CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-065

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 22-065, IXEMPRA (ixabepilone) for Injection
Date: October 15, 2007

Introduction

IXEMPRA (ixabepilone) for Injection is supplied as a **kit** (in a paper carton) containing a — vial of the lyophilized drug substance (ixabepilone) and a—— vial of DILUENT for IXEMPRA, which is used to constitute the lyophilized drug substance.

Two strengths of the drug product are proposed. In one configuration, a 15 mg vial of ixabepilone for injection (in 10 mL—— vials) is co-packaged with an 8 ml DILUENT for IXEMPRA, also in 10 mL— vials. In a second configuration, 45 mg ixabepilone in 50 mL ——vials will be co-packaged with 23.5 mL DILUENT for IXEMPRA in 30 mL —— vials.

The drug substance is photosensitive and degrades in the presence of light; the outer carton provides protection from light. Prior to intravenous (IV) administration the constituted solution (lyophilized powder plus copackaged diluent) must be further diluted with Lactated Ringer's Injection, USP to a final concentration between 0.2 mg/mL and 0.6 mg/mL.

The carton is labeled to protect the contents from light. Also, the co-packaged diluent cannot be used for another drug product; likewise no other diluent may be used to solubilize the lyophilized drug substance. These cautions do appear in the labeling.

Adminstrative

The application is recommended for an approval (AP) action from chemistry, manufacturing and controls (CMC) perspective. Acceptable recommendations have been received form Microbiology and the Office of Compliance.

There are two CMC Phase-IV post-approval ***agreements***. These are:

The inclusion of tests ——————————— : in the Specification for the 8 mL and 23.5 mL vials of DILUENT for Ixempra is being evaluated by the company. The company has indicated that a decision on the inclusion of these tests will be provided at a later date.

The company has also indicated that the representative certificates of analysis (COAs) for polyoxyethylated castor oil, purified and dehydrated alcohol will be provided at a later date. The COAs have not been received as of the date of this review. The COAs, should be sent as soon as feasible.

Drug Substance

Ixabepilone (USAN and INN name) is a new chemical entity, (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1- methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9- dione (cas# 219989-84-1). It has a molecular weight of

506.7 and has low water solubility [redacted] which is unaffected by pH.

However, solution stability is affected by pH; the maximum stability for ixabepilone in aqueous solution is between 6 and 10. [redacted] indicative of the hydrophobic nature of ixabepilone.

Ixabepilone is a non-sterile, semisynthetic analog of the natural product epothilone B. The commercial manufacture involves isolation of the final intermediate [redacted]

Drug Product

IXEMPRA (ixabepilone) for Injection vials will be manufactured at Baxter Oncology, Halle, Germany. IXEMPRA is a single-use, sterile, lyophilized powder for intravenous (IV) infusion following constitution with supplied diluent and further dilution with Lactated Ringer's Injection, USP. Two different strengths, 15 mg and 45 mg, have been proposed for commercial product. The lyophilized powder vials, do not contain any excipients and only contain lyophilized drug substance.

IXEMPRA for Injection, 15 mg and 45 mg, are packaged in [redacted] vials, [redacted]

The DILUENT consist of a 50/50 (v/v)[or 52.8%/39.8% (w/v), [redacted]] mixture of purified polyoxyethylated castor oil (also known as Cremophor, or Polyoxyl 35 castor oil, NF) and dehydrated alcohol, USP. Purified polyoxyethylated (POE) castor oil is a nonionic surfactant [redacted]

Two presentations, 8 mL and 23.5 mL (extractable volume), for DILUENT for IXEMPRA are proposed. The 8 mL DILUENT is used for 15 mg ixabepilone for injection vial and 23.5 mL DILUENT is used for 45 mg ixabepilone for injection vial. Both presentations are packaged in [redacted] vials, [redacted]

Adequate data are provided to support the requested expiration dating period of 24 month when stored in a refrigerator at 2°-8°C (36°-46°F) and retained in the original package to protect from light. Samples [redacted] refrigerator or room temperature [redacted]. The product is required to have the statement "Protect from light" on the label.

Since diluent and the drug are co-packaged, the expiration dating period for the package is 24 months. The storage condition for the copackaged product is to store in a refrigerator at 2°-8°C (36°-46°F) and retain in the original package to protect from light.

Special Use Considerations

Prior to use the IXEMPRA Kit needs to be taken out of the refrigerator and brought to room temperature.

The IXEMPRA (ixabepilone) for injection is constituted with the DUILUENT for IXEMPRA at room temperature. The concentration of ixabepilone in the constituted product in either case is 2 mg/mL. Solubility of ixabepilone in the supplied DILUENT is [redacted] and the powder dissolves rapidly when constituted. The constituted solution is clear to slightly hazy (opalescent), colorless to pale yellow in appearance. The constituted ixabepilone solution is to be kept in the original vial and must be used (i.e. further diluted with Lactated Ringer's Injection, USP) within one hour.

To achieve an infusion solution concentration of 0.2 mg/mL, each mL of the aforementioned consitituted solution (containing 2.0 mg/ml ixabepilone) will need to be diluted [redacted] with with Lactated Ringer's Injection, USP.

To achieve an infusion solution concentration of 0.6 mg/mL, each mL of the consitituted solution (containing 2.0 mg/ml ixabepilone) will need to be diluted to a final volume [redacted] with Lactated Ringer's Injection, USP.

Ixabepilone concentrations between 0.2 mg/mL and 0.6 mg/mL are well below the saturation solubility of ixabepilone at both room temperature (23°C) and refrigerated (2°C). Thus, ixabepilone is not likely to precipitate from the infusion solution. NOTE: Only DEHP(di[2-ethylhexyl]phthalate) free infusion bags and sets may be used to administer dilutions of ixabepilone for injection. This is to be reflected in the labeling.

The dilution of ixabepilone in Lactated Ringer's Injection, USP is to be administered over 3 hours using an infusion set equipped with an in-line or final filter with a microporous membrane size of 0.2 to 1.2 microns. The ixabepilone solution in Lactated Ringer's Injection, USP has a shelf life of 6 hours at room temperature and room light, and the infusion should be completed within this 6-hour period.

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

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/s/

Richard Lostritto
10/15/2007 03:27:44 PM
CHEMIST

NDA 22-065

IXEMPRA™ **Kit**
(ixabepilone) for injection
15 mg & 45 mg

Bristol-Myers Squibb Company
5 Research Parkway
P.O. Box 5100, Mailstop 3 sig-509
Wallingford, CT 06492

Ravindra K. Kasliwal, Ph.D.
CMC Reviewer
Division of Pre-marketing Assessment and
Manufacturing Science,
Branch V, ONDQA
CDER, FDA

For The Division of Drug Oncology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA **22-065**

2. REVIEW #: 1

3. REVIEW DATE: 19-Sep-2007 (Revised 25-Sep-2007)

4. REVIEWER: Ravindra K. Kasliwal, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	16-Apr-2007
Amendment (BC)	30-Aug-2007
Amendment (BC)	05-Sep-2007
Amendment (BC)	11-Sep-2007
Amendment (BI)	14-Sep-2007
Amendment (C)	14-Sep-2007
Amendment (BC)	14-sep-2007
Amendment (BC)	20-Sep-2007
Amendment (BC)	21-Sep-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Bristol-Myers Squibb Company
Address:	5 Research Parkway P. O. Box 5100, Mailstop 3Sig-509 Wallingford, CT 06492
Representative:	A. Heather Knight-Trent, Pharm. D. Director, Global Regulatory science
Telephone:	(203) 677-3858

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ixempra™ (proposed)
b) Non-Proprietary Name (USAN): Ixabepilone
c) Code Name/# (ONDC only): BMS247550-1; BMS 247550
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Microtubule Inhibitor

11. DOSAGE FORM: Single-use, Sterile, Lyophilized Powder For Injection

12. STRENGTH/POTENCY: 15 mg and 45 mg

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

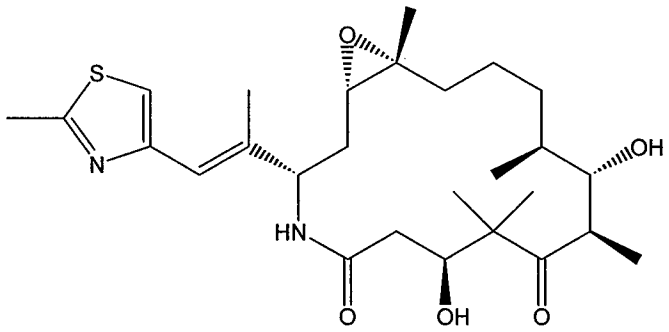
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

CAS Name: (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1- methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9- dione.

IUPAC Name: (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(*E*)-1-methyl- 2-(2-methyl-1,3-thiazol-4-yl)vinyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione



$C_{27}H_{42}N_2O_5S$
Mol. Wt.: 506.70
C, 64.00; H, 8.35; N, 5.53; O, 15.79; S, 6.33

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]				There is enough

Chemistry Review Data Sheet

				4	N/A	N/A	data in the application, therefore the DMF did not need to be reviewed
	III			3, 4	N/A	Marla Stevens – Riley, PH>D 11-Dec-2006	process has been determined to be adequate in previous DMF reviews.
	III			3, 4	Adequate	10-Jul-2003 by David Lewis, Ph.D.	Adequate
	III			3,4	Adequate	Marla Stevens – Riley, Ph.D. 27-Jan-2007	and has been determined to be adequate in previous DMF reviews.
	III			3,4	Adequate	S. Prasad Peri, Ph.D - 4405/50 Grey formulation – 31-mar-2003; Elsbeth Chikale, Ph.D. – B2-40 coating 14-Nov-2005; Mark Sassaman, Ph.D. –fluorotec formulation – 23-Mar-2007	These formulations have been used in many intravenous pharmaceutical products and are acceptable.

[1] 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")

[2] 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

BMS IND for Ixabepilone	IND 58,546	N/A
NCI IND for Epothilone B analog	IND 59,699	N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	10-Sep-2007	S. Ferguson
Pharm/Tox	——— in Lyophilized powder vial and ——— levels in drug substance are acceptable. Tox studies for impurity qualification are satisfactory.	21-Sep-2007	Robeena Aziz, Ph.D.
Biopharm	N/A		
LNC	N/A		
Methods Validation	Analytical methods are conventional, DPA verification will not be requested.		
ODS	PENDING		
EA	Claim for categorical exclusion is justified	Review Date	Ravindra K. Kasliwal, Ph.D.
Microbiology	PENDING		

The Chemistry Review for NDA 22-065

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for an approval action for chemistry, manufacturing and controls under section 505 of the Act, provided an acceptable recommendation has been received form product quality microbiology, and the trademark acceptability has been determined by Office of drug safety. The Office of Compliance recommeds that the manufacturing facilities are acceptable as of 10-Sep-2007.

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

The company has also indicated that the representative certificates of analysis for polyoxyethylated castor oil, purified and dehydrated alcohol will be provided at a later date. The COAs have not been received as of the date of this review. The coamny should also be reminded of this issue.

II. Summary of Chemistry Assessments

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

The IXEMPRA™ drug product will be supplied as a **kit** (in a paperboard folding carton) containing a vial of IXEMPRA (ixabepilone) for injection as lyophilized drug substance and a vial of DILUENT for IXEMPRA, which is used to constitute the lyophilized drug substance. Configurations containing two strengths of the drug product are proposed. In one configuration a 15 mg vial of IXEMPRA (ixabepilone) for injection (in 10 cc vial) will be co-packaged with a 8 ml DILUENT for IXEMPRA, also in 10 mL vial. In the second configuration 45 mg vial of IXEMPRA (ixabepilone) for injection in 50 cc vial will be co-packaged with 23.5 ml DILUENT for IXEMPRA in 30 mL vial. The paperboard folding carton is used to copackage the two vials and is also intended to provide protection from light as ixabepilone drug substance is photosensitive (degrades upon exposure to light).

IXEMPRA contains a new chemical entity, (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1- methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9- dione (cas# 219989-84-1). The USAN and INN name for the drug substance is ixabepilone. It has a molecular weight of 506.7.

Ixabepilone drug substance (also referred to as BMS-247550 in the review) will be manufactured at the BMS facility in Swords, Ireland. Ixabepilone is a non-sterile, semisynthetic analog of the natural product epothilone B. The

Adqquate CMC information has been provided for the manufature and control of ixabepilone drug substance. The long-term drug substance stability data support the period when stored in a refrigerator at 2°-8°C (36°-46°F) and protect from light (ixabepilone is photosensitive).

IXEMPRA (ixabepilone) for Injection vials will be manufactured at Baxter Oncology, Halle, Germany. Ixabepilone for injection is a single-use, sterile, lyophilized powder for intravenous (IV) infusion following constitution with supplied diluent and further dilution with Lactated Ringer's Injection, USP. Two different strengths, 15 mg and 45 mg, have been proposed for commercial product. IXEMPRA (ixabepilone) for Injection vials do not contain any excipients

Except for a different fill volume and a slightly different lyophilization cycle, the manufacturing process for the 15 mg and 45 mg drug product vials are identical.

Adqquate CMC information has been provided for the manufature and control of ixabepilone for injection. The two presentations exhibit a comparable stability profile. Adequate data are provided to support the requested expiration dating period of 24 month when stored in a refrigerator at 2°-8°C (36°-46°F) and retained in the original package to protect from light.

. The product is required to have the statement "Protect from light" on the label.

Since ixabepilone has very poor water solubility, a specific DILUENT has been developed to constitute ixabepilone for injection. Throughout the NDA the DILUENT is refered to as the Vehicle for Constitution for IXEMPRA. However, labeling review of this and similar product led us to conclude that it should be labeld as DILUENT for IXEMPRA. The company has accepted this name, as evident in the submission of the revised label in the amendment dated 14-Sep-2007. The DILUENT consist of a 52.8%/39.8% (w/v) mixture of purified polyoxyethylated castor oil (also known as Cremophor, or Polyoxyl 35 castor oil, NF) and dehydrated alcohol, USP.

Two presentations, 8 mL and 23.5 mL (extractable volume), for DILUENT for IXEMPRA are proposed. The 8 mL DILUENT is used for 15 mg ixabepilone for injection vial and 23.5 mL DILUENT is used for 45 mg ixabepilone for injection vial. Both presentations are packaged in vials. The DILUENT is not photosensitive, however, since it is co-packaged with the ixabepilone for injection vial it is also to have the statement "protect from light" on the label. The longterm stability data for DILUENT to be confirmed when stored in a refrigerator (2°-8°C).

Since diluent and the drug are co-packaged, the expiration dating period for the package is 24 months. The storage condition for the copackaged product is to store in a refrigerator at 2°-8°C (36°-46°F) and retain in the original package to protect from light.

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

IXEMPRA, constituted and diluted, product is intended for intravenous infusion over a 3-hour period.

Prior to use the IXEMPRA Kit needs to be taken out of the refrigerator and brought to room temperature. The primary reason for this is that the DLUENT for IXEMPRA vial contains polyoxyethylated castor oil, which due to its solubility renders the contents of the DILUENT vial cloudy at refrigerator temperature. The solution, however, becomes clear when warmed to room temperature. This risk to human subject is minimal from this product

III. Administrative

A. Reviewer's Signature

Ravindra K. Kasliwal, Ph.D. (signed in DFS)

B. Endorsement Block

Ravindra K. Kasliwal/Date: Dee DFS
Ravi S. Harapanhalli/Date: See DFS
Sharon Thomas/Date: See DFS

C. CC Block – See DFS

164 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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

/s/

Ravi Kasliwal
9/25/2007 06:04:36 PM
CHEMIST

Ravi Harapanhalli
9/25/2007 06:12:28 PM
CHEMIST

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:	22-065
Applicant:	Bristol-Myers Squibb
Stamp date:	16-APR-2007
PDUFA Date:	16-OCT-2007 (priority)
Proposed Trade Name:	IXEMPRA (proposed)
Established Name:	Ixabepilone for injection
Laboratory Code:	BMS-247550-01, BMS-247550
Dosage Form:	Lyophilized powder for injection
Route of Administration:	Intravenous
Indication:	Treatment of metastatic or locally advanced breast cancer following failure of cytotoxic chemotherapy, or as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to cytotoxic chemotherapy.

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

	YES	NO
ONDQA Fileability:	√	___
Draft Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summaries

Background Summary

NDA 22-065 is submitted for ixabepilone for injection, 15 and 45 mg/vial, intended for the treatment of refractory metastatic or locally advanced breast cancer. The drug development for ixabepilone is filed under IND 58,546 (originally submitted 30-JUN-1999). A clinical EOP2 meeting was conducted on 26-MAR-2003, and an EOP2 CMC meeting was held on 18-FEB-2004. Clinical pre-NDA meetings were conducted on 06-MAR-2006 and 15-FEB-2007. A CMC-only pre-NDA meeting was conducted on 09-MAY-2006, and additional CMC comments were conveyed as part of the clinical pre-NDA meetings. Additional CMC pre-NDA correspondence via email is outlined in DFS.

Drug Substance Summary

Ixabepilone is a white to off-white powder, which possesses the structure and solubility profile shown below (Figure 1, Table I). Additional solubility data for various concentrations of Cremophor are located in Table 2.3.S.1.T01. Ixabepilone possesses several stereocenters, which are established via the initial fermentation process (see discussion below). Ixabepilone also contains a lactone moiety that probably renders the molecule susceptible to hydrolysis in the presence of bases.

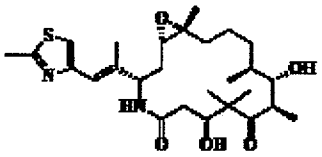


Figure 1. Ixabepilone (MW=506.7 g/mole)

Table I. Solubilities of Ixabepilone in Various Solvents.

Solvent	Approximate Solubility (mg/mL)	Equilibrium Solubility (mg/mL)

Ixabepilone is manufactured, tested, labeled, and packaged at the following site:

Swords Laboratories
Watery Lane
Swords, County Dublin, Ireland
Establishment Number: FCEI009

for ixabepilone manufacture is manufactured, tested, labeled, and packaged at the following site:

Bristol-Myers Squibb Company
6000 Thompson Road
East Syracuse, New York 13057
Establishment Number: 1317461

Ixabepilone is manufactured via a semi-synthetic process using a fermentation process.

The Agency's position on the appropriate starting material for ixabepilone manufacture is captured in the following comment, which was transmitted to the Applicant on 16-FEB-2007:

Throughout development, the synthetic sequence for the drug substance has remained unchanged. However, the reagents, reaction solvents, and conditions, and purification strategies have changed and optimized to afford the final developed scheme. The Applicant details the process development, including all revisions to the fermentation process

Once manufactured, ixabepilone is tested for conformance to specifications for the following attributes: appearance, color, identification (IR and HPLC), assay, impurity profile (HPLC), water content (KF), heavy metals, residual solvents (GC), and bacterial endotoxins. The Applicant indicates that ixabepilone should be protected from light.

The Applicant provides 36 months of long-term stability data generated using three commercial-scale batches of ixabepilone, manufactured using the proposed commercial process. The Applicant also provides 36 months of accelerated stability data generated using the same batches, along with stress and

forced degradation data obtained at temperatures ranging from 30 to 50 degrees Celsius. Photostability data was generated in accordance with ICH Q1B.

The Applicant proposes a [redacted] retest period when stored at 2-8°C, and is protected from light.

Drug Product Summary
Ixabepilone for injection is proposed as a 15 or 45 mg/vial presentation. The lyophilized powder is co-packaged with a specific vehicle for constitution, prior to further dilution with Lactated Ringer's Injection, USP. The lyophilized powder formulation [redacted]. The vehicle is supplied in two volumes (8 and 23.5 mL), and the composition includes purified polyoxyethylated castor oil [redacted] and dehydrated alcohol [redacted]

The Applicant proposes the following sites for drug product manufacture:

Baxter Oncology GmbH (lyophilized powder and vehicle for constitution)
Pharmaceutical Production
Kantstrasse 2
33790 Halle/Westfalen, Germany
Establishment Number: 9611095

[redacted]

Ixabepilone for injection is packaged into [redacted] vials (10-cc or 50-cc) [redacted]

The Applicant's stability data package includes data generated for both the lyophilized powder and vehicle, under frozen (-20°C/~30 months), long term (5°C/~25 months), and accelerated (25°C/~25 months, and 30°C/~6 months) conditions. Photostability data is also provided in accordance with ICH Q1B. Primary stability batches of the 15 mg/vial presentation were manufactured at two sites: Baxter-Mayaguez (Puerto Rico) and Baxter-Halle (Germany). Primary stability data for the 45 mg/vial presentation were obtained from two lots manufactured only at the Baxter-Halle site. The Applicant also provides freeze-thaw data for the 15 mg/vial presentation.

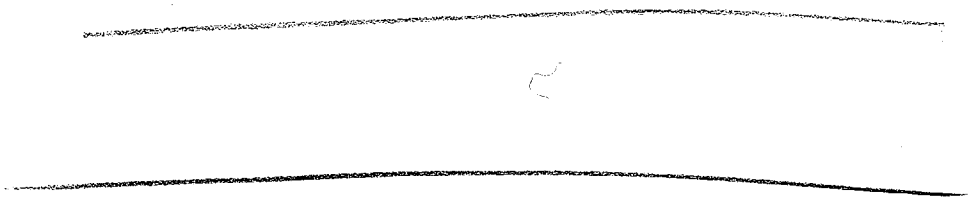
The Applicant proposes a 24-month expiration dating period for the lyophilized powder for injection, when stored under refrigerated conditions (2-8°C) and protected from light. The Applicant proposes a [redacted] month expiration dating period for both presentations of the vehicle for constitution.

B. Critical issues for review and recommendation

Drug Substance

a. Ixabepilone 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.

[redacted]



Drug Product

a. The enclosed drug product stability package is complex in nature, as it includes data generated from two manufacturing sites for two presentations of the lyophilized powder. Additionally, the vehicle is presented in two volumes, and the related vehicle stability data is provided. This should be carefully assessed for acceptability. Please reference pre-NDA phase correspondences (located in DFS) for additional information regarding the stability data package.

b. The Applicant provides significant amounts of drug product stability data, and an update will not be requested at this time. However, the reviewer should immediately examine the stability data package in detail, to determine if additional stability data are required to further support the proposed expiration dating period.

d. The manufacturing process used to manufacture primary stability batches should be confirmed as representative of that proposed for commercial supplies.

e. Due to the use of a specific constitution solution for this drug product, it is probable that the container/carton labeling review process will be complicated. The reviewer should ensure that the container/carton review is commenced in a timely fashion.

C. Comments for 74-day Letter:

None.

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 street 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 (done)** Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CBER **LNC** DMETS/ODS **EER (done)**

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LOA Included
			Yes
			Yes
			Yes
			Yes
			Yes

Recommendation for Team Review:

This NDA contains a significant amount of CMC information, with multiple possibilities for review complexities (e.g., starting material designation, container/carton labeling). Additionally, it is likely that this NDA will be targeted for an early action. This review should be easily conducted by a single reviewer, provided that prompt attention is given to the completion of a timely review.

Sarah C. Pope, Ph.D. — 14-JUN-2007
Pharmaceutical Assessment Lead — Date

Ravi Harapanhalli, Ph.D. — 14-JUN-2007
Branch Chief — Date

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

/s/

Sarah Pope
6/14/2007 02:58:11 PM
CHEMIST

Ravi Harapanhalli
6/14/2007 03:14:47 PM
CHEMIST
No comments being included for the 74-day letter.