the carton labeling:

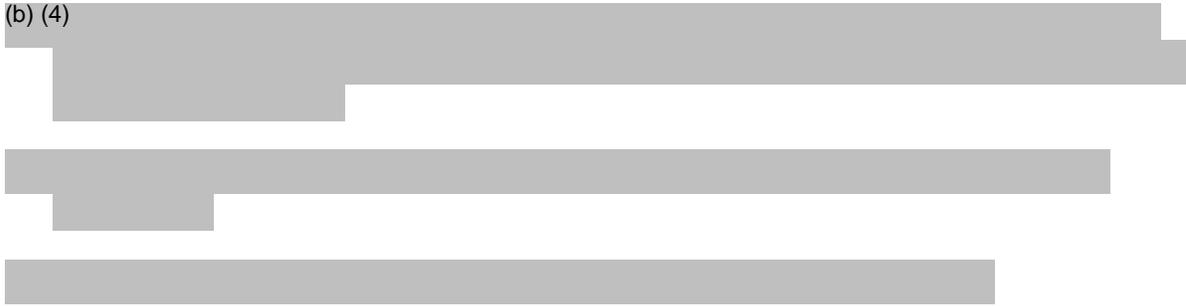
- (a) Comments #1(a) through #1(d) for container labels, as listed above, also apply to carton labeling. Revise the carton labeling accordingly.
- (b) The graphic design containing “Genzyme” appears to take too much space. Remove or reduce the graphic design to create more space to accommodate better prominence for drug name, total amount and strength, and other important information.
- (c) Revise the quantitative ingredient information on the side panel of the carton to the following:

Each mL of the sterile solution contains 20 mg of plerixafor. Each single-use vial delivers 1.2 mL of the sterile solution that contains 24 mg of plerixafor and 5.9 mg of sodium chloride in Water for Injection adjusted to a pH of 6.0 to 7.5 with hydrochloric acid and with sodium hydroxide, if required. Contains no preservatives.

- (d) Move the statement of “For single use only” from the (b) (4)  to the main display panel.

3. The following comments pertain to the Drug Listing Data Element (DLDE) of the Structured Product Labeling (SPL):

(b) (4)

The text "(b) (4)" is followed by three large rectangular grey redaction boxes covering the majority of the page's content.

We also have the following comments from the Division of Medication Error Prevention and Analysis (DMEPA):

1. The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proprietary name, Mozobil, for this product at this time. If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding. Furthermore, this name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approval of other proprietary or established names from the signature date of this document
2. The Division of Medication Error Prevention and Analysis has identified the areas of needed improvement in the container labels and carton labeling and provides the following recommendations:

Revise the font color used to display the proprietary name 'Mozobil' and the established name, 'Plerixafor Injection' on container labels and carton labeling to a more prominent and visible color and increase the size of the established name to at least half that of the proprietary name in accordance with 21CFR 201.10(g)(1). The font color used to display the proprietary name and the established name is very light, does not afford sufficient color contrast and makes it difficult to visualize on both the container labels and carton labeling. The proprietary name is a critical identifier of a drug product and as such, should be the most prominently displayed feature in order to assure accurate product selection and minimize medication error that could result from name confusion.

3. Resolve the discordance between the expression of units of measure on container labels/carton labeling (b) (4)) and the expression of units of measure in the package insert labeling (b) (4)). This inconsistent presentation of the units of measure could lead to dosage calculation error occurring due to inaccurate conversion of (b) (4) or vice versa, potentially resulting in under-dosing or overdosing of Mozobil. Though the package insert labeling defines the unit of measure, along with the calculation for dosing administration, discordance between units of measure

used on container labels/carton labeling, and the package insert labeling could potentially cause confusion in dose calculation should practitioners fail to cross-reference all labeling sources. In order to provide clear communication of product information in labeling, and avoid the need to convert between different units of measure, labeling should be consistently reflected in the same units of measure for container labels, carton labeling and package insert labeling. Since the container labels and carton labeling currently provide a clear presentation of the units of measure in milligrams, **we recommend you use milligrams as the unit of measure for all labeling including container labels, carton labeling, and package insert labeling.**

If you have any questions, call Susan Jenney, Regulatory Project Manager, at (301) 796-0062.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
(Acting) Chief, Project Management Staff
Division of Drug Oncology Products
Office of Drug Oncology Products
Center of Drug Evaluation and Research

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/s/

Alice Kacuba
10/30/2008 06:28:25 PM

FAX



**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705

To: Laura Mondano

From: Susan Jenney, MS

FAX:

FAX: 301-796-9845

E-mail: Laura.Mondano@genzyme.com

E-mail: Susan.Jenney@fda.hhs.gov

Phone: 617-591-5994

Phone: 301-796-0062

Pages, including cover sheet: 3

Date: October 22, 2008

RE: Information Requests for NDA 22-311

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address below by mail. Thank you.

Dear Ms. Mondano:

Please refer to your New Drug Application (NDA 22-311) for Mozobil (plerixafor) Injection submitted on June 16, 2008. During our review of the Clinical Pharmacology section of your submission, we have the following Information Requests:

Please replicate the table on page 17 of the AMD31001101 PK report (below) for the data that were not dose normalized.

(b) (4)



These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application.

In order for us to complete our review, please respond to these requests by no later than October 29, 2008, at noon. Please submit an amendment to your application with your response to the deficiencies using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Susan.Jenney@fda.hhs.gov) or FAX (301-796-9845).

Thank you,

Susan Jenney, MS
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Drug Oncology Products
FDA/CDER/OND

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/s/

Susan Jenney
10/22/2008 04:01:47 PM

Jenney, Susan

From: Jenney, Susan
Sent: Wednesday, October 08, 2008 11:51 AM
To: 'Mondano, Laura'
Cc: Jenney, Susan
Subject: NDA 22-311
Attachments: Mozobil Clinical Pharmacology Findings.ppt

Good morning Laura:

Please refer to your NDA 22-311 for Mozobil (plerixafor) submitted on June 16, 2008. During the review of your submission, the Clinical Pharmacology reviewer has the following response:

We would like to share our preliminary clinical pharmacology findings and seek feedback on an alternative dosing regimen that will match exposure across body weight and renal function, i.e.

Body weight < 85 kg	20 mg (fixed dose)
Body weight ≥ 85 kg	240 mcg/kg
CrCL < 50 mL/min	1/3 dose reduction (240 to 160 mcg/kg or 20 to 13.5 mg)

The three key findings that form the basis for proposing an alternative dosing regimen are:

- The response rate ($\geq 5 \times 10^6$ CD34+ cells/kg in 4 or less days of apheresis) was found to be significantly lower in lighter (<85 kg, 48% (95% CI 36-60%)) compared to heavier (>85 kg, 72% (95% CI 61-82%)) non-Hodgkin's lymphoma patients in study 3101.
- The exposure (AUC) increases with increasing body weight following the proposed dose of 240 mcg/kg leading to a 61% difference in AUC for a 50 and 150 kg patient.
- In order to match exposure across renal function, the proposed 1/3 dose reduction in severe renal impaired patients (CrCL < 30 mL/min) should be extended to patients with moderate renal impairment (CrCL < 50 mL/min).

Please provide your comments before October 22, 2008. The reviewer has also shared the attached Power Point presentation. Please confirm you have received this e-mail. If you have any comments or questions, contact me.

Thank you,
Susan

Susan Jenney, MS
 Regulatory Project Manager
 Division of Drug Oncology Products
 Office of Oncology Drug Products
 OND/CDER/FDA
 301-796-0062
 301-796-9845 (FAX)
Susan.Jenney@fda.hhs.gov

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Susan Jenney
10/8/2008 11:57:54 AM



NDA 22-311

INFORMATION REQUEST LETTER

Genzyme Corporation
Attention: Laura Mondano
Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Mondano:

Please refer to your new drug application (NDA) submitted on June 16, 2008, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mozobil™ (plerixafor injection).

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. As requested during the July 25, 2006, Type B, CMC meeting for IND 55,851, please provide the following information for the starting material (b) (4):
 - (a) For (b) (4) starting material (b) (4), provide data from purging studies using impurities in starting materials to demonstrate the ability of the manufacturing process to remove and control the impurities to desired levels.
 - (b) The specification for (b) (4) which indicates that you will only perform description and identification tests, is not adequate. Although it is acceptable that you perform testing for description and identification for confirmatory purposes, upon the receipt of the materials with certificate of analysis from the suppliers whose reliability has been established, the complete tests should be performed for such suppliers at appropriate intervals. The complete specification should also be used to qualify new suppliers. Accordingly, provide a complete specification with validated analytical methods that you will perform for (b) (4).
 - (c) Clarify whether the theoretical impurity in starting material (b) (4) as described in Figure 3.2.S.3.2-1, is the same impurity that has an RRT=(b) (4) in the specification of (b) (4) (Table 3.2.S.2.3-2). If this is the case, revise the (b) (4) specification with the specific compound name and structure for RRT=(b) (4). If not, please provide the potential carry-over of impurity RRT=(b) (4) to the final drug substance. It should be noted that, unless a validated analytical procedure is provided in the NDA for the impurity test, a

designation of an impurity by RRT only, without structure identification, is not acceptable.

2. Tighten the acceptance criteria for the following tests in the proposed drug substance specification: assay, specified impurities, total impurities, (b) (4) and water content. It is noted that drug substance manufacturing process was optimized during development to reduce impurities and the drug substance containers have been changed due to stability failure observed in earlier batches. Establish the acceptance criteria based on the capability of the proposed drug substance manufacturing process (after process optimization) and the proposed containers.
3. It is noted that page 10 of the drug substance stability section in Quality Overall Summary (section 2.3.S.7.1.6) was missing from the CTD submission. Please provide page 10 of this section and remove the duplicated page 5.
4. In section 3.2.S.7.2, provide a commitment to report stability data obtained from the ongoing drug substance stability batches and from annual stability batches in the Annual Reports.
5. In section 3.2.S.7.1.7, revise the statement for the extension of the retest period for drug substance from “the retest date may be extended an additional (b) (4) months, for a total retest period of (b) (4) months, upon a successful retest after (b) (4) months” to “extension of the retest period to (b) (4) months will be based on satisfactory (b) (4) -month stability data on a minimum of three commercial-scale batches.”

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope, Ph.D.
Branch Chief (Acting)
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Richard Lostritto
10/2/2008 02:50:08 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Division/Office): CDER Maternal Health			FROM: Susan Jenney, Project Manager, OND/DDOP WO-22 Room 2169, 301-796-0062		
DATE: September 30, 2008	IND NO.:	NDA NO.: 22-311	TYPE OF DOCUMENT: New NDA	DATE OF DOCUMENT: June 16, 2008	
NAME OF DRUG: Mozobil (plerixafor) Injection		PRIORITY CONSIDERATION: Priority	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: November 1, 2008 Please contact Luan Lee	
NAME OF FIRM: Genzyme Corporation					
REASON FOR REQUEST					
I. GENERAL					
NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY		PRE-NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT	RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): New NDA		
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER:			CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER:		
III. BIOPHARMACEUTICS					
DISSOLUTION BIOAVAILABILITY/PK STUDIES PHASE IV STUDIES			DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
CLINICAL			PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review the teratogenic findings section of the package insert. The Pharm Tox reviewer is Shwu-Luan Lee and the Clinical reviewer is Michael Brave. Please contact Luan. Luan would like you to assist her with this labeling early. The submission is electronic (link: \\Cdsub1\evsprod\NDA022311\0000) PDUFA Goal date: December 16, 2008.					
SIGNATURE OF REQUESTER: Susan Jenney <i>{See appended electronic signature page}</i>			METHOD OF DELIVERY (Check one): <input checked="" type="checkbox"/> DFS/DARRTS EMAIL MAIL HAND		
SIGNATURE OF RECEIVER:			SIGNATURE OF DELIVERER:		

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/s/

Susan Jenney
9/30/2008 04:58:50 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): IRT		FROM: Division of Drug Oncology Products/Alice Kacuba for Susan Jenney (301) 796-1381		
DATE 9-28-08	IND NO.	NDA NO. 22-311	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 6-16-08
NAME OF DRUG Mozobil (AMD3100, plerixafor injection)	PRIORITY CONSIDERATION Priority NDA	CLASSIFICATION OF DRUG Oncology	DESIRED COMPLETION DATE Nov 1, 2008	
NAME OF FIRM: Genzyme				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY	<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	
COMMENTS/SPECIAL INSTRUCTIONS: Background: The purpose of this consult is to request a IRT consult review of this new NDA as discussed with Devi K on 9-26-08. The NDA is in the EDR. Thank you for your assistance.				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Alice Kacuba
9/28/2008 02:31:13 PM
Signing for Susan Jenney.

FAX



**FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705

To: Laura Mondano **From:** Susan Jenney, MS
E-mail: Laura.Mondano@genzyme.com **E-mail:** Susan.Jenney@fda.hhs.gov
Phone: 617-591-5994 **Phone:** 301-796-0062
Pages, including cover sheet: 2 **Date:** September 12, 2008
RE: Information Request for NDA 22,311

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address below by mail. Thank you.

Dear Ms. Mondano:

Please refer to your New Drug Application (NDA 22-311) for Mozobil (plerixafor) Injection submitted on June 16, 2008. During our review of the Clinical Pharmacology section of your submission, we have the following Information Request:

1. The time-courses of CD34 count increases (Peripheral blood CD34+ cell counts for individual patients) for the studies AMD3100-2106, -1002, -1101, -C201 and -1005.

These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application.

In order for us to complete our review, please respond to these requests as soon as possible. Please submit an amendment to your application with your response to the comments using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Susan.Jenney@fda.hhs.gov) or FAX (301-796-9845).

Thank you,

Susan Jenney, MS
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Drug Oncology Products
FDA/CDER/OND

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/s/

Susan Jenney
9/12/2008 02:38:56 PM

proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? N/A YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: 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.” Applicant may not use wording such as “To the best of my knowledge . . .”

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
Electronic submissions are not required based on the “Guidance to Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications” June 2008 section II K: “FDA District offices have access to documents submitted in electronic format. Therefore, when sending submissions in electronic format, you need not provide any documentation to the FDA Office of Regulatory Affairs District Office.”
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 55,851

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meetings? Dates September 10, 2004 NO
November 17, 2004
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting? Date October 1, 2007 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) November 29, 2008 NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application: N/A

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical N/A

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?

YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 4, 2008
NDA #: 22-311
DRUG NAMES: Mozobil (plerixafor) for Injection
APPLICANT: Genzyme Corporation

BACKGROUND:

Genzyme submitted NDA 22-311 on June 16, 2008, (received on June 16, 2008) to enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma.

ATTENDEES:

Robert Justice, M.D., Director, DDOP
Ramzi Dagher, MD, Deputy Division Director, DDOP
Michael Brave, MD, Medical Officer, DDOP
Sarah Pope, Ph.D., Acting Branch Chief, ONDQA
Sue-Ching Lin, MS, CMC Reviewer
Haleh Saber, PhD, PharmTox Acting Team Leader
Shwu-Luan Lee, PhD, Pharm Tox Reviewer
Jeanne Fourie, PhD, Clin Pharm Reviewer
Kun He, PhD, Acting Biostat Team Leader
Christoffer Tornoe, PhD, Pharmacometrics Reviewer
Terrance Ocheltree, PhD, Acting Pharmaceutical Assessment Lead, ONDQA
Brian Booth, PhD, Deputy Director, DCP5
Vinayak Pawar, PhD, Microbiology Reviewer
Vivian Yuan, Biostat Reviewer
Susan Jenney, M.S., Regulatory Health Project Manager
Frank Cross, Jr., CPMS

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	M. Brave
Secondary Medical:	R. Dagher
Statistical:	W. Yuan
Pharmacology:	L. Lee
Statistical Pharmacology:	N/A
Chemistry:	S. Lin
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	J. Fourie
Microbiology, sterility:	V. Pawar
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	TBD
OPS:	N/A
Regulatory Project Management:	S. Jenney
Risk Management Plan (OSE):	TBD

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
- If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:
Any comments: eCTD submission

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional): CMC

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Susan Jenney
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If “No,” skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an “old” antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If “Yes,” skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If “Yes “contact your ODE’s Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If “No,” to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If “Yes,” (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If “No,” to (c) list the pharmaceutical equivalent and contact your ODE’s Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If “Yes,” to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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this page is the manifestation of the electronic signature.**

/s/

Susan Jenney
8/29/2008 10:10:37 AM
PROJECT MANAGER FOR QUALITY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-311

Genzyme Corporation
Attention: Laura Mondano
Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Mondano:

Please refer to your new drug application (NDA) dated June 16, 2008, received June 16, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Mozobil™ (plerixafor) for Injection, 20 mg/mL.

During our filing review of your application, we identified the following potential review issues:

1. Insufficient stability data are provided to justify the proposed expiration dating period of 36 months. Updated stability data for the drug product should be provided as soon as possible. Stability data analysis and the appropriate SAS transport files should also be provided in this update.

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 review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. The purpose of cross-reference to DMF **(b) (4)** and **(b) (4)** are not adequately described in your NDA submission. Please clarify the applicability of these cross-references.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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, call Susan Jenney, Regulatory Project Manager, at (301) 796-0062.

Sincerely,

{See appended electronic signature page}

Robert Justice, M.D.
Division Director
Division of Drug Oncology Products
Office of Drug Oncology Products
Center of Drug Evaluation and Research

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/s/

Alice Kacuba
8/29/2008 01:18:37 PM
Signing for Dr. Justice.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Division/Office): CDER OSE Consults			FROM: Susan Jenney, Project Manager, OND/DDOP WO-22 Room 2169, 301-796-0062		
DATE: August 12, 2008	IND NO.:	NDA NO.: 22-311	TYPE OF DOCUMENT: New NDA	DATE OF DOCUMENT: June 16, 2008	
NAME OF DRUG: Mozobil (plerixafor) for Injection		PRIORITY CONSIDERATION: Priority	CLASSIFICATION OF DRUG: Oncology	DESIRED COMPLETION DATE: November 4, 2008 Due (6 mo.): Dec. 16, 2008	
NAME OF FIRM: Genzyme Corporaiaon					
REASON FOR REQUEST					
I. GENERAL					
NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY		PRE--NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT	RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Risk Management Plan review		
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER:			CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER:		
III. BIOPHARMACEUTICS					
DISSOLUTION BIOAVAILABILTY/PK STUDIES PHASE IV STUDIES			DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
CLINICAL			PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This consult requests an evaluation of the proposed Risk Management Plan for a new NDA. The submission is electronic (link: \\Cdsub1\evsprod\NDA022311\0000 ; link to Risk Management Plan: \\Cdsub1\evsprod\NDA022311\0000\m1\us\risk-management-plan.pdf) PDUFA Goal date: 6 months: December 16, 2008.					
SIGNATURE OF REQUESTER: Susan Jenney <i>{See appended electronic signature page}</i>			METHOD OF DELIVERY (Check one): <input checked="" type="checkbox"/> DFS/DARRTS EMAIL MAIL HAND		
SIGNATURE OF RECEIVER:			SIGNATURE OF DELIVERER:		

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/s/

Susan Jenney
8/12/2008 09:46:44 AM



NDA 22-311

PRIORITY REVIEW DESIGNATION

Genzyme Corporation
Attention: Laura Mondano
Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Mondano:

Please refer to your new drug application (NDA) dated June 16, 2008, received June 16, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Mozobil™ (plerixafor) for Injection, 20 mg/mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is December 16, 2008.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before August 29, 2008

If you have any questions, call Susan Jenney, Regulatory Project Manager, at (301) 796-0062.

Sincerely,

{See appended electronic signature page}

Robert Justice, M.D.
Division Director
Division of Drug Oncology Products
Office of Drug Oncology Products
Center of Drug Evaluation and Research

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/s/

Robert Justice
8/12/2008 04:47:15 PM

DSI CONSULT: Request for Clinical Inspections

Date: July 17, 2008

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Michael Brave, Medical Officer, DDOP
Ramzi Dagher, Medical Team Leader, DDOP

From: Susan Jenney, Regulatory Health Project Manager, DDOP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application #: NDA 22-311

Applicant/ Applicant contact information:
Genzyme Corporation
Attention: Laura Mondano phone: 617-591-5994
Director of Regulatory Affairs FAX: 617-761-8414
500 Kendall Street e-mail: laura.mondano@genzyme.com
Cambridge, MA 02142

Drug Proprietary Name: Mozobil (plerixafor) for Injection
NME or Original BLA (Yes/No): NME
Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Mozobil is indicated to enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma

PDUFA: December 16, 2008
Action Goal Date: December 16, 2008
Inspection Summary Goal Date: November 16, 2008

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	No. of Subjects	Indication
Washington University School of Medicine PI: John DiPersio (b) (4) Phone: (314) 362-3520 Fax: 314-454-5904 (b) (4) St. Louis School of Medicine Division of Oncology Campus Box 8007 660 South Euclid Avenue St. Louis, MO 63110-1093	AMD 3100-3101 and AMD 3100-3102	68	Stem cell mobilization for patients with non-Hodgkin's lymphoma (3101) or multiple myeloma (3102) undergoing autologous stem cell transplantation
University of Pennsylvania PI: Edward Stadtmauer (b) (4) Phone: 215-662-4610 (b) (4) Hospital of the University of Pennsylvania 16 Penn Tower, 3400 Spruce Street Philadelphia, PA 19104	AMD 3100-3102	33	Stem cell mobilization for patients with multiple myeloma undergoing autologous stem cell transplantation
Mayo Clinic Rochester PI: Ivana Micallef (b) (4) Phone: (507) 266-4612 Fax: 507-266-2157 (b) (4) Mayo Clinic Rochester 200 First Street SW Rochester, MN 55905	AMD3100-3101	36	Stem cell mobilization for patients with non-Hodgkin's lymphoma undergoing autologous stem cell transplantation

III. Site Selection/Rationale

NDA 22-311 is for plerixafor, a new molecular entity intended to facilitate the collection of hematopoietic stem cells for use by patients with non-Hodgkin's lymphoma or multiple myeloma undergoing autologous stem cell transplantation. The application is supported by two randomized clinical trials, AMD3100-3101 and AMD3100-3002, which were conducted at 40 centers in the United States. The Division of Drug Oncology Products Clinical Review Team proposes auditing The University of Washington, the University of Pennsylvania, and the Mayo Clinic Medical School.

The University of Washington enrolled the highest number of patients (68) and reported the second highest number of total protocol violations (460) and the highest number of major protocol violations (40). The University of Pennsylvania enrolled the third highest number of patients, had the highest number of total protocol violations (638) and the second highest number of major protocol violations (30). The Mayo Clinic Medical School had the second highest number of total (351) and major protocol violations.

The clinical review team has so far not identified any evidence of fraud or that the efficacy results of the two randomized clinical trials may have been driven by any particular site(s).

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): High number of protocol violations (University of Washington and Mayo Medical School)

International Inspections:

Reasons for inspections (please check all that apply): None

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

None

Should you require any additional information, please contact Susan Jenney at 301-796-0062 or Michael Brave at 301-796-2330.

Concurrence: (as needed)

_____ Ramzi Dagher, Medical Team Leader
_____ Michael Brave, Medical Reviewer

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/s/

Michael Brave
7/30/2008 03:43:32 PM

Robert Justice
7/30/2008 06:30:56 PM

MEMORANDUM

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

DATE: July 29, 2008

TO: Susan Jenney
Regulatory Project Manger
Division of Drug Oncology Products, HFD 150

FROM: CDER DCRP QT Interdisciplinary Review Team

SUBJECT: NDA 22311 QT IRT Consult
Mozobil (plerixafor) for Injection

Please refer to your request for consultation from the CDER DCRP QT Interdisciplinary Review Team (QT IRT) dated July 17, 2008 for NDA 22311, Mozobil (plerixafor) for Injection.

Based on the email communication, dated July 29, 2008, with the Regulatory Health Project Manager, Susan Jenney, this request is being cancelled.

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. In particular, we look forward to providing a review of the sponsor's QT/QTc plan when submitted to the IND.

Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

Thank you.

Devi Kozeli
Regulatory Project Manger
QT Interdisciplinary Review Team
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Office of New Drugs
Center of Drug Evaluation and Research
U.S. Food and Drug Administration

From: Jenney, Susan

Sent: Tuesday, July 29, 2008 2:28 PM

To: Kozeli, Devi

Cc: Kacuba, Alice; Garnett, Christine

Subject: RE: NDA 22-311- Information Request (fax/e-mail dated July 22,2008) - from the QT Group - (1 of 4)

Good afternoon Devi:

Thank you for your work in trying to review our consult request. Since this NDA does not have any studies for you to review at this time, please disregard our consult request.

Thank you,
Susan

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/s/

Devi Kozeli
7/29/2008 04:18:12 PM
CSO

These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application.

In order for us to complete our review, please respond to these requests as soon as possible. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Susan.Jenney@fda.hhs.gov) or FAX (301-796-9845).

Thank you,

Susan Jenney, MS
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Drug Oncology Products
FDA/CDER/OND

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) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax 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)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	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 Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

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/s/

Susan Jenney
7/22/2008 01:37:09 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (<i>Division/Office</i>): OSE, Sharon R. Mills, Patient Prod. Info. WO-22 Room 4485, 301-796-2036			FROM: Susan Jenney, Project Manager, OND/DDOP WO-22 Room 2169, 301-796-0062		
DATE: July 17, 2008	IND NO.:	NDA NO.: 22-311	TYPE OF DOCUMENT: New NDA	DATE OF DOCUMENT: June 16, 2008	
NAME OF DRUG: Mozobil (plerixafor) for Injection		PRIORITY CONSIDERATION: Priority or Standard (to be determined)	CLASSIFICATION OF DRUG: Oncology	DESIRED COMPLETION DATE: November 16, 2008 Due 6 mo.: 12/16/08 Due 10 mo.: 4/16/09	
NAME OF FIRM: Genzyme Corporation					
REASON FOR REQUEST					
I. GENERAL					
NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY		PRE-NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT	RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>):		
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER:			CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER:		
III. BIOPHARMACEUTICS					
DISSOLUTION BIOAVAILABILITY/PK STUDIES PHASE IV STUDIES			DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
CLINICAL			PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This consult requests the evaluation of the proposed Patient Information Leaflet. The submission is electronic (link: \\Cdsub1\evsprod\NDA022311\0000). PDUFA Goal date: 6 months: December 16, 2008 10 months: April 16, 2009.					
SIGNATURE OF REQUESTER: Susan Jenney <i>{See appended electronic signature page}</i>			METHOD OF DELIVERY (Check one): <input checked="" type="checkbox"/> DFS/DARRTS EMAIL MAIL HAND		
SIGNATURE OF RECEIVER:			SIGNATURE OF DELIVERER:		

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/s/

Susan Jenney
7/18/2008 09:56:47 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Division/Office): CDER OSE Consults			FROM: Susan Jenney, Project Manager, OND/DDOP WO-22 Room 2169, 301-796-0062		
DATE: July 17, 2008	IND NO.:	NDA NO.: 22-311	TYPE OF DOCUMENT: New NDA	DATE OF DOCUMENT: June 16, 2008	
NAME OF DRUG: Mozobil (plerixafor) for Injection		PRIORITY CONSIDERATION: Standard or Priority (to be determined)	CLASSIFICATION OF DRUG: Oncology	DESIRED COMPLETION DATE: November 16, 2008 Due (6 mo.): 12/16/08 Due (10 mo.): 4/16/09	
NAME OF FIRM: Genzyme Corporation					
REASON FOR REQUEST					
I. GENERAL					
NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY		PRE-NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT	RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review		
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER:			CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER:		
III. BIOPHARMACEUTICS					
DISSOLUTION BIOAVAILABILITY/PK STUDIES PHASE IV STUDIES			DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
CLINICAL			PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This consult requests an evaluation of the proposed trade name for a new NDA. The submission is electronic (link: \\Cdseub1\evsprod\NDA022311\0000) PDUFA Goal date: 6 months: December 16, 2008 10 months: April 16, 2009.					
SIGNATURE OF REQUESTER: Susan Jenney <i>{See appended electronic signature page}</i>			METHOD OF DELIVERY (Check one): <input checked="" type="checkbox"/> DFS/DARRTS EMAIL MAIL HAND		
SIGNATURE OF RECEIVER:			SIGNATURE OF DELIVERER:		

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/s/

Susan Jenney
7/18/2008 10:01:01 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): OPS, Microbiology Staff (HFD-805) Attn: James McVey (301-769-1572) WO-51 Room 4162		FROM: Susan Jenney, Project Manager, OND/DDOP WO-22 Room 2169, 301-796-0062		
DATE: July 10, 2008	IND NO.:	NDA NO.: 22-311	TYPE OF DOCUMENT:	DATE OF DOCUMENT: June 16, 2008
NAME OF DRUG: Mozobil (Plerixafor Injection)	PRIORITY CONSIDERATION: Standard or Priority (to be determined)	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: October 16, 2008	
NAME OF FIRM: Genzyme Corporation				
REASON FOR REQUEST				
I. GENERAL				
NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY	PRE-NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY <input checked="" type="checkbox"/> PAPER NDA CONTROL SUPPLEMENT	RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW OTHER (SPECIFY BELOW):		
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER:		CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER:		
III. BIOPHARMACEUTICS				
DISSOLUTION BIOAVAILABILITY/PK STUDIES PHASE IV STUDIES		DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
CLINICAL		PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This consult requests a micro review of a new NDA. This new NDA is indicated to enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma. Please evaluate this submission from the sterility assurance standpoint. This submission is electronic (\\Cdsub1\evsprod\NDA022311\0000). PDUFA Goal date: December 16, 2008 (Priority) or April 16, 2009 (Standard).				
SIGNATURE OF REQUESTER: Susan Jenney {See appended electronic signature page}		METHOD OF DELIVERY (Check one): <input checked="" type="checkbox"/> DFS/DARRTS EMAIL MAIL HAND		
SIGNATURE OF RECEIVER:		SIGNATURE OF DELIVERER:		

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/s/

Susan Jenney
7/18/2008 09:26:50 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Division/Office): DDMAC Attention: Keith Olin and JuWon Lee			FROM: Susan Jenney, Project Manager, OND/DDOP WO-22 Room 2169, 301-796-0062		
DATE: July 18, 2008	IND NO.:	NDA NO.: 22-311	TYPE OF DOCUMENT: New NDA	DATE OF DOCUMENT: June 16, 2008	
NAME OF DRUG: Mozobil (plerixafor) for Injection		PRIORITY CONSIDERATION: Priority or Standard (to be determined)	CLASSIFICATION OF DRUG: Oncology	DESIRED COMPLETION DATE: November 16, 2008 Due 6 mo.: 12/16/08 Due 10 mo.: 4/16/09	
NAME OF FIRM: Genzyme Corporation					
REASON FOR REQUEST					
I. GENERAL					
NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY		PRE-NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT	RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Proposed labeling Review		
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER:			CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER:		
III. BIOPHARMACEUTICS					
DISSOLUTION BIOAVAILABILITY/PK STUDIES PHASE IV STUDIES			DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
CLINICAL			PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This consult requests the evaluation of the proposed labeling. You will be invited to all labeling meetings. The submission is electronic (link: \\Cdseub1\evsprod\NDA022311\0000) PDUFA Goal date: 6 month: December 16, 2008 10 month: April 16, 2009.					
SIGNATURE OF REQUESTER: Susan Jenney <i>{See appended electronic signature page}</i>			METHOD OF DELIVERY (Check one): <input checked="" type="checkbox"/> DFS/DARRTS EMAIL MAIL HAND		
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/s/

Susan Jenney
7/18/2008 02:50:33 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (<i>Division/Office</i>): Devi Kozeli, Project Manager, OND/DCRP WO-22 Room 4183, 301-796-1128			FROM: Susan Jenney, Project Manager, OND/DDOP WO-22 Room 2169, 301-796-0062		
DATE: July 17, 2008	IND NO.:	NDA NO.: 22-311	TYPE OF DOCUMENT: New Protocol	DATE OF DOCUMENT: June 16, 2008	
NAME OF DRUG: Mozobil (plerixafor) for Injection		PRIORITY CONSIDERATION: Standard or Priority (to be determined)	CLASSIFICATION OF DRUG: Oncology		DESIRED COMPLETION DATE: November 1, 2008 6 mo.: 12/16/08 10 mo.: 4/16/09
NAME OF FIRM: Genzyme					
REASON FOR REQUEST					
I. GENERAL					
NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY		PRE-NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT	RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): IRT		
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER:			CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER:		
III. BIOPHARMACEUTICS					
DISSOLUTION BIOAVAILABILITY/PK STUDIES PHASE IV STUDIES			DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
CLINICAL			PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This consult requests a review the protocol in the submission which involves a QT study (Study 06-H-0156: "Phase 1 open-label QT/QTc and PK study in healthy volunteers with two escalating doses of AMD3100"). Contact Jeanne Fourie (Clin Pharm) or Michael Brave (Clinical) for any questions. The submission is electronic (link: \\Cdsub1\evsprod\NDA022311\0000). PDUFA Goal date: December 16, 2008, (Priority) or April 16, 2008 (Standard).					
SIGNATURE OF REQUESTER: Susan Jenney <i>{See appended electronic signature page}</i>			METHOD OF DELIVERY (Check one): <input checked="" type="checkbox"/> DFS/DARRTS EMAIL MAIL HAND		
SIGNATURE OF RECEIVER:			SIGNATURE OF DELIVERER:		

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this page is the manifestation of the electronic signature.**

/s/

Susan Jenney
7/18/2008 09:53:43 AM



NDA 22-311

NDA ACKNOWLEDGMENT

Genzyme Corporation
Attention: Laura Mondano
Director, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Mondano:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Mozobil™ (plerixafor) Solution for Injection, 20 mg/mL

Date of Application: June 16, 2008

Date of Receipt: June 16, 2008

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 15, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] 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 under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA 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
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-0062.

Sincerely,

{See appended electronic signature page}

Susan Jenney, MS
Regulatory Project Manager
Division of Drug Oncology Products
Office of Drug Oncology Products
Center of Drug Evaluation and Research

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/s/

Susan Jenney
7/18/2008 09:23:04 AM

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Friday, October 05, 2007 1:46 PM
To: 'Sattarzadeh, Sherwin'
Subject: RE: IND 55,851 pre-NDA FDA Minutes
Attachments: pre-NDA 10-1-07 MINUTES.pdf

Our minutes

Dotti

10/5/2007

phase 3 studies (AMD3100-3101 study in NHL and AMD 31003102 study in multiple myeloma) will be submitted.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Clinical

1. Efficacy data from the two Phase III studies (AMD3100-3101 and AMD3100-3102), the proof of principle study (AMD3100-2101), and the Phase II study in Hodgkin's Disease (AMD3100-2106) will be presented in Section 2.7.3.3, to satisfy the requirements of an ISE in support of the proposed efficacy claims. Due to the different study designs and patient populations investigated in the studies supporting the efficacy of Mozobil, Genzyme proposes not to pool the data across the studies but to summarize the data individually in Section 2.7.3.3. Therefore, a separate integrated summary of efficacy (ISE) will not be provided in Module 5. Individual study data tables and listings will be provided as part of the CSRs in Module 5.

Does the Agency find this plan to summarize the study data individually acceptable?

FDA – Yes.

2. In the planned NDA, Genzyme is intending to submit all analysis and listing datasets for studies AMD3100-2101, -2106, -3101, and -3102 in support of the Mozobil efficacy claims. In addition, the NDA will include datasets to support the PK and the ISS analyses.

Does the Agency find this plan for submitting electronic datasets acceptable?

FDA – Yes. All data sets used to support PK claims should be included, specifically Study 1002, C201, 2106 and 1101.

3. Does the Agency find the proposed ISS analyses as outlined in **Section 10.2.5** acceptable?

FDA – Yes.

Does the Agency agree that the proposed efficacy and safety data packages included in the NDA, as defined in **Section 12.2**, are sufficient for the review and approval of the Mozobil application?

FDA – Final determination of the acceptability of the efficacy and safety data packages will be made at the time of NDA submission and determined at the filing meeting. Approval of the Mozobil application will be a review issue.

Please submit data on graft durability at 6 months for all patients in the initial NDA submission.

SPONSOR RESPONSE: In advance of the pre-NDA meeting we are seeking clarification to better understand what has led to the difference between the agreement at the End of Phase II meeting and the FDA's pre-NDA response in regards to the 3 versus 6 month graft durability data in the initial NDA. As you are aware, at the End of Phase II meeting, it was agreed that the NDA would be filed with 100 day graft durability data from the Phase III studies. Six month data would be provided with or prior to the 120 day safety update, with one year data provided for all patients at the completion of the trial. The FDA response to the pre-NDA package includes a request for data on graft durability at 6 months for all patients in the initial NDA submission. This request by FDA significantly impacts our planning for the NDA submission and we would appreciate additional insight so that we can develop plans which best meet the Division's review needs.

DISCUSSION: See proposal in Sponsor's slides. FDA noted that this proposal is acceptable.

4. Does the Agency accept the proposed CSR formats outlined in **Table 23** of **Section 12.3**?

FDA – Yes.

Clinical Pharmacology

5. Does the Agency agree that the completed metabolism studies are adequate to describe the metabolic pathway of plerixafor?

FDA - The studies appear reasonable, but their adequacy to describe the metabolic pathway will be a review issue.

6. Does the Agency agree that the completed (AMD3100-1002, -1101, -C201, and -2106) and ongoing studies (AMD3100-2112) will adequately describe the pharmacokinetics of plerixafor relative to its intended clinical use?

FDA - Yes. The adequacy of the studies will be a review issue.

Nonclinical

7. Does the Agency agree that the Nonclinical data package, outlined in **Section 11**, adequately supports approval of the Mozobil NDA?

FDA – Possibly, pending review of the NDA submission.

Labeling

8. Does the Agency agree that the proposed draft labeling statements identified in the TPP are adequately supported by the clinical data package?

FDA - Determination of the acceptability of labeling statements will be made at the time of review of the NDA application.

9. Does the Agency find the wording of the proposed indication in Section (c) of the TPP acceptable?

FDA - The indication must reflect the study design, patients enrolled and results in the randomized trials. The exact wording of the indication will depend on our complete review of the data submitted with the NDA.

Additional Question for Pre-NDA Meeting

11. Does the Agency agree that the Mozobil NDA submission package may be considered fileable and the NDA review clock begin if the original submission lacks an Integrated Analysis of Safety (ISS) and Clinical Study Reports for studies AMD3100-2102, -2103, -2104, -2105, -2108, -2109, -2112, -2113, -EU21, and -CUP001? Genzyme will submit these components to the NDA within 3 months of the original submission.

- Would such a submission approach affect the consideration of Mozobil for priority review status?

FDA - Absence of the ISS in the initial NDA submission will result in a Refusal to File. You should submit the complete NDA application including the ISS. See below regarding priority review.

- Is FDA's answer to the above influenced by whether the product has officially been designated Fast Track or not?

FDA - Determination of the review designation (standard or priority) will be made at the time of the NDA submission.

ADDITIONAL FDA COMMENTS:

1. We recommend that you submit the datasets in the Study Data Tabulation Model (SDTM) format.

DISCUSSION: See Genzyme slides for sponsor's proposal. FDA noted that this is a recommendation and that the datasets may be submitted in the 1999 guideline format.

2. Please include preferred term, lower level term and verbatim terms in the adverse events datasets and specify the MedDRA version used.

3. Please provide Case Report Forms and narratives for all Serious Adverse Events in the initial NDA submission.
4. You will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the thorough QT study may be appropriate. Your proposal should be submitted for review by FDA prior to initiating the study.

DISCUSSION: See sponsor's slides for QT proposal. FDA noted that the results of the NIH study supportive of their QT plan should be submitted with the NDA. A thorough QT study should be conducted as soon as feasible. Sponsor will submit a protocol design for a thorough QT study for FDA review, the results of which would be submitted after the NDA action date.

Additional questions arising at meeting:

1. Would Mozobil likely go to ODAC? FDA noted that any decision about ODAC would be premature at this point.
2. Does FDA need all completed phase 2 study final reports? FDA replied that anything related to this indication and to dose-finding must be included in final reports. Genzyme will submit a proposal for the phase 2 studies in regard to which would have final reports provided in the NDA submission.

ACTION ITEMS:

Genzyme will submit a proposal for the phase 2 studies in regard to which would have final reports provided in the NDA submission.

Genzyme will submit their NDA when ready. It is targeted for 2nd quarter 2008.

Dotti Pease
Chief, Project Management Staff

Concurrence Chair: _____
Ramzi Dagher, M.D.
Medical Team Leader

ATTACHMENT: Genzyme Slides

10 Page(s) Withheld after this page as B4 (CCI/TS)

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/s/

Ramzi Dagher
10/4/2007 08:48:01 AM

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/s/

Dotti Pease
10/18/2007 06:43:28 AM

Staten, Ann M

From: Staten, Ann M
Sent: Wednesday, December 01, 2004 9:56 AM
To: Bem Atsma
Subject: Meeting minutes attached

Dear Bem,

Please find attached a copy of the EOP2 CMC meeting.

Sincerely,
Ann

Ann M. Staten, R.D., CDR, USPHS

Senior Regulatory Project Manager

Division of Oncology Drug Products

Center for Drug Evaluation and Research, FDA

301.594.0490 (phone)

301.827.4590 (fax)

12/1/2004

T-COM MEETING MINUTES

MEETING DATE: November 15, 2004

IND/NDA: IND 55,851 **Meeting Request Submission Date:** Sept. 20, 2004 (N190)
FDA Response Date: September 28, 2004
Briefing Document Submission Date: Oct. 21, 2004 (N198)

DRUG: AMD3100

SPONSOR/APPLICANT: AnorMed, Inc.

TYPE of MEETING/TELECON:

End of Phase 2 - CMC

FDA PARTICIPANTS (internal meeting):

Nallaperum Chidambaram, PhD, Chemistry Team Leader
Ruth Wager, PHD, Chemistry Reviewer
Ann Staten, RD, Project Manager

BACKGROUND: FDA responses were sent to the sponsor via e-mail on November 10, 2004 (attached). On November 15, 2004, AnorMED communicated in a phone call that the responses were clear and a meeting was not necessary.

MEETING/TELECON OBJECTIVES:

To discuss the development and manufacture of AMD3100 drug substance and drug product.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

See attached e-mail.

ACTION ITEMS: None identified.

Ann Staten, Project Manager

Concurrence Chair: _____
Nallaperum Chidambaram, PhD, Chemistry Team
Leader

Attachments: FDA email dated November 10, 2004

Staten, Ann M

From: Staten, Ann M
Sent: Wednesday, November 10, 2004 10:39 AM
To: Bem Atsma
Subject: IND 55,851 AMD3100

Dear Bem,

Please refer to your September 20, 2004 EOP2 CMC meeting request for AMD3100 and to the briefing package.

Attached are the FDA answers to your questions. You have the option of canceling our meeting of November 17, 2004 if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible if you are canceling the meeting.

Regards,
Ann

11/10/2004

1. The information package contains information on numerous studies examining the identity, general properties and physicochemical characterization of AMD3100. Does the Agency agree that these studies are sufficient for registration of AMD3100 and that no further characterization is required (see Sections S1 General Information and S3 Characterization)?

FDA Response: In general, your proposal appears to be acceptable. We recommend that you include melting point as part of the physicochemical characterization.

2. Does the Agency agree that (b) (4) are the GMP Starting Material (of the synthesis of AMD3100 Drug Substance (see Section S2.3 Control of Materials)?

FDA Response: Yes, (b) (4)

3. Does the Agency agree that the specifications for AMD3100 Drug Substance are appropriate and justified for the current stage of development and for future registration of AMD3100 (see Section S4.1 Specification and Section S4.5 Justification of Specification)?

FDA Response: Your proposed specifications appear to be acceptable. However, please note that the acceptance of limits is a review issue. Please provide safety data for (b) (4).

4. Does the Agency agree that the three Drug Substance batches (batch numbers 46446-02, 46771-03 and 47191-04) qualify as Primary Stability Batches and are suitable for use in registration of AMD3100 (see Section S2.2 Description of Manufacturing Process and Process Controls)?

FDA Response: The drug substance batches appear to qualify as stability and registration batches as long as your manufacturing process remains unchanged.

5. Does the Agency agree that the stability program to study the stability of AMD3100 Drug Substance is suitable and sufficient for registration of AMD3100 (see Section S7 Stability)?

FDA Response: Your proposed stability protocol is found to be acceptable. Please include a sterility test at release and annually thereafter.

6. AMD3100 stability studies at accelerated conditions (40 °C/75% RH) indicate that the current packaging material may not provide a suitable moisture barrier as water content results have not met specifications. Water content has not increased at ambient conditions (25 °C/60% RH). AMD3100 is known to be hygroscopic and as a result, provisions are made to correct for moisture content during analysis and drug product manufacture. AMD3100 has been shown to remain stable with regard to assay and impurities, even at high water content levels. To resolve this issue, AnorMED will look into improving the secondary package of AMD3100 Drug Substance. Provided that AMD3100 Drug Substance is continuously stable at 25 °C/60% RH, does the Agency agree that a new stability study at 40 °C/75% RH (with improved secondary package) can be re-initiated, that the remaining samples at 25 °C/60%RH can be transferred to the improved secondary package and that the three Drug Substance batches can be accepted as registration stability batches? The improved secondary package will be used throughout the stability program for the validation batches (see Section S7 Stability)?

FDA Response: This is a review issue but your approach appears to be acceptable.

7. AnorMED has made several attempts to set up and validate the assay for microbial growth according to USP. Due to the high pH, a solution of AMD3100 Drug Substance seems to inhibit growth of several bacteria. With the modified assay described in Section S4.5.b Justification of Specification it is possible to (b) (4) (total aerobic count, yeast and molds). No attempt to grow the specified microorganisms according to USP <61> has succeeded. Does the Agency agree that it is appropriate to test for microbiological growth with the assay described (validated) and (b) (4) is an appropriate limit for total aerobic count, yeast and molds?

FDA Response: The assay seems appropriate at this stage. Upon submission of the NDA, a microbiologist will review the assay for final approval.

8. Does the Agency agree that the three Drug Product batches (batch numbers PD04047, PD04084 and PD04121) qualify as Primary Stability Batches and are suitable for use in registration of AMD3100 (see Section P2.c, e, f, g Drug Product)?

FDA Response: The drug product batches appear to qualify as stability and registration batches.

9. Does the Agency agree that the specifications for AMD3100 Drug Product are appropriate and justified for the current stage of development and for future registration of AMD3100 (see Sections P5.1 Specification and P5.6 Justification of Specification)?

FDA Response: This is a review issue but the majority of specifications appear reasonable at this time. However, for fill volume, please specify a range (upper as well as lower limits). Please refer to USP <1151> for guidance on overages.

10. Does the Agency agree that the impurities found in the AMD3100 Drug Product batches have been qualified in previous nonclinical and clinical studies (see Section P5.6 Justification of Specification and the Appended Report "Qualified Impurity Levels in AMD3100 for Dose of 240 pg/kg", Appendix 3)?

FDA Response: Yes. Please note that your proposed limits should be based on actual test data and manufacturing capability.

11. Does the Agency agree that the stability program to study the stability of AMD3100 Drug Product is suitable and sufficient for registration of AMD3100 (see Section P7 Stability)?

FDA Response: Your proposed stability program appears to be acceptable.

12. Does the Agency agree that AnorMED may introduce the described batches (batch numbers PD04084 and PD04121) of 20 mg/ml AMD3100 Drug Product into the ongoing and future Phase II clinical trials and to use them for the Phase III clinical trials (see section P Drug Product)?

FDA Response: Yes. Please note that the product used in Phase 3 clinical trials should be identical to the product to be marketed.

13. The pH result for Batch PD04047 was at the upper specification limit. Review of the literature suggests that the specification limit may be too narrow for the manufacture of an unbuffered formulation. If the pH results approach the upper limit for the upcoming batches, AnorMED could consider widening the limit before NDA submission. Does the Agency agree with the proposed approach (see Section P5.4 Batch Analyses and Section P5.6 Justification of Specification)?

FDA Response: The approach seems reasonable. However, if the need to broaden a specification arises, the appropriate justification should be provided.

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/s/

Ann Staten
11/30/04 10:33:24 AM

Nallaperumal Chidambaram
11/30/04 05:05:28 PM

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Tuesday, October 05, 2004 12:01 PM
To: 'batsma@anormed.com'
Cc: Staten, Ann M
Subject: Minutes of AMD3100 EOP2 meeting 9-10-04



55851 9-10-04
p2 minutes.pdf

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
301-594-5742/301-594-0498 (fax)

MEETING MINUTES

MEETING DATE: September 10, 2004 **TIME:** 1:00 **LOCATION:** E

IND: 55,851 **Meeting Request Receipt Date:** 7-28-04
FDA Response Date: 8-3-04
Briefing Document Receipt Date: 8-16-04

DRUG: AMD3100 **INDICATION:** stem cell mobilization for transplant
(multiple myeloma/NHL)

SPONSOR: AnorMed **TYPE of MEETING:** EOP2

FDA PARTICIPANTS: Donna Przepiorka, M.D., ODAC Cons. (review and pre-meeting)
Richard Pazdur, M.D. Dir., DODP (pre-meeting)
Grant Williams, M.D., Dep. Dir., DODP
Ann Farrell, M.D., Medical Team Leader, DODP
Maitreyee Hazarika, M.D., Medical Officer, DODP
John Leighton, Ph.D., Pharm. Supervisor, DODP (pre-meeting)
Luan Lee, Ph.D., Pharmacologist, DODP (pre-meeting)
Brian Booth, Ph.D., Clin. Phar./Biopharm. Team Leader, DODP
Raji Sridhara, Ph.D., Acting Stat. Team Leader, DODP
Ning Li, Ph.D., Statistician, DODP
Tan Nguyen, M.D., Orphan Products Development
Dotti Pease, Project Manager, DODP

SPONSOR: Bem Atsma, Reg. Affairs, Specialist, AnorMed
Gary Bridger, Ph.D., VP, Res. & Dev., Chief Sci. Off., AnorMed
Gary Calandra, M.D., Ph.D., VP, Clin. Dev., AnorMed
Beth Cameron, Ph.D., Proj. Man., AnorMed
John DiPersio, M.D., Onc. Consultant, Wash. Univ. of St. Louis
(b) (4)
Birgitta Hedin, Dir., Reg. Affairs, AnorMed
Ron MacFarland, Ph.D., Dir., Pharm. & Tox., AnorMed
(b) (4)

MEETING OBJECTIVES: Discuss proposed phase 3 trials and respond to sponsor's questions

BACKGROUND: An EOP1 meeting had been held April 7, 2004 during which it was agreed the sponsor would submit a concept sheet for each of the two proposed pivotal trials (one in multiple myeloma, and one in NHL). This was done on May 25, 2004, and AnorMed

followed with the request for an EOP2 meeting and two phase 3 protocols. The NHL trial is proposed for accelerated approval, with the multiple myeloma trial as the confirmatory study.

FDA draft responses were faxed to AnorMed on September 7, 2004 and the meeting was held for clarification and further discussion. AnorMed faxed us their responses to our comments on September 8, and these responses were presented and discussed at the meeting (indicated by italics).

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Phase III Protocols

1. Through the Phase I and Phase II program to 28 July 2004, 82 healthy volunteers, 40 HIV patients, and 134 cancer patients (MM, NHL, plus others via compassionate use) have been dosed with AMD3100. Of the cancer study subjects, 25 patients have been treated with a morning dose of AMD3100 followed by an afternoon apheresis while 94 patients have been treated with an evening dose of AMD3100 followed by apheresis in the morning. The patients in the Phase II trials have been in stage 1 complete remission (CR), 1 partial remission (PR), 2CR, or 2PR. No more severe disease than this has been entered except in the compassionate use program. An overview of the safety of AMD3100 is provided in Section 7.2.8. Does the Agency agree that the safety data from these populations are acceptable and sufficient to proceed with the proposed Phase III clinical trials with AMD3100?

FDA - Yes, the safety profiles are acceptable to continue with the Phase 3 studies. Please also provide the safety/efficacy data on your compassionate use program.

Sponsor concurs.

2. AnorMED intends to file an NDA on the Phase III NHL protocol (all NHL except chronic lymphoid leukemia) with the Phase III MM study (both single and tandem transplant) as the confirmatory study. Does the Agency agree that this Phase III design will support registration of AMD3100 with the proposed indication?

FDA - Yes, two randomized trials demonstrating safety and efficacy could support an indication for autologous stem cell transplantation. The exact indication wording will depend on our complete review of the data.

AnorMED understands this.

3. Does the Agency agree with the Primary endpoints of the Phase III clinical trials (Section 10.1.6 and Section 10.2.6)?

FDA - See above and attached comments.

DISCUSSION: see below re: statistical analysis

4. Does the Agency agree with the proposed statistical analyses of the Phase III protocols (Section 10.1.8 and Section 10.2.8)?

FDA - See above and attached comments. Please submit a complete statistical analysis plan (SAP) with your revised protocols. Generally we consider the ITT analysis the primary analysis. Every effort should be made to minimize dropouts as imbalance between treatment arms could confound the analysis.

DISCUSSION: See below. The sponsor prefers a modified ITT or per-protocol as the primary analysis. The sponsor will provide details in a revised protocol. Sponsor asked when the SAP should be submitted. FDA – as early as possible, at least well before blind is broken. Also, include an update of the statistical analysis plan in the SPA. You will also need CRFs with the SPA protocols.

5. AnorMED will submit 12-month follow-up for the patients in the Phase II clinical trials, a maximum total of 82 MM and NHL patients dosed with AMD3100 plus G-CSF mobilized cells under this IND. AnorMED proposes to close the database of the Phase III clinical trials for the writing of the NDA after 3-month follow-up for all patients transplanted in the Phase III trials. AnorMED expects 30-50 NHL patients and 15-20 MM patients from the Phase III trials to have reached the 12-month follow-up point at the closing of the database. Does the Agency agree this will provide sufficient follow-up data for the NDA submission?

FDA - Yes, as long as graft durability at 6-months for all patients is provided with or prior to your 120 day safety update.

DISCUSSION: Sponsor – agree, and they will also provide a one year follow-up. The sponsor stated they will have graft durability at 100 days available at time of NDA submission. The Agency requested that 6 months durability data be submitted as soon as possible.. Sponsor agreed and will provide “rolling” durability data.

6. AnorMED will report all adverse events out to 30 days after the last apheresis. AnorMED will report all serious adverse events out to 6 months post-transplantation regardless of

causality. AnorMED proposes not to report those adverse events commonly associated with stem cell transplantation (list included in Appendix D the Phase III protocols) during and after the transplantation phase of the Protocols. Does the Agency agree with this procedure and the list of adverse events to not be reported?

FDA - All SAEs and any graft failure through 6 months after transplantation or until relapse, whichever is shorter, should be collected and eventually documented in the NDA.

In your revised protocol, please re-submit the list with graded AEs that you propose do not need expedited reporting.

DISCUSSION: Sponsor really intended to ask if they should collect AEs expected from after transplant. See presentation. FDA – agree in principle, but we will discuss with our consultant.

7. The Agency has suggested that AnorMED use the National Cancer Institute Common Toxicity Criteria (NCI CTC) to record adverse events in our clinical trials. To date AnorMED has included a modified WHO adverse event grading scale as reference in our clinical trial protocols. AnorMED will include the NCI CTC criteria with the protocols as reference for the investigators, but proposes to continue reporting the adverse events by the same defining codes as before (ie., grade = mild/moderate/severe/life-threatening; terms as per the Medical Dictionary for Regulatory Activities (MedDRA)). This will allow comparability of the safety across the Phase II and Phase III trials. Does the Agency agree with this approach?

FDA - Reporting toxicity according to the WHO criteria is acceptable.

Clinical Pharmacology

8. AnorMED does not intend to study the effects of renal impairment in humans on the dosing of AMD3100. This is justified by the short-term administration of AMD3100 (up to 4 days), the short half-life of AMD3100 in plasma from normal subjects (3-6 hours), and the current safety window (40 fold lower than the maximum human exposure). AnorMED proposes instead to compare the safety of AMD3100 across calculated creatinine clearance values. Does the Agency agree this is a suitable course of action?

FDA - Since patients with myeloma on dialysis are eligible for transplantation, it would be useful to have information on how to dose this drug in that population.

DISCUSSION: Sponsor – Agree to study; must renal insufficiency pts be multiple

myeloma patients, or can they be noncancer patients? FDA – we'll check with consultant.

9. Does the Agency agree with the studies proposed in Section 9 to examine the metabolism of AMD3100 and that these studies are sufficient for registration?

FDA - Yes, these studies seem reasonable.

Package Insert

10. Does the Agency agree with the wording of the proposed indication?

FDA - This is a review issue. The exact labeling will depend on the design, patients enrolled and results of the clinical trials. Your proposed indication is unsatisfactory, and specifics of the wording would be discussed following completion of our review of your NDA. A possible indication may be "increase in number of CD34 cells..."

AnorMED understands this.

Compassionate Use Program

11. Reference is made to the compassionate use protocol AMD3100-CUP001 and to the discussion regarding this protocol at the End of Phase I meeting on 7 April 2004. Does the Agency agree there is sufficient safety information on AMD3100 to allow AnorMED to enroll patients into the Compassionate Use program without the prior approval of each patient by the Agency?

FDA – Yes. You are reminded that the patients enrolled in the Compassionate Use program should be included and submitted in the NDA Safety database.

Sponsor concurs. 48 patients have been enrolled so far. Fifteen of 24 patients who received AMD3100 achieved adequate CD34⁺ cells for transplant and 12 patients were transplanted. The sponsor commented that one out of five requests for AMD3100 are turned down.

ADDITIONAL FDA COMMENTS:

General Comments for trials involving NHL patients and MM patients

1. We would recommend excluding patients for whom selection or purging of the apheresis product is planned, since such manipulation may alter engraftment characteristics and impact analysis of the secondary objectives.

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