

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-311**

**CHEMISTRY REVIEW(S)**

# Memorandum

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**To:** NDA 22-311  
**CC:** Sue-Ching Lin, M.S., R.Ph.; Terrance Ocheltree, Ph.D.; Rik Lostritto, Ph.D.  
**From:** Sarah C. Pope, Ph.D.  
**Date:** 12/12/2008  
**Re:** Final CMC recommendation for NDA 22-311

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NDA 22-311 was initially submitted on 16-JUN-2008 and was granted a priority review by the Agency. Resolution of all CMC deficiencies is captured in Chemistry Review #1 (dated 02-DEC-2008), with the exception of a final recommendation from the Office of Compliance. Chemistry Review #1 (p. 130) also captured the following outstanding recommendation regarding the container/carton labels, which was conveyed to the Applicant on 17-NOV-2008:

*Please refer to the revised container label and carton labeling submitted in your 11/12/08 amendment. The font color for the proprietary name on the container label and carton labeling is too light and hardly visible, whereas the company name "Genzyme" appears to be much more prominent than the drug name. Therefore, increase the prominence (darkness) of the font color for the drug name and remove or lighten the background color for the areas containing "Genzyme."*

The Applicant responded to this recommendation in a 03-DEC-2008 submission, which included revised container/carton labeling. However, while the Applicant revised the font color according to the Agency's previous recommendation, additional unacceptable revisions to the trade name font size were made. Therefore, the following comment was conveyed to the Applicant on 04-DEC-2008:

*Note that the non-proprietary name is not half the prominence of the proprietary name. The proprietary name is too wide compared to the non-proprietary name. Increase the prominence of the non-proprietary name in relation to the proprietary name.*

The following additional comments were generated by DMEPA and were conveyed to the Applicant on 05-DEC-2008:

*The current presentation of the font lettering for the established name (plerixafor injection)*

*appears crowded. This presentation makes the established name difficult to read. Revise the presentation of the established name accordingly, to comply with the regulation.*

*We also note that the tradename "Mozobil" is presented in an unconventional mixed upper/lower case font style. This style does not provide the most ideal presentation of the last letter "L", which makes the letter appear more like a capital letter 'I'.*

The Applicant responded with updated and revised container/carton labels in an amendment dated 12-DEC-2008. Note that this updated labeling includes two minor revisions.

(b) (4) of the drug name (Mozobil to (b) (4)) was further revised, and the (b) (4) statement was repositioned to the first line following the trade name. These revisions were discussed internally with members of DMEPA, the SEALED team, and the chair of ONDQA's Labeling and Nomenclature committee (Dr. Rik Lostritto) on 12-DEC-2008. All contacted parties agreed that these revisions were acceptable. However, the Applicant's 12-DEC-2008 submission did not conform precisely to previously-negotiated language. In the Highlights section, a minor revision of the (b) (4)

This memo serves to update the overall CMC recommendation for NDA 22-311. The Office of Compliance issued an overall acceptable recommendation for this application on 10-DEC-2008. All major CMC labeling issues are resolved, and acceptable container/carton labels were submitted on 12-DEC-2008. There is one outstanding labeling recommendation (see above), which is not a CMC approvability issue.

Accordingly, from a CMC perspective, approval of NDA 22-311 is recommended.

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/s/

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Sarah Pope  
12/12/2008 04:05:36 PM  
CHEMIST

ONDQA Division Director's Memo  
NDA 22-311, Mozobil 20 mg/mL subcutaneous injection  
Date: 08-DEC-2008

## Introduction

Mozobil (plerixafor injection) 20 mg/mL for subcutaneous injection is indicated for use in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkins lymphoma and multiple myeloma.

This solution formulation drug product is proposed to be packaged as 1.2 mL (containing 24 mg) in single-use glass vials. The recommended dose is 0.24 mg per kg of body weight.

The shelf life of the drug product is thirty six (36) months at controlled room temperature.

## Administrative

The original submission of this 505(b)(1) NDA was received 16-JUN-2008 from Genzyme Corporation. Five amendments to the NDA were received and reviewed between 04-SEP-2008 and 26-NOV-2008 and were either responses to CMC deficiencies or stability updates.

The associated IND is 55,851. During the IND phase, three CMC meetings occurred.

There are no outstanding CMC deficiencies or agreements. On 12-NOV-2008, the microbiology review recommended approval.

**A recommendation for approval (AP) from ONDQA is pending an overall acceptable recommendation from The Office of Compliance.** As of the date of this writing, the pre-approval inspections are in progress.

## Drug Substance (plerixafor)

The active ingredient (plerixafor,  $C_{28}H_{54}N_8$ ), is synthesized in (b) (4) steps as a free base and it is a new molecular entity. During development, the synthesis was optimized which resulted in lower impurity levels. This optimization included improved in-process, starting material, and intermediate controls.

Interestingly, all eight (8) nitrogens per molecule are aliphatic and may be protonated in aqueous media depending on the pH. pKa's 1 through 6 have been measured; pKa's 7 and 8 are estimated. The situation is such that four (4) nitrogen atoms are protonated in solution over the proposed pH range of range of the drug product (6.0 to 7.5)

Plerixafor free base exists in a single hygroscopic crystalline form. It is stored in (b) (4) bags (triple bagged, with desiccant) and has a (b) (4) month retest period.

### **Drug Product (Mozobil)**

Mozobil is a sterile, preservative-free, clear, colorless to pale yellow, isotonic solution of plerixafor for subcutaneous injection. Each mL of the sterile solution contains 20 mg of plerixafor. Each single-use vial is filled to deliver 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 as required.

During development, the use of buffers to more tightly control the pH resulted in unacceptable stability (buffer catalysis). The applicant decided to not use any buffer. Thus, the pH range (of very low buffer capacity) of the drug product is justified. Note that the pKas of plerixafor are such that the buffer capacity exerted by the drug substance in the formulation is also very small.

Plerixafor injection is manufactured for Genzyme by a contract manufacturing facility, Patheon UK Ltd. The drug product is manufactured by dissolving the drug substance water for injection and sodium chloride. This pH of this bulk solution is adjusted and brought to the specified final concentration using water for injection. (b) (4)  
The (b) (4) product is then filled into glass vials (b) (4).

The submitted stability data from 12 batches support the proposed 36-month expiration dating period for the drug product stored at the proposed controlled room temperature. .

Rik Lostritto, Ph.D., Director, ONDQA Division III

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/s/

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Richard Lostritto  
12/8/2008 05:54:03 PM  
CHEMIST

**NDA 22-311**

**Mozobil<sup>®</sup>**  
**(plerixafor injection)**

**Genzyme Corporation**

**Sue-Ching Lin**

**Review Chemist**

**Office of New Drug Quality Assessment**  
**Division of Pre-marketing Assessment and Manufacturing Science**  
**Branch V**

**Chemistry, Manufacturing, and Controls (CMC) Review of Original NDA**  
**For the Division of Drug Oncology Products (HFD-150)**

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# CMC Review Data Sheet

1. NDA 22-311
2. REVIEW #: 1
3. REVIEW DATE: 28-Nov-2008
4. REVIEWER: Sue-Ching Lin
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original IND 55,851 submission	04-May-1998
End-of Phase 1 guidance meeting	07-Apr-2004
CMC end-of-phase-2 meeting	15-Nov-2004
CMC only telecom	25-Jul-2006
CMC only telecom	06-Jun-2007
Pre-NDA meeting (clinical)	01-Oct-2007

6. SUBMISSION(S) BEING REVIEWED:

<b>Submission(s) Reviewed</b>	<b>Document Date</b>
Original NDA Submission	16-Jun-2008
Amendment (BC) (Response to CMC comments in filing letter)	04-Sep-2008
Amendment (BZ) (DS and DP stability update and partial response to 10/2/08 IR)	15-Oct-2008
Amendment (BZ) (Revised container label and carton labeling, revised drug substance and starting material specifications)	12-Nov-2008
Amendment (BC) (Response to 11/6/08 IR)	21-Nov-2008
Amendment (BC) (Purging studies using impurities in starting material (b) (4))	26-Nov-2008

## CMC Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Genzyme Corporation  
Address: 500 Kendall Street, Cambridge, MA, 02142  
Representative: Laura Mondano, Director, Regulatory Affairs  
Telephone: (617) 591-5994

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Mozobil
- b) Non-Proprietary Name: plerixafor injection
- c) Code Name/# (ONDQA only): Laboratory Codes: AMD3100
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 1 (new molecular entity)
  - Submission Priority: P (priority review)

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: stem cell mobilization (antagonist of CXCR4 chemokine receptor)

11. DOSAGE FORM: injection

12. STRENGTH/POTENCY: 20 mg/mL

13. ROUTE OF ADMINISTRATION: subcutaneous

14. Rx/OTC DISPENSED:  Rx  OTC

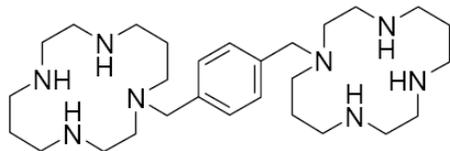
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

CMC Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



C<sub>28</sub>H<sub>54</sub>N<sub>8</sub>  
MW: 502.79

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	4	N/A	11/28/08 (See current CMC review)	Starting material, see section 3.2.S.2.3
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	11/28/08 (See current CMC review)	See section 3.2.S.6
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	11/28/08 (See current CMC review)	See section 3.2.P.7
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	3/23/07	Reviewed by Mark Sassaman
			(b) (4)	3	Adequate	4/12/07	Reviewed by Mark Sassaman
			(b) (4)	1	Adequate	11/18/08	Reviewed by Sue-Ching Lin

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

CMC Review Data Sheet

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	55,851	AMD3100, plerixafor

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	Pending	Pending
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA*	The proposed proprietary name Mozobil is acceptable.	10/31/08	Cathy A. Miller
EA	Categorical exclusion (see review)	11/28/08	Sue-Ching Lin
Microbiology	Approval from microbiology product quality standpoint.	11/12/08	Vinayak Pawar

\*DMEPA: Division of Medication Error Prevention and Analysis

## Executive Summary Section

# The CMC Review for NDA 22-311

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA may be approved, pending an “acceptable” overall recommendation from the Office of Compliance for the inspections of the manufacturing and testing facilities for the drug substance and drug product.

The proposed 36-month expiration dating period is acceptable for the drug product stored at the proposed controlled room temperature.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of CMC Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

The active ingredient is plerixafor, which is a new molecular entity. Detailed information regarding the drug substance is provided in the NDA.

Plerixafor is chemically synthesized as a free base. The manufacture of plerixafor from starting materials involves (b) (4) steps. Potential and actual impurities arising from the starting materials, the synthetic process, and degradation were identified. During the development, a significant reduction in impurities was observed, (b) (4)

(b) (4) the manufacturing process is able to remove and control the impurities to desired levels.

Plerixafor has been isolated as a single crystalline form through all stages of development. It is hygroscopic. The drug substance is packaged in double (b) (4) bags which are placed inside a (b) (4) outer bag. A 100-gram desiccant unit is used to control moisture. The outer bag is heat-sealed

## Executive Summary Section

and then placed into a (b) (4). Plerixafor is soluble, to levels over (b) (4) in aqueous solution, when the pH is adjusted to between 1 and 10.

The submitted stability data, including up to 36 months for 4 primary stability batches and 3 supportive batches, support the proposed retest period of (b) (4) months when packaged in the proposed container system and stored at controlled room temperature.

**(2) Drug Product**

Plerixafor injection is a sterile, preservative-free, clear, colorless to pale yellow, isotonic solution of plerixafor for subcutaneous injection. Each mL of the sterile solution contains 20 mg of plerixafor. Each single-use vial is filled to deliver 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.

Plerixafor injection is manufactured for Genzyme by a contract manufacturing facility, Patheon UK Ltd. The drug product is manufactured by initial formulation of the drug substance in a bulk solution containing water for injection and sodium chloride. The resulting bulk solution is pH-adjusted and is brought to a final weight with water for injection. The resulting solution is (b) (4) into a pre-sterilized disposable receiving bag. The (b) (4) product is then filled into glass vials (b) (4).

The submitted stability data from 12 batches support the proposed 36-month expiration dating period for the drug product stored at the proposed controlled room temperature.

**B. Description of How the Drug Product is Intended to be Used**

The drug product is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkins lymphoma and multiple myeloma. The drug product is administered approximately 11 hours prior to initiation of apheresis and up to 4 consecutive days following the start of G-CSF administration.

The recommended dose is 0.24 mg/kg body weight by subcutaneous injection. Each vial of Mozobil is intended for single use only. Any unused drug remaining after injection must be discarded.

## Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

A detailed pharmaceutical development report and manufacturing process descriptions were provided in the NDA for the drug substance and drug product. Adequate data have been provided to ensure the quality of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable for subcutaneous injection from the microbiology perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Mozobil.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling negotiations of the NDA. The revised container labels and carton labeling, as amended by the applicant on November 12, 2008, and modified on November 21, 2008 with more prominent font color for the drug name, are acceptable.

The inspections for some of the facilities are still pending. This NDA is approvable pending an “acceptable” overall recommendation from the Office of Compliance.

**III. Administrative****A. Reviewer’s Signature:**

*(See appended electronic signature page)*

Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

Terrance Ocheltree, R.Ph., Ph.D., Acting Pharmaceutical Assessment Lead, Branch V, ONDQA

Sarah Pope, Ph.D., Acting Branch Chief, Branch V, ONDQA

**C. CC Block:** entered electronically in DFS

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/s/

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Sue Ching Lin  
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Terrance Ocheltree  
12/2/2008 12:06:49 PM  
CHEMIST

Sarah Pope  
12/2/2008 12:56:52 PM  
CHEMIST  
Concur

**Initial Quality Assessment  
Branch V  
Pre-Marketing Assessment and Manufacturing Science Division III  
Office of New Drug Quality Assessment**

OND Division: Division of Drug Oncology Products  
NDA: 22-311  
Applicant: Genzyme Corporation  
Stamp date: 16-JUN-2008  
PDUFA Date: 16-APR-2008 (standard review anticipated)  
Proposed Trade Name: Mozobil  
Established Name: Plerixafor  
Laboratory Code: AMD3100  
Dosage Form: Solution for injection  
Route of Administration: Subcutaneous injection  
Indication: For use to enhance mobilization of HSC's to peripheral blood for collection and transplantation in lymphoma and multiple myeloma patients.  
Regulatory filing: 505 (b)(1)

Pharmaceutical Assessment Lead: Sarah C. Pope, Ph.D.

	YES	NO
ONDQA Fileability:	<u>√</u>	—
Draft Comments for 74-Day Letter:	<u>√</u>	—

## Summary, Critical Issues and Comments

### A. Summaries

#### Background Summary

NDA 22-311 is submitted for Mozobil (plerixafor for injection), 20 mg/mL, intended for use to enhance mobilization of HSC's to peripheral blood for collection and transplantation in lymphoma and multiple myeloma patients. The drug development for plerixafor is filed under IND 55,851 (originally submitted 05-MAY-1998). Multiple pre-submission meetings were held with all disciplines, including clinical EOP1 and EOP2 meetings (07-APR-2004 and 10-SEP-2004 respectively), a CMC-specific EOP2 meeting (15-NOV-2004), a clinical pre-NDA meeting (01-OCT-2007), and a treatment protocol (submitted 20-FEB-2008; see CMC review dated 21-APR-2008). The NDA was submitted to the Agency on 16-JUN-2008.

#### Drug Substance Summary

Plerixafor is a white to off-white crystalline solid, which possesses the structure shown below (Figure 1). Plerixafor has a typical melting point of 131.5°C, and additional morpic forms have not been identified. Plerixafor does have one tetrahydrate form that is present at high humidity levels, and the structure does not contain any stereocenters.

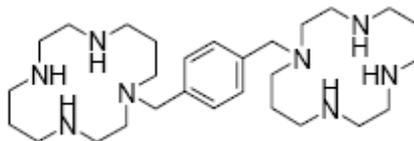


Figure 1. Plerixafor (MW=502.79 g/mol, anhydrous)

Plerixafor is manufactured at the following site:

(b) (4)

Plerixafor is chemically synthesized via a moderately complex synthetic process involving a (b) (4) (b) (4)

The Applicant proposes specifications for (b) (4) isolated intermediates as well as for the crude plerixafor material.

Once manufactured, plerixafor is tested for conformance to specifications for the following attributes: appearance, color of solution, identification (FTIR and HPLC), assay (HPLC), impurity profile (HPLC), (b) (4) content (HPLC), water content (KF), (b) (4) content (HPLC), heavy metals, residual solvents (GC), residue on ignition, microbial limits, and bacterial endotoxins. The final drug substance is

packaged in double (b) (4) bags which are placed inside a (b) (4) outer bag. A 100-gram dessicant unit is used to control moisture. The outer bag is heat-sealed and then placed into a (b) (4).

The Applicant provides 24 months of long-term (25°C/60%RH) stability data generated using three batches of plerixafor, manufactured using a representative process. The Applicant also provides 6 months of accelerated (40°C/75% RH) stability data generated using the same batches. The Applicant provides supportive stability data for batches manufactured via earlier processes. The applicability of these data will be assessed during the review cycle.

The Applicant proposes a (b) month retest period for plerixafor when stored at 25°C, with excursions permitted to 15°C to 30°C.

### **Drug Product Summary**

Plerixafor injection is proposed as a 20 mg/mL solution intended for subcutaneous injection. The sterile, isotonic, and aqueous solution also contains sodium chloride and a buffering system (hydrochloric acid/sodium hydroxide).

The Applicant proposes the following site for drug product manufacture:

Patheon UK Ltd.  
Kingfisher Drive  
Covingham  
Swindon, Wiltshire  
SN3 5BZ UK  
Establishment Number: 3003171805

The drug product is manufactured by initial formulation of the API in a bulk solution containing the remaining excipients. The resulting bulk solution is pH-adjusted and is brought to a final weight with Water for Injection. The resulting solution is (b) (4) pre-sterilized disposable receiving bag. The (b) (4) product is then filled into the primary packaging components (glass vials) (b) (4). Once manufactured, the product is sampled and tested for conformance with (4) specifications for description, identification (HPLC and FTIR), potency (HPLC), degradant profile (HPLC), pH, osmolality, volume in container, particulate matter, sterility, and bacterial endotoxins.

The Applicant's stability data package includes data generated under long term (25°C/60%RH, 12 months) and accelerated (40°C/75%RH, 6 months) conditions for three primary stability batches. Photostability data are also provided in accordance with ICH Q1B. Additional studies conducted under stressed conditions include a freeze-thaw study, an in-use stability and compatibility study, and a sterilization stress study.

The Applicant proposes a 36-month expiration dating period for the drug product, when stored at 25°C, with excursions permitted to 15°C to 30°C.

## **B. Critical issues for review and recommendation**

### **Drug Substance**

- a. The cross-reference of DMF (b) (4) is not adequately described in the submission. DMF (b) (4) is a Type 2 DMF, and while a LOA is provided in the NDA, the applicability of the cross-referenced information is not clearly specified. This will be transmitted as a comment in the 74-day letter, but this aspect should also be pursued completely during the subsequent CMC review.

- b. Plerixafor is a New Molecular Entity. The proposed impurity profile should be carefully assessed for adequacy, relative to historical pre-clinical lots as well as generated batch data to date. This should be discussed with the Pharmacology/Toxicology reviewer, if necessary.
- c. The Applicant's proposed manufacturing scheme is highly complex and involves multiple convergent synthetic pathways leading to the final drug substance. For the purposes of this initial assessment, manufacturing sites for intermediates have not been entered into EES. However, if consequent review determines that a compliance recommendation is required for any of the intermediate manufacturing sites, these sites should be entered as soon as possible.
- d. Based on the synthetic information provided, it appears that at least (b) (4) potential starting materials (b) (4) are used in the synthesis of plerixafor. The acceptability of the Applicant's proposed starting materials should be carefully assessed during the review.
- e. The synthetic process development for plerixafor incorporates many revisions which should be carefully assessed for potential impact on overall drug substance purity and quality. Given the complexity of the multi-step synthesis, the provided batch history (Section 3.2.S.2.6) should be thoroughly reviewed.

#### **Drug Product**

- a. The cross-reference of DMF (b) (4) is not adequately described in the submission. While a LOA is provided in the NDA, the applicability of the cross-referenced information is not clearly specified. This will be transmitted as a comment in the 74-day letter, but this aspect should also be pursued completely during the subsequent CMC review.
- b. The proposed drug product specifications do not include testing for any identified degradants or impurities, and the currently-proposed acceptance criterion for all single impurities is NMT (b) (4). This proposal should be carefully examined.
- c. The Applicant employs an overage in the glass vials, in order to effect withdrawal of the required amount. Acceptability of this overage should be confirmed as part of the CMC review.
- d. Insufficient stability data are provided to justify the proposed expiration dating period of 36 months. A comment will be transmitted in the 74-day letter. However, this should be further assessed during the review.

#### **C. Comments for 74-day Letter:**

- 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.
- 2. 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.

**D. Recommendation for fileability: Fileable**  
**Fileability Template**

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √		Microbiology Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CBER LNC DMETS/ODS EER
		√		
		√		

**Have all DMF References been identified? Yes (✓) No ( )**

DMF Number	Holder	Description	LOA Included
(b) (4)	(b) (4)	Unclear (see comments)	Yes
(b) (4)	[REDACTED]	Unclear (see comments)	Yes
(b) (4)	[REDACTED]	2-mL, Type 1 clear glass vial	Yes
(b) (4)	[REDACTED]	13-mm grey rubber stoppers and flip-off seals	Yes

**Recommendation for Team Review:**

While this NDA contains a significant amount of CMC information, this review should be easily conducted by a single reviewer experienced in synthetic chemistry and sterile manufacture. The team approach is not recommended for this NDA.

Sarah C. Pope, Ph.D.  
Pharmaceutical Assessment Lead

16-JUL-2008  
Date

Ravi Harapanhalli, Ph.D.  
Branch Chief

16-JUL-2008  
Date

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

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Sarah Pope  
7/24/2008 10:09:23 AM  
CHEMIST

Ravi Harapanhalli  
7/24/2008 04:14:14 PM  
CHEMIST