APPLICATION NUMBER:
050823Orig1s000

MICROBIOLOGY REVIEW(S)
Product Quality Microbiology Review

28-APR-2011

NDA 50-823/N-000

Drug Product Name
Proprietary: None.
Non-proprietary: Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® Container, 1g and 2g

Review Number: 1

Dates of Submission(s) Covered by this Review

<table>
<thead>
<tr>
<th>Submit</th>
<th>Received</th>
<th>Review Request</th>
<th>Assigned to Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>27-APR-2011</td>
<td>27-APR-2011</td>
<td>N/A</td>
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<tr>
<td>12-AUG-2010</td>
<td>13-AUG-2010</td>
<td>19-AUG-2010</td>
<td>19-AUG-2010</td>
</tr>
</tbody>
</table>

Applicant/Sponsor
Name: B. Braun Medical
Address: 901 Marcon Blvd.
Allentown, PA 18109
Representatives: Rebecca Stolarick
Director, Regulatory Affairs
Rebecca.Stolarick@bbraun.com
Patti Smith
Manager, Regulatory Affairs
Patti.Smith@bbraun.com
Telephone: Rebecca Stolarick: 610-596-2536
Patti Smith: 610-596-2638

Name of Reviewer: Steven Fong, Ph.D.

Conclusion: CMC-Microbiology Recommends APPROVE.
Product Quality Microbiology Data Sheet

A.  
1. **TYPE OF SUBMISSION:** Original NDA.
2. **SUBMISSION PROVIDES FOR:** New drug product.
3. **MANUFACTURING SITE:**
   Sterile Ceftazidime for Injection USP (CFI) drug product powder is manufactured at:

   CFI drug product and 5% Dextrose Injection USP (5% DI) diluent are filled into Duplex® containers at:
   B. Braun Medical Inc.
   2206 Alton Parkway
   Irvine, CA 92614
   Establishment Number 2021236

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
   - 1g and 2g Sterile Powder for Injection packaged with 50 mL of 5% DI in a Duplex® flexible plastic-foil container.
   - Intravenous route of administration.

5. **METHOD(S) OF STERILIZATION:**

6. **PHARMACOLOGICAL CATEGORY:** Cephalosporin anti-infective.

B. **SUPPORTING/RELATED DOCUMENTS:**
   1) Type II DMF describing manufacture of Sterile Sodium Carbonate by 
   2) Type II DMF describing manufacture of Ceftazidime by 
   3) Type II DMF describing manufacture of CFI (Sterile Bulk) by 
   4) LOAs from , each dated 04-SEP-2010, permitting Agency review of DMFs
   7) 14-APR-2011 reviews of DMFs.
C. REMARKS:
1) The application was submitted electronically in CTD format.

2) On 25-MAR-2011 B. Braun notified the Agency that Regulatory Affairs Director Rebecca Stolarick had replaced Susan Olinger as the representative for the subject NDA, and that Regulatory Affairs Manager Patti Smith would handle routine correspondence.

3) On 18-APR-2011 the Reviewer sent an e-mail to Patti Smith requesting a clarification regarding the e-mail response was provided 25-APR-2011.

4) On 27-APR-2011 the Applicant submitted an Amendment (Supporting Document 6) withdrawing a Comparability Protocol within Section R of the subject NDA.
Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommended for approval from a microbiology quality standpoint.

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 – Sterile, processed CFI powder from the source vendor is filled into one compartment of a sterile, dual compartment Duplex® container. The other compartment is filled with processed 5% DI diluent. The Duplex® container is sterilized.

B. Brief Description of Microbiology Deficiencies – None.

C. Assessment of Risk Due to Microbiology Deficiencies – N/A.

III. Administrative

A. Reviewer's Signature

Steven E. Fong, Ph.D.
Microbiology Reviewer

B. Endorsement Block

John Metcalfe, Ph.D.
Senior Microbiology Reviewer

C. CC Block—N/A
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/s/

STEVEN E FONG
04/28/2011
Recommended for approval from a microbiology quality standpoint.

JOHN W METCALFE
04/28/2011
I concur.
NAME AND ADDRESS OF SPONSOR
B. Braun Medical Inc.
Irvine CA 92614-5895

CONTACT PERSON
Susan Olinger, JD
Corporate Vice President Regulatory Affairs
901 Marcon Boulevard
Allentown, PA 18109
610-596-2517

DRUG PRODUCT NAME
Proprietary Name: Ceftazidime for Injection and Dextrose injection in the Duplex Container
Established Name/Code Name(s): None
Chemical Name: Pentahydrate of pyridinium, 1-[[7-[[2-amino-4-thiazolyl][1-carboxy-1-methylethoxy]imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl][methyl], hydroxide, inner salt, [6R-[6alpha,7beta(Z)]]]. It has the following structure:

![Chemical Structure](image)

Chemical Formulae: C_{22}H_{32}N_{6}O_{12}S_{2}

Hydrous Dextrose USP has the following structural (molecular) formula:

![Dextrose Structure](image)
DIVISION OF ANTIINFECTIVE AND OPHTHALMOLOGY PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW
NDA 50-823 Ceftazidime   Date review completed: 3-17-2011

DRUG CATEGORY:
Antibiotic

PROPOSED INDICATION(S)
Treatment of the following infections caused by susceptible strains of the designated microorganisms: Lower respiratory tract infections, skin and skin structure infections, bacterial septicemia, bone and joint infections, gynecologic infections, intra-abdominal infections, central nervous system infections.

PROPOSED DOSAGE FORM, DOSAGE, ROUTE OF ADMINISTRATION, STRENGTH AND DURATION OF TREATMENT

See package insert (below)

DISPENSED:
Rx

RELATED DOCUMENTS:
NDA 050634
NDA 050646
NDA 050578 Fortaz

REMARKS
B. Braun is seeking approval to market Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex container. The Applicant has stated that this drug is bioequivalent to the reference listed drug, Fortaz in the 1 and 2 gm strengths. The application was submitted as type 505(b)(2).

CONCLUSIONS
The format of this package insert has been updated (below), however, additional updates to the interpretive criteria and quality control parameters are recommended. Before further revisions to the microbiology section of the B. Braun package insert may be made, the package insert for Fortaz, the reference listed drug (NDA 050578) should be updated.
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/s/

KERIAN K GRANDE
03/17/2011

FREDERIC J MARSIK
03/17/2011

Reference ID: 2919735
PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 050-823/N-000  Applicant: B Braun Medical  Letter Date: 12-AUG-2010
Drug Name: Ceftazidime for Injection & Dextrose Injection  NDA Type: Original NDA  Stamp Date: 13-AUG-2010

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

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>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?</td>
<td></td>
<td>X</td>
<td>Submission provided electronically in CTD format.</td>
</tr>
<tr>
<td>2. Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?</td>
<td></td>
<td>X</td>
<td>Sections 2.3.P and 3.2.P.3.3</td>
</tr>
<tr>
<td>3. Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?</td>
<td></td>
<td>X</td>
<td>Section 3.2.P.3.5</td>
</tr>
<tr>
<td>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?</td>
<td></td>
<td>X</td>
<td>Submission was provided in English.</td>
</tr>
<tr>
<td>5. Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?</td>
<td></td>
<td>X</td>
<td>Product is not preserved. Container closure integrity described in section 3.2.P.2.7</td>
</tr>
<tr>
<td>6. Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?</td>
<td></td>
<td>X</td>
<td>Sections 2.3.P.5.1 and 3.2.P.5.1</td>
</tr>
<tr>
<td>7. Has the applicant submitted the results of analytical method verification studies?</td>
<td></td>
<td>X</td>
<td>Sections 2.3.P.5.1.4, 2.3.P.5.1.5, 3.2.P.5.2, and 3.2.P.5.3.</td>
</tr>
<tr>
<td>8. Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?</td>
<td>N/A</td>
<td>N/A</td>
<td>Pre-submission microbiology quality requests were not made.</td>
</tr>
<tr>
<td>9. Is this NDA fileable? If not, then describe why.</td>
<td></td>
<td>X</td>
<td></td>
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</table>

**Additional Comments:** The drug product consists of Ceftazidime for Injection USP and Dextrose Injection USP provided in a dual chamber Duplex® Container. One chamber contains sterile Ceftazidime for Injection powder. The second contains a sterilized Dextrose Injection diluent. Manufacture of sterile ceftazidime drug substance is described in DMF.

Steven Fong, Ph.D.
Review Microbiologist  13-OCT-2010

James L. McVey  13-OCT-2010
New Drug Microbiology Team Leader
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/s/

STEVEN E FONG
10/13/2010
Application recommended for filing from a microbiology quality viewpoint.

JAMES L MCVEY
10/13/2010
I concur.
Clinical Microbiology: 45-Day Filing Meeting Checklist  
NDA 50-823: Ceftazidime in a Duplex Container  
Reviewer: Kerian Grande          Date Review completed: 9-30-2010

<table>
<thead>
<tr>
<th>NDA Number: 50-823</th>
<th>Applicant: B. Braun Medical, Inc.</th>
<th>Stamp Date: 8-13-2010</th>
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</thead>
<tbody>
<tr>
<td>Drug Name: Ceftazidime</td>
<td>NDA Type: 505(b)(2)</td>
<td></td>
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On initial overview of the NDA application for filing:

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<th>Content Parameter</th>
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<th>No</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Is the microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?</td>
<td></td>
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<tr>
<td>2</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Is the microbiology information (preclinical/nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td></td>
<td>Yes</td>
<td></td>
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<tr>
<td>Is the microbiology information (preclinical/nonclinical and clinical) legible so that substantive review can begin?</td>
<td></td>
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<td>4</td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>On its face, has the applicant submitted in vitro data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Has the applicant submitted the clinical microbiology datasets in a format which intents to correlate baseline pathogen with clinical and microbiologic outcome?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Has the applicant submitted draft/proposed interpretive criteria/breakpoint along with quality control (QC) parameters and interpretive criteria, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA/BLA studies, and in a manner to allow substantive review to begin?</td>
<td></td>
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<tr>
<td>9</td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Has the applicant submitted a clinical microbiology dataset in an appropriate/standardized format which intents to determine resistance development by correlating changes in</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N/A
Clinical Microbiology: 45-Day Filing Meeting Checklist
NDA 50-823: Ceftazidime in a Duplex Container
Reviewer: Kerian Grande       Date Review completed: 9-30-2010

<table>
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<th>No</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>the phenotype (such as in vitro susceptibility) and/or genotype (such as mutations) of the baseline pathogen with clinical and microbiologic outcome?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Has the applicant used standardized or nonstandardized methods for measuring microbiologic outcome? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?</td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>11 Has the applicant submitted draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?</td>
<td>✓</td>
<td></td>
<td>The format of the label may need to be updated.</td>
</tr>
<tr>
<td>12 Has the applicant submitted annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?</td>
<td>✓</td>
<td></td>
<td>The format of the label may need to be updated.</td>
</tr>
<tr>
<td>13 Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes___

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The format of the clinical microbiology subsection of the drug label may need to be updated.

Reviewing Microbiologist : Kerian Grande
Date: 9-28-2010

Microbiology Team Leader
Fred Marsik, Ph.D.
MicroTL HFD-520 FIN 9/30/10
Clinical Microbiology: 45-Day Filing Meeting Checklist
NDA 50-823: Ceftazidime in a Duplex Container
Reviewer: Kerian Grande     Date Review completed: 9-30-2010

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/s/

KERIAN K GRANDE
09/30/2010

FREDDIE J MARIK
09/30/2010