

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
50-821

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

11 JUNE 2009

NDA: 50-821/N-000

Drug Product Name

Proprietary: N/A

Non-proprietary: Cefepime for Injection USP and
Dextrose Injection USP in the Duplex[®]
Container

Review Number: 1

Dates of Submission(s) Covered by this Review

<u>Letter</u>	<u>Stamp</u>	<u>Review Request</u>	<u>Assigned to Reviewer</u>
25 SEPTEMBER 2008	25 SEPTEMBER 2008	30 SEPTEMBER 2008	01 OCTOBER 2008
21 NOVEMBER 2008	21 NOVEMBER 2008	n/a	n/a
03 DECEMBER 2008	(resubmission to EDR)	n/a	n/a

Submission History (for amendments only): N/A

Applicant/Sponsor

Name: B. Braun Medical Inc.
Address: 901 Marcon Boulevard
Allentown, PA 18109
Representative: Susan Olinger, J.D.
Corporate VP, Regulatory Affairs
Telephone: 610-596-2517

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is recommended for approval from microbiology product quality standpoint (with two COMMENTS in Section 3).

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** New Drug Application
 - 2. SUBMISSION PROVIDES FOR:** Marketing Authorization
 - 3. MANUFACTURING SITE:**
Drug Substance; [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

Drug Product; B. Braun Medical Inc.
2206 Alton Parkway
Irvine, CA 92614
(CFN# 2021236)
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile Powder for Injection plus 5% Dextrose Injection, USP; Intravenous route of administration; 1g and 2g sterile powders packaged with 50ml Dextrose Injection in a Duplex® flexible plastic/foil container.
 - 5. METHOD(S) OF STERILIZATION:** [REDACTED] (b) (4)
 - 6. PHARMACOLOGICAL CATEGORY:** Anti-infective
- B. SUPPORTING/RELATED DOCUMENTS:**
- Type II [REDACTED] (b) (4) For production of Cefepime for Injection USP sterile powder.
 - Annual Report Update Amendment to Type II [REDACTED] (b) (4), (covering the period October 2007 to September 2008 for the production of Cefepime for Injection USP sterile powder).
 - Type II [REDACTED] (b) (4)
 - Type III [REDACTED] (b) (4)
 - OGD Microbiology Review #1 of [REDACTED] (b) (4)
 - OGD Microbiology Review #1a1 of [REDACTED] (b) (4)
 - OGD Microbiology Review #1 of [REDACTED] (b) (4)
 - OGD Microbiology Review #1a1 of [REDACTED] (b) (4)
 - NDMS Microbiology Review #1 of [REDACTED] (b) (4)
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- NDMS Microbiology Review #2 of [REDACTED] (b) (4)
 - NDMS Microbiology Review #1 [REDACTED] (b) (4)
and NDMS Microbiology Review #2 [REDACTED] (b) (4)
 - NDMS Microbiology Review #1 NDA 50-779/N-000 (by N.S. dated 02 AUGUST 2000).
 - NDMS Microbiology Review #1 of NDA 50-779/SCS-012 (by B.R., dated 20 June 2007).
 - NDMS Microbiology Review #1 of NDA 50-796/SCP-010 (by V.P., dated 29 JULY 2008).

C. REMARKS:

- This is a 505(b)(2) submission.
- No ONDQA PAL Initial Quality Assessment was on file in DFS.
- The submission is a full technical submission, in eCTD format.

Filename: N050821N000R1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – Recommend Approval
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The process involves an (b) (4) and an (b) (4) of dextrose diluent into a presterilized, two-compartment Duplex III flexible IV bag.
- B. Brief Description of Microbiology Deficiencies** – No deficiencies. However, two COMMENTS are to be transmitted to the applicant concerning ongoing stability program commitments and container/closure part number inconsistencies.
- C. Assessment of Risk Due to Microbiology Deficiencies** – Risk to the sterility assurance of the product from the COMMENTS noted is minimal.

III. Administrative

- A. Reviewer's Signature** _____
Robert Mello, Ph.D.
- B. Endorsement Block** _____
Bryan S. Riley, Ph.D.
- C. CC Block**
NDA 50-821

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

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/s/

Robert Mello
6/12/2009 10:09:04 AM
MICROBIOLOGIST

Recommend Approval

Bryan Riley
6/12/2009 10:38:45 AM
MICROBIOLOGIST
I concur.

**DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS
CLINICAL MICROBIOLOGY REVIEW**

NDA: 50-821

DATE REVIEW COMPLETED: 4/29/2009

Date Company Submitted: May 9th, 2008

Date received by CDER: May 27th, 2008

Date Assigned: May 14th, 2008

Reviewer: Avery Goodwin, Ph.D

NAME AND ADDRESS OF APPLICANT:

B. Braun Medical Inc.
901 Marcon Boulevard
Allentown, PA 18109

CONTACT PERSON:

Patti Smith
Tel No: 610-596-2638
Fax No: 610-266-4962

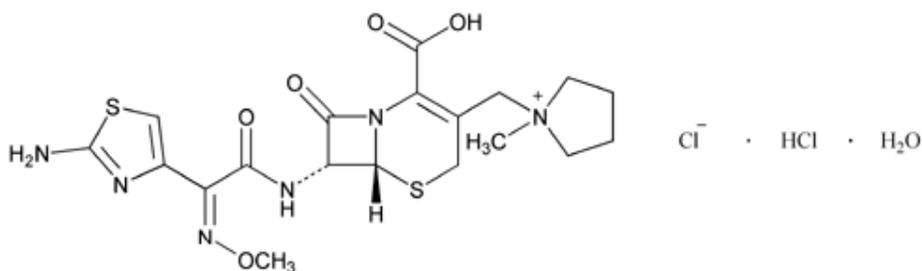
DRUG PRODUCT NAMES:

Proprietary Name: Cefepime Hydrochloride

Established Name: Maxipime, Cefepime

Chemical Name: Pyrrolidinium, 1-[[7-[[2-amino-4-thiazolyl](methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-, chloride, monohydrochloride, monohydrate, [6*R*-[6*α*,7*β*(*Z*)]-1-[[6*R*,7*R*)-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, 7*Z*-(*O*methylxime), monohydrochloride, monohydrate.

Structural Formula:



Molecular Formula:

$\text{C}_{19}\text{H}_{25}\text{ClN}_6\text{O}_5\text{S}_2 \cdot \text{HCl} \cdot \text{H}_2\text{O}$

Molecular Mass:

571.50

**DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS
CLINICAL MICROBIOLOGY REVIEW**

NDA: 50-821

DATE REVIEW COMPLETED: 4/29/2009

PROPOSED DOSAGE FORM AND STRENGTH:

Baxter's proposed 1 g/50 mL and 2 g/100 mL premixed products are for IV use only and are stored frozen (at or below -20°C) for long-term storage and thawed prior to intravenous administration.

ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:

The proposed indications, route of administration, and dosage regimen (dose, frequency, and duration) for Baxter's 1 g/50 mL and 2 g/100 mL Cefepime Injection products will be identical to the approved indications, route of administration, and dosage regimen (dose, frequency, and duration) for the 1 g and 2 g IV doses of MAXIPIME.

INDICATION:

Cefepime is a fourth-generation cephalosporin antibacterial agent indicated for use in the treatment of pneumonia, chemotherapy-induced febrile neutropenia, urinary tract infections, uncomplicated skin infections, and complicated intra-abdominal infections.

RELATED SUBMISSION REVIEWED:

NDA 50-679; 50-821

TYPE OF SUBMISSION:

505(b)(2).

PURPOSE OF SUBMISSION:

The Sponsor is requesting a meeting to discuss a potential 505(b)(2) filing for cefepime for injection and duplex injection in the Duplex® Container. The Sponsor proposes to submit this NDA using Bristol-Myers Squibb's (BMS), Maxipime, as the reference listed drug in ADD-Vantage® vials as basis for submission. The ADD-Vantage® vials are said to be comparable to B. Braun's Duplex® Container System in administration, dosage form, conditions of use and strength.

Remarks

The interpretive criteria and the quality control parameters of the cefepime label provided by the Sponsor do not match what is in the current Clinical and Laboratory Standards Institute (CLSI) document (1) for the interpretation of in vitro susceptibility testing with cefepime. Therefore, the microbiology section of the label does not reflect current scientific thinking on in vitro susceptibility test interpretive criteria and quality control parameters for cefepime.

CONCLUSION

The microbiology in vitro susceptibility test interpretive criteria and quality control parameters need to be revised to be consistent with what is in the CLSI document (1). This revision would need to be done first by the reference listed drug company Bristol-Myers Squibb before B. Braun Medical, Inc. can change the package insert for cefepime.

**DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS
CLINICAL MICROBIOLOGY REVIEW**

NDA: 50-821

DATE REVIEW COMPLETED: 4/29/2009

Therefore the microbiology section of the package insert provided by B. Braun Medical, Inc. is acceptable.

**DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS
CLINICAL MICROBIOLOGY REVIEW**

NDA: 50-821

DATE REVIEW COMPLETED: 4/29/2009

INTRODUCTION AND BACKGROUND:

The Applicant, B. Braun, has submitted a New Drug Application for the approval of cefepime injection in Add-Vantage vials. B. Braun has requested to file the NDA under a 505(b)(2) status, and thus has not suggested any changes to the microbiology section of the label; however, there are sections of the label that will need to be updated to reflect the current in vitro susceptibility test interpretive criteria and quality control parameters in the CLSI document (1). The updates should be made following BMS's revision of the microbiology section of label.

MAXIPIME is a semi-synthetic, broad spectrum, cephalosporin antibiotic that is indicated in the treatment of pneumonia caused by *Streptococcus pneumoniae* including cases associated with concurrent bacteremia, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or *Enterobacter* species. MAXIPIME is also indicated for the treatment of Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis) caused by *Escherichia coli* or *Klebsiella pneumoniae*, when the infection is severe, or caused by *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*, when the infection is mild to moderate, including cases associated with concurrent bacteremia with these microorganisms. Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*. Complicated Intra-abdominal Infections (used in combination with metronidazole) caused by *Escherichia coli*, viridans group streptococci, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter* species, or *Bacteroides fragilis*. For more information refer to the MAXIPIME label.

See "REMARKS" and "CONCLUSION" above.

REFERENCE

1. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; 19th Informational Supplement. CLSI document M100-S19, CLSI 940 West Valley Rd., Suite 1400, Wayne, PA 19087-1898, 2009.

Avery Goodwin, Ph.D.
Microbiology Reviewer
DAIOP

Fred Marsik, Ph.D.
Microbiology Team Leader
DAIOP
22 May 09 FIN FJM

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/s/

Avery Goodwin
6/5/2009 04:49:55 PM
MICROBIOLOGIST

Frederic Marsik
6/8/2009 07:15:39 AM
MICROBIOLOGIST

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 50-821 **Applicant:** B. Braun Medical **Letter Date:** 25 SEPT 2008

Drug Name: Cefepime for Injection USP and Dextrose Injection USP (Duplex Container, 1g, and 2g) **NDA Type:** New Drug (505(b)(2)) **Stamp Date:** 25 SEPT 2008

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		Submission is in eCTD format. All applicable links are functioning
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		
7	Has the applicant submitted the results of analytical method verification studies?	X		
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	-	-	Not Applicable to product quality microbiology
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The submission was submitted in eCTD format and available in the Global Submit file system.

From a microbiological product quality perspective, the applicant appears to have submitted the requisite documentation for review of manufacturing and controls for the above described drug product. This NDA submission is fileable from a Microbiology Product Quality standpoint.

Robert Mello, Ph.D.,
Reviewing Microbiologist

Date

Microbiology Secondary Reviewer

Date

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/s/

Robert Mello
11/3/2008 09:02:34 AM
MICROBIOLOGIST

Application is fileable for micro product quality

James McVey
11/3/2008 11:26:00 AM
MICROBIOLOGIST
I concur.