

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
50-821

CHEMISTRY REVIEW(S)

MEMORANDUM

DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY
DRUG PRODUCTS
OFFICE OF NEW DRUGS
CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

DATE: April 27, 2010

TO: NDA #50-821, Review #2

THROUGH : Stephen Miller, Ph.D., Acting Branch Chief, Branch IV, Pre-Marketing Assessment Division II, Office of New Drug Quality Assessment

FROM: Milton J. Sloan, Ph. D., Chemist, Branch IV, Pre-Marketing Assessment Division II, Office of New Drug Quality Assessment

SUBJECT: Final overall site recommendation from Office of Compliance for NDA 50-821, Cefepime for Injection and Dextrose Injection in Duplex[®] Container

A final overall site recommendation from the Office of Compliance has been made. Approval of this application is recommended from the Chemistry, Manufacturing, and Controls perspective. There are no outstanding inspection issues or labeling comments. The sponsor has agreed to, and accepted the proposed labeling revisions. The changes are to be incorporated in the combined final printed label.

Attachment: EES Detailed Report

ATTACHMENT

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 50821/000 **Action Goal:**
Stamp Date: 25-SEP-2008 **District Goal:** 07-MAR-2010
Regulatory: 06-MAY-2010

Applicant: B BRAUN MEDCL INC **Brand Name:** CEFEPIME
901 MARCON BLVD **Estab. Name:**
ALLENTOWN, PA 18109 **Generic Name:** CEFEPIME

Priority: 5 **Product Number; Dosage Form; Ingredient; Strengths**
Org. Code: 520 001; INJECTABLE; CEFEPIME HYDROCHLORIDE; 1GM
002; INJECTABLE; CEFEPIME HYDROCHLORIDE; 2GM

Application Comment: B. BRAUN HAS RESUBMITTED A COMPLETE RESPONSE TO THIS NDA (11/06/2009).ALL FACILITIES ARE TO BE THE SAME AS ORIGINAL NDA. (on 13-NOV-2009 by M. SLOAN ()) 301-796-1464

FDA Contacts: J. DAVI Project Manager (HFD-520) 301-796-0702
M. SLOAN Review Chemist 301-796-1464
N. SCHMUFF Team Leader 301-796-1454

Overall Recommendation: ACCEPTABLE on 03-MAY-2010 by E. JOHNSON (HFD-320) 301-796-3334
WITHHOLD on 14-DEC-2009 by A. INYARD ()
WITHHOLD on 06-MAY-2009 by C. CRUZ (HFD-323) 301-796-3254

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: (b) (4) **AADA:** (b) (4)

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Estab. Comment: (b) (4)
 (b) (4) IS READY FOR REINSPECTION OF THEIR FACILITY (on 13-NOV-2009 by M. SLOAN () 301-796-1464)

Profile: (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-JAN-2009				SLOANM
SUBMITTED TO DO	22-JAN-2009	10-Day Letter			ADAMSS
DO RECOMMENDATION	05-FEB-2009			WITHHOLD PEND REG ACTION - WARNING LTR	ADAMSS
OC RECOMMENDATION	06-MAY-2009			WITHHOLD DISTRICT RECOMMENDATION	CRUZC
SUBMITTED TO OC	16-NOV-2009				SLOANM
SUBMITTED TO DO	17-NOV-2009	GMP Inspection			INYARDA
DO RECOMMENDATION	23-NOV-2009			WITHHOLD PEND REG ACTION - WARNING LTR	JOHNSONE
OC RECOMMENDATION PEND REG ACTION - WARNING LTR	30-NOV-2009			WITHHOLD DISTRICT RECOMMENDATION	CRUZC
SUBMITTED TO OC	12-JAN-2010				DAVIDJE
SUBMITTED TO DO	13-JAN-2010	10-Day Letter			INYARDA
ASSIGNED INSPECTION TO IB	20-JAN-2010	GMP Inspection			JOHNSONE
DO RECOMMENDATION	03-MAY-2010			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	03-MAY-2010			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 2021236 FEI: 2021236

B BRAUN MEDICAL INC

2525 MCGAW AVE
IRVINE, CA 926145841

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

Estab. Comment:

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	

SUBMITTED TO OC	22-JAN-2009				SLOANM
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SUBMITTED TO DO	22-JAN-2009	10-Day Letter			KIEL
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ASSIGNED INSPECTION TO IB	28-JAN-2009	Product Specific			CEVERLY
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INSPECTION SCHEDULED	29-JAN-2009		06-MAR-2009		CEVERLY
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INSPECTION PERFORMED	05-MAR-2009		05-MAR-2009		BINH.NGUYEN
----------------------	-------------	--	-------------	--	-------------

This pre-announced pre-approval and comprehensive cGMP inspection of NDA 50-821 Cefepime 1 g and 2 g for injection and (b) (4) was conducted per FY 09 CDER Performance Goals and in accordance with CP 7345.832, Pre-approval inspection and CP 7356.002 Drug Manufacturing inspection. Drug profiles SVS (sterile-filled small volume parenteral drugs), (b) (4) (b) (4) and LVP (large volume parenteral drugs) were covered. This inspection covers all (b) (4) drug systems.

The previous inspection conducted in June 2008 covering general drug GMP (quality and facility/equipment systems) was classified as NAI.

(b) (4)

INSPECTION PERFORMED	05-MAR-2009		05-MAR-2009		CEVERLY
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DO RECOMMENDATION	13-MAR-2009			ACCEPTABLE	CEVERLY
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A PRODUCT SPECIFIC AND PRE-APPROVAL INSPECTION WAS CONDUCTED AT THE FIRM FROM 2/23/09 - 3/5/09 (*INSPECTION DATE CORRECTED ON 2/23/10 - TYPO). THERE FIRM WAS CITED FOR THE FOLLOWING DEFICIENCIES:

(b) (4)

THERE WERE NO PRODUCT SPECIFIC ISSUES RELATED TO CEFEPIME NDA 50-821. THESE ISSUES ARE NOT SIGNIFICANT ENOUGH TO WARRANT WITHHOLDING APPROVAL OF THE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

NDA, THEREFORE (b) (4) RECOMMENDS APPROVAL.

CARYN MCNAB, PAI MANAGER

OC RECOMMENDATION	16-MAR-2009		ACCEPTABLE	STOCKM
			DISTRICT RECOMMENDATION	
SUBMITTED TO OC	12-JAN-2010			DAVIDJE
SUBMITTED TO DO	13-JAN-2010	10-Day Letter		INYARDA
DO RECOMMENDATION	23-FEB-2010		ACCEPTABLE	CEVERLY
	FIRM WAS INSPECTED FOR THIS APPLICATION ON 2/23-3/5/09 AND RECOMMENDED APPROVABLE. (b) (4) CONTINUES TO RECOMMEND APPROVAL.		BASED ON FILE REVIEW	
	CARYN MCNAB, PAI MANAGER			
OC RECOMMENDATION	24-FEB-2010		ACCEPTABLE	INYARDA
			DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Estab. Comment:

Profile: (b) (4)

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-JAN-2009				SLOANM
OC RECOMMENDATION	22-JAN-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	12-JAN-2010				DAVIDJE
SUBMITTED TO DO	13-JAN-2010	GMP Inspection			INYARDA
DO RECOMMENDATION THE FIRM IS ACCEPTABLE FOR PROFILE (b) (4) CARYN MCNAB, PAI MANAGER	20-JAN-2010			ACCEPTABLE BASED ON FILE REVIEW	CEVERLY
OC RECOMMENDATION	26-JAN-2010			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Estab. Comment:

Profile: (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-JAN-2009				SLOANM
OC RECOMMENDATION	22-JAN-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	16-NOV-2009				SLOANM
SUBMITTED TO DO	18-NOV-2009	10-Day Letter			FERGUSONS
DO RECOMMENDATION	19-NOV-2009			WITHHOLD	CEVERLY
WARNING LETTER RECOMMENDATION SUBMITTED BY (b) (4) IS STILL PENDING IN CDER. CARYN MCNAB, PAI MANAGER				PEND REG ACTION - WARNING LTR	
SUBMITTED TO DO	01-DEC-2009	10-Day Letter			CRUZC
DO RECOMMENDATION	10-DEC-2009			ACCEPTABLE	CEVERLY
THE INSPECTION OF 6/2-15/09 WAS ORIGINALLY CLASSIFIED OAI WITH A RECOMMENDATION FOR W/L. THE FIRM'S RESPONSE WAS ADEQUATE AND THE INSPECTION WAS DOWNGRADED TO VAI BY (b) (4) THE FIRM NOW HAS AN ACCEPTABLE PROFILE OF (b) (4) AS OF 11/30/09. CARYN MCNAB, PAI MANAGER				ADEQUATE FIRM RESPONSE	
OC RECOMMENDATION	14-DEC-2009			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	12-JAN-2010				DAVIDJE
OC RECOMMENDATION	13-JAN-2010			ACCEPTABLE	INYARDA
				BASED ON PROFILE	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Estab. Comment:

Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	22-JAN-2009				SLOANM
OC RECOMMENDATION	22-JAN-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	12-JAN-2010				DAVIDJE
OC RECOMMENDATION	13-JAN-2010			ACCEPTABLE BASED ON PROFILE	INYARDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50821	ORIG-1	B BRAUN MEDICAL INC	CEFEPIME

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

/s/

MILTON J SLOAN
05/03/2010

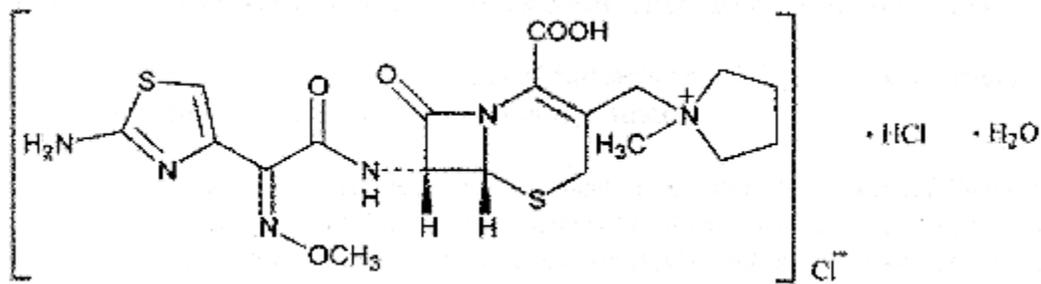
STEPHEN P MILLER
05/04/2010

I concur - recommended for approval from the CMC perspective

NDA 50-821

Cefepime for Injection USP and Dextrose Injection USP in Duplex® Container

B Braun



Milton J. Sloan, Ph.D.

ONDQA Pre-Marketing Assessment Division II Branch IV

For Division of Anti-Infective and Ophthalmology Drug
Products

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Chemistry Review Data Sheet

1. NDA 50-821
2. REVIEW #: 2
3. REVIEW DATE: 26-Jan-2010
4. REVIEWER: Milton J. Sloan, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	25-Sep-2008
Amendment (BC)	21-Nov-2008
Amendment (AC)	03-Dec-2008
Amendment (BC)	18-Feb-2009
Amendment (BC)	20-Feb-2009
Amendment (BC)	21-Nov-2008
Amendment (BC)	07-Apr-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission	06-Nov-2009
Amendment	08-Dec-2009

7. NAME & ADDRESS OF APPLICANT:

Name: B. Braun Medical Inc.
Address: 901 Marcon Boulevard
Allentown, PA
Representative: Susan Olinger, VP Regulatory Affairs
Telephone: (610) 266-0500

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] Container
- b) Non-Proprietary Name (USAN): Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] Container

Chemistry Review Data Sheet

- c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Powder/Solution for Injection

12. STRENGTH/POTENCY: 1g/50mL and 2g/50mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

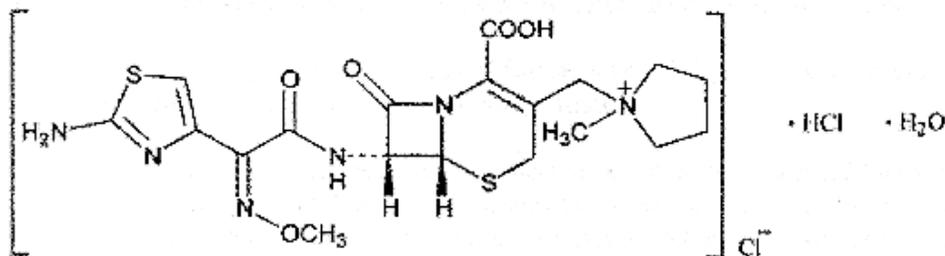
Not a SPOTS product

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

Chemical name for cefepime hydrochloride:

1-[[[(6R,7R)-7-[2-(2-amino-4-thiazolyl)-glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride, 7²-(Z)-(O-methyloxime), monohydrochloride, monohydrate

Structural formula:



Cefepime hydrochloride (monohydrate) has a molecular mass of 571.50 and a molecular formula of $C_{19}H_{25}ClN_6O_5S_2 \cdot HCl \cdot H_2O$.

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	July 12, 2009 (M. Sloan)	Review #4
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			

¹ Action codes for DMF Table:

Chemistry Review Data Sheet

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
Maxipime	50-679	Reference label drug

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold Withhold	06-May-2009 14-Dec-2009	C. Cruz A. Inyard
Pharm/Tox	Acceptable		
Biopharm	N/A		N/A
LNC	N/A		N/A
Methods Validation	Not requested per ONDQA policy		N/A
DMETS	No outstanding issues		
EA	Request for Categorical Exclusion-Acceptable		Milton Sloan, Ph.D.
Quality Microbiology	Acceptable	11-June-2009	Robert Mello, Ph.D.
OSE/RMS		24-Feb-2010	Brantley Dorch

The Chemistry Review for NDA 50-821

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not recommended for approval from Chemistry, Manufacturing, and Controls (CMC). The Office of Compliance previously issued a withhold recommendation on this NDA due to unresolved deficiencies with [REDACTED] (b) (4) manufacturing facility the contracted drug substance facility. The facility inspection is still outstanding and this review does not incorporate any potential facility inspection issues. Therefore, approval is not recommended for this NDA until all supporting sites have an acceptable recommendation. Once an overall recommendation is provided in EES, the recommendation will be incorporated as a review addendum or memoranda.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance

Cefepime hydrochloride is the drug substance. Cefepime for Injection, USP (sterile bulk) manufactured by [REDACTED] (b) (4) is a sterile mixture of cefepime hydrochloride, USP and L-arginine, USP. [REDACTED] (b) (4) manufactures the crude cefepime hydrochloride (non sterile) active ingredient which is then further processed by [REDACTED] (b) (4) to cefepime hydrochloride sterile bulk buffered with L-arginine, USP (sterile bulk). The final product of this processing is Cefepime for Injection, USP (sterile bulk) and is what is provided by [REDACTED] (b) (4) to B. Braun for use in the manufacture of Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] Container. B. Braun has provided in Module 1.4.1 of the NDA submission, the Letter of Authorization (LOA) for [REDACTED] (b) (4) for the Cefepime for Injection, USP (sterile bulk). Within [REDACTED] (b) (4) . A clarification letter from [REDACTED] (b) (4) is also provided. Although B. Braun refers to cefepime for injection as the sterile bulk active pharmaceutical ingredient (API), Cefepime for Injection is the subject of an official drug product monograph in the United States Pharmacopoeia.

Executive Summary Section

Finished Drug Product

Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] III Container is sterile, nonpyrogenic and packaged in a single use, dual chamber container. The finished drug product consists of sterile Cefepime for Injection USP in one chamber (drug chamber) and 5% Dextrose Injection USP in the other chamber (diluent chamber). The drug chamber filled with sterile Cefepime for Injection USP, is referred to as the sterile bulk API by the sponsor. Cefepime for Injection USP, sterile bulk is a blend of cefepime hydrochloride USP and L-Arginine USP. It contains the equivalent of not less than (b) (4) and not more than (b) (4) of the labeled amount of Cefepime. The patented Duplex[®] III dual chamber container drug delivery system is made from a specially formulated material. The product (diluent and drug) contact layer is a mixture of thermoplastic rubber and a polypropylene ethylene copolymer that contains no plasticizers. Just prior to administration the unit is “activated” and the drug powder is constituted in the diluent. The formulation provided was used in the manufacture of the registration stability batches included in the NDA and is also proposed for commercial manufacturing.

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

The two chambers are separated by a peelable seal which is activated prior to use. Prior to administration, the peelable foil is removed to permit the powder to be inspected. To constitute the drug with the diluent vehicle, the peelable seal separating the chambers is activated by applying pressure on the diluent chamber, followed by activation of the second seal between the drug chamber and forward compartment containing the administration port. Cefepime for Injection USP, is then mixed and dissolved in the diluent in a closed and sterile system. The reconstituted drug product cannot be administered until the second peelable seal is activated. Application of pressure to the diluent/drug chamber allows the reconstituted drug product to flow to the set port for administration. After thorough mixing, the reconstituted finished product is then ready to be delivered to the patient. The Duplex[®] III container is designed to maintain the integrity of the contents of the drug chamber and diluent chamber during shipping and storage while maintaining them in a ready-to-administer configuration without the need for freezing or other special storage conditions. The reconstituted drug product is intended for single intravenous use and not for intramuscular use. The fill volume specifications for the diluent have been established to deliver not less than 50 mL after reconstitution of the powdered drug with the diluent. Each 50 mL contains cefepime hydrochloride equivalent to either 1 gram or 2 grams of cefepime. Cefepime for injection and Dextrose injection should be administered intravenously over approximately 30 minutes. Reconstituted solutions of Cefepime for injection and Dextrose injection range in color from colorless to amber. Following reconstitution (activation), product must be used within 12 hours if stored at room temperature or within 5 days if stored under refrigeration. Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] Container is expected to remain stable on storage throughout the proposed shelf life of 12 months at 25°C and for seven days after removal of foil strip. The reconstituted solution can be used for up to twelve hours at after activation if stored at 25°C, or up to 5 days if stored under refrigeration (5°C).

Executive Summary Section

Data provided support the proposed storage statement: Store the unactivated unit at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F)[See USP Controlled Room Temperature.].

C. Basis for Approvability or Not-Approval Recommendation

B. Braun originally submitted this NDA (09/25/2008) and now has re-submitted this NDA for Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] Container in accordance with section 505(b)(2) of the Federal Food Drug and Cosmetic Act. The NDA submission describes an already marketed dosage form presented in the Duplex[®] III container closure system. The reference listed drug (RLD) for B Braun's NDA is MAXIPIME, BMS's NDA 50-679 approved on 01/18/96. Therefore, B. Braun relies on FDA's previous determination of the safety and effectiveness of MAXIPIME and no additional clinical studies are provided to support its 505(b)(2) NDA application. The proposed specifications are found adequate and suitable for a quality drug product. The sponsor has demonstrated via CMC data submitted in this NDA that the drug product can be manufactured with a compatible diluent to meet established quality standards. The final constitution of Cefepime for Injection USP and Dextrose Injection USP has suitable quality and stability, and is consistent with the USP monograph for Cefepime for Injection. In addition, interaction between the finished product and the components of the container system have been determined not to adversely affect the identity, purity, potency, safety, strength, efficacy, or stability of the product. The stability (registration) batches for Cefepime for Injection, USP in the Duplex Container were manufactured with the already approved set port and set port cover. B. Braun is proposing the use of both set ports and both set port covers for the commercial batches. Data from studies demonstrated that the drug product, stored at recommended conditions, met all chemical, microbiological, and particulate matter requirements. Stability indicators demonstrate that the integrity of the product will be maintained throughout its shelf life. The statistical evaluation of the stability data from the registration lots supported the suitability of the Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] container for the product shelf life proposed in this application. The Office of Drug Safety's Division of Medication Errors and Technical Support have no outstanding concern with labeling in the NDA. Other minor labeling comments are ongoing and will be reevaluated at final printed label. The quality microbiology consult review was found acceptable and approval is recommended. B. Braun's request for a categorical exclusion from the preparation of an Environmental Assessment provided under 21 CFR § 25.31(a) is acceptable. The current status of the supporting DMF (b) (4) for this NDA is acceptable.

Previously a withhold recommendation on this NDA was issued by the Office of Compliance due to unresolved deficiencies with (b) (4) manufacturing facility the contracted drug substance facility. A request for re-inspection was made for the resubmission. The facility inspection is still outstanding. Approval is not recommended for this NDA until all supporting sites have an acceptable recommendation. This review does not address or incorporate any potential facility inspection issues that may be provided in the attached detail establishment report

Executive Summary Section

(Attachment 1). Once an overall recommendation is provided in EES, the recommendation will be incorporated as a review addendum or memoranda.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemist: Milton J. Sloan, Ph.D.

Date: 04-March-10

Final Draft: 19-April-10

Acting Branch Chief: Stephen Miller, Ph.D. Date:

C. CC Block

9 Pages has been withheld in full immediately following this page as B4
(CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50821	ORIG-1	B BRAUN MEDICAL INC	CEFEPIME

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/s/

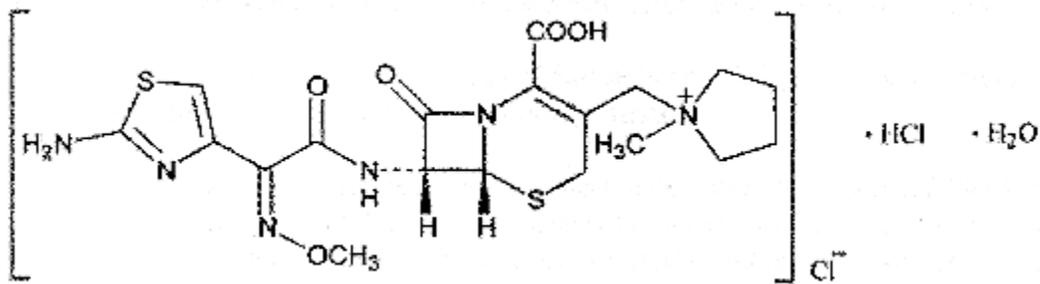
MILTON J SLOAN
04/22/2010

STEPHEN P MILLER
04/23/2010

NDA 50-821

Cefepime for Injection USP and Dextrose Injection USP in Duplex® Container

B Braun



Milton J. Sloan, Ph.D.

ONDQA Pre-Marketing Assessment Division II Branch IV

For Division of Anti-Infective and Ophthalmology Drug
Products

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Chemistry Review Data Sheet

1. NDA 50-821
2. REVIEW #: 1
3. REVIEW DATE: 26-June-2009
4. REVIEWER: Milton J. Sloan, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	25-Sep-2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC)	21-Nov-2008
Amendment (AC)	03-Dec-2008
Amendment (BC)	07-Apr-2009

7. NAME & ADDRESS OF APPLICANT:

Name: B. Braun Medical Inc.
Address: 901 Marcon Boulevard
Allentown, PA
Representative: Susan Olinger, VP Regulatory Affairs
Telephone: (610) 266-0500

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] Container
- b) Non-Proprietary Name (USAN): Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] Container
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: S

Chemistry Review Data Sheet

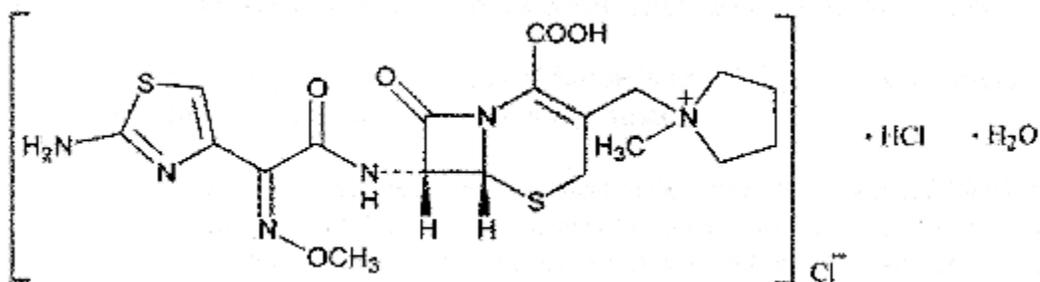
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: Antibacterial
11. DOSAGE FORM: Powder/Solution for Injection
12. STRENGTH/POTENCY: 1g/50mL and 2g/50mL
13. ROUTE OF ADMINISTRATION: Intravenous
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product

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

Chemical name for cefepime hydrochloride:

1-[[[(6R,7R)-7-[2-(2-amino-4-thiazol yl)- glyox ylamido]-2-carboxy-8-oxo-5-thia-l-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-l-methylpyrrolidinium chloride, 7² -(Z)-(O-methyloxime), monohydrochloride, monohydrate

Structural formula:



Cefepime hydrochloride (monohydrate) has a molecular mass of 571.50 and a molecular formula of C₁₉H₂₅ClN₆O₅S₂·HCl·H₂O.

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Outstanding Deficiencies		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 –Type 1 DMF

Chemistry Review Data Sheet

- 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
Maxipime	50-679	Reference label drug

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold	06-May-2009	By C. Cruz
Pharm/Tox	Acceptable		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Not requested per ONDQA policy		
DMETS	No outstanding issues		
EA	Request for Categorical Exclusion-Acceptable		Milton Sloan, Ph.D.
Quality Microbiology	Acceptable	11-June-2009	Robert Mello, Ph.D.

The Chemistry Review for NDA 50-821

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not recommended for approval from Chemistry, Manufacturing, and Controls (CMC). The Office of Compliance has issued a withhold recommendation on this NDA due to the potential of pending action against the contracted drug substance facility. Therefore, approval is not recommended for this NDA until all supporting sites have an acceptable recommendation.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance

Cefepime hydrochloride is the drug substance. Cefepime for Injection, USP (sterile bulk) manufactured by (b) (4) is a sterile mixture of cefepime hydrochloride, USP and L-arginine, USP. (b) (4) manufactures the crude cefepime hydrochloride (non sterile) active ingredient which is then further processed by (b) (4) to cefepime hydrochloride sterile bulk buffered with L-arginine, USP (sterile bulk). The final product of this processing is Cefepime for Injection, USP (sterile bulk) and is what is provided (b) (4) to B. Braun for use in the manufacture of Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] Container. B. Braun has provided in Module 1.4.1 of the NDA submission, the Letter of Authorization (LOA) (b) (4) for the Cefepime for Injection, USP (sterile bulk). (b) (4)

Although B. Braun refers to cefepime for injection as the sterile bulk active pharmaceutical ingredient (API), Cefepime for Injection is the subject of an official drug product monograph in the United States Pharmacopoeia.

Drug Product

Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] III Container is sterile, nonpyrogenic and packaged in a single use, dual chamber container. The

Executive Summary Section

finished drug product consists of sterile Cefepime for Injection USP in one chamber (drug chamber) and 5% Dextrose Injection USP in the other chamber (diluent chamber). The drug chamber filled with sterile Cefepime for Injection USP, is referred to as the sterile bulk API by the sponsor. Cefepime for Injection USP, sterile bulk is a blend of cefepime hydrochloride USP and L-Arginine USP. It contains the equivalent of not less than (b) (4) and not more than (b) (4) of the labeled amount of Cefepime. The patented Duplex[®] III dual chamber container drug delivery system is made from a specially formulated material. The product (diluent and drug) contact layer is a mixture of thermoplastic rubber and a polypropylene ethylene copolymer that contains no plasticizers. Just prior to administration the unit is “activated” and the drug powder is constituted in the diluent. The formulation provided was used in the manufacture of the registration stability batches included in the NDA and is also proposed for commercial manufacturing.

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

The two chambers are separated by a peelable seal which is activated prior to use. Prior to administration, the peelable foil is removed to permit the powder to be inspected. To constitute the drug with the diluent vehicle, the peelable seal separating the chambers is activated by applying pressure on the diluent chamber, followed by activation of the second seal between the drug chamber and forward compartment containing the administration port. Cefepime for Injection USP, is then mixed and dissolved in the diluent in a closed and sterile system. The reconstituted drug product cannot be administered until the second peelable seal is activated. Application of pressure to the diluent/drug chamber allows the reconstituted drug product to flow to the set port for administration. After thoroughly mixing, the reconstituted finished product is then ready to be delivered to the patient. The Duplex[®] III container is designed to maintain the integrity of the contents of the drug chamber and diluent chamber during shipping and storage while maintaining them in a ready-to-administer configuration without the need for freezing or other special storage conditions. The reconstituted drug product is intended for single intravenous use and not for intramuscular use. The fill volume specifications for the diluent have been established to deliver not less than 50 mL after reconstitution of the powdered drug with the diluent. Each 50 mL contains cefepime hydrochloride equivalent to either 1 gram or 2 grams of cefepime. Cefepime for injection and Dextrose injection should be administered intravenously over approximately 30 minutes. Reconstituted solutions of Cefepime for injection and Dextrose injection range in color from colorless to amber. Following reconstitution (activation), product must be used within 12 hours if stored at room temperature or within 5 days if stored under refrigeration. Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] Container is expected to remain stable on storage throughout the proposed shelf life of 12 months at 25°C; Seven days after removal of foil strip; Twelve hours at after activation at 25°C or 5 days under refrigeration (5°C). Data provided support the proposed storage statement: Store the unactivated unit at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F)[See USP Controlled Room Temperature.].

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

B. Braun has submitted this NDA for Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] Container in accordance with section 505(b)(2) of the Federal Food Drug and Cosmetic Act. The NDA submission describes an already marketed dosage form presented in the Duplex[®] III container closure system. The reference listed drug (RLD) for B Braun's NDA is MAXIPIME, BMS's NDA 50-679 approved on 01/18/96. Therefore, B. Braun relies on FDA's previous determination of the safety and effectiveness of MAXIPIME and no additional clinical studies are provided to support its 505(b)(2) NDA application. The proposed specifications have been found adequate and suitable for a quality drug product. The sponsor has demonstrated via CMC data submitted in this NDA that the drug product can be manufactured with a compatible diluent to meet established quality standards. The final constitution of Cefepime for Injection USP and Dextrose Injection USP appear to have the same quality and stability as the final constitution of Maxipime and is consistent with the USP monograph for Cefepime for Injection. In addition, interaction between the finished product and the components of the container system have been determined not to adversely affect the identity, purity, potency, safety, strength, efficacy, or stability of the product. The stability (registration) batches for Cefepime for Injection, USP in the Duplex Container were manufactured with the already approved set port and set port cover. B. Braun is proposing the use of both set ports and both set port covers for the commercial batches. Data from studies demonstrated that the drug product, stored at recommended conditions, met all chemical, microbiological, and particulate matter requirements. Stability indicators demonstrate that the integrity of the product will be maintained throughout its shelf life. The statistical evaluation of the stability data from the registration lots supported the suitability of the Cefepime for Injection USP and Dextrose Injection USP in the Duplex[®] container for the product shelf life proposed in this application. The Office of Drug Safety's Division of Medication Errors and Technical Support have no outstanding concern with labeling in the NDA. The quality microbiology consult review was found acceptable and approval is recommended. B. Braun's request for a categorical exclusion from the preparation of an Environmental Assessment provided under 21 CFR § 25.31(a) is acceptable. In conclusion, this NDA is not recommended for approval due to a manufacturing site not found acceptable by the Office of Compliance. The supporting DMF (b) (4) currently has a deficient status for this NDA.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemist: Milton J. Sloan, Ph.D.

Date: 26-June-09

Final Draft: 02-July-09

Branch Chief: Norman Schmuff, Ph.D.

Date:

C. CC Block

58 pages have been withheld in full immediately following this page as B4 (CCI/TS).

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

/s/

Milton Sloan
7/2/2009 12:15:39 PM
CHEMIST
Not recommended for approval

Norman Schmuff
7/5/2009 08:40:54 PM
CHEMIST