

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**050823Orig1s000**

**CHEMISTRY REVIEW(S)**

Chemistry Assessment Section

**MEMORANDUM****Date:** June 8, 2011**To:** **NDA 50-823****Through:** Stephen Miller, Ph. D., CMC Lead, Division of Pre-marketing Assessment 2

For Rapti D. Madurawe, Ph.D., Branch Chief, Division of Pre-marketing Assessment 2

**From:** Milton J. Sloan, Ph. D., Chemistry Reviewer, Division of Pre-marketing Assessment 2**Subject:** Final Draft Printing of Label for Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex<sup>®</sup> Container

The sponsor has revised their draft labeling as indicated in the attachments. The revisions have been reviewed and found acceptable to DMEPA and Review Team. There are no other outstanding labeling comments. Approval of this application is recommended from CMC perspective.

Memorandum Prepared by

\_\_\_\_\_  
Milton J. Sloan, Ph. D. Chemist Reviewer\_\_\_\_\_  
Date

For Concurrence:

\_\_\_\_\_  
Stephen Miller Ph. D., CMC Lead for,  
Rapti D. Madurawe, Ph.D., Branch Chief  
Division of Pre-marketing Assessment 2\_\_\_\_\_  
Date

3 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

## Chemistry Assessment Section

**From:** Merchant, Lubna  
**Sent:** Monday, June 06, 2011 2:20 PM  
**To:** Davi, Christopher  
**Cc:** Holquist, Carol A; Pohlman, Janice; Dillon Parker, Maureen P; Sloan, Milton J; Nambiar, Sumathi  
**Subject:** RE: NDA 50-823 (Additional Container Label Comments)

Chris,

We find the labels acceptable

Thanks.  
Lubna

Lubna Merchant, M.S., Pharm.D.  
Acting Team Leader  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Office 301.796.5162  
lubna.merchant@fda.hhs.gov

**From:** Patti.Smith@bbraun.com [mailto:Patti.Smith@bbraun.com]  
**Sent:** Friday, June 03, 2011 3:53 PM  
**To:** Davi, Christopher  
**Cc:** Holquist, Carol A; Pohlman, Janice; Merchant, Lubna; Dillon Parker, Maureen P; Sloan, Milton J; Nambiar, Sumathi; Rebecca.Stolarick@bbraun.com  
**Subject:** Re: NDA 50-823 (Additional Container Label Comments)

Hi Chris,

The below attached pdf versions of the annotated and final label versions are attached below for the 1g, 2g and drug chamber label for the Ceftazidime NDA 050823 application review. B. Braun completed all the changes as requested by the FDA in both the May 25, 2011 and May 27, 2011 email.

Please let me know if there is agreement with these versions. Once I have confirmation, I will submit these labels via an amendment to the application through the eCTD gateway.

Please let me know if there is anything further.

Thanks, Patti

Drug Chamber:

(Please note, we are having an internal issue with the part number that we assigned to this drug chamber and need to assign a new part number but this doesn't affect the text update - just a note that the (b)(4) number will update and I will submit this new version and correct this annotation when I complete the amendment through the gateway)

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

MILTON J SLOAN  
06/08/2011

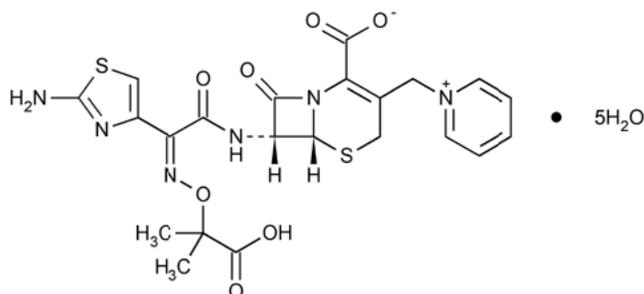
STEPHEN P MILLER  
06/08/2011

I concur - this NDA is recommended for approval from the CMC perspective.

## NDA 50-823

### Ceftazidime for Injection USP and Dextrose Injection USP in Duplex<sup>®</sup> Container

**B Braun**



**Milton J. Sloan, Ph.D.**

**ONDQA Pre-Marketing Assessment Division II Branch V**

**For Division of Anti-Infective and Ophthalmology Drug  
Products**

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# Chemistry Review Data Sheet

1. NDA 50-823
2. REVIEW #: 2
3. REVIEW DATE: 09-May-2011
4. REVIEWER: Milton J. Sloan, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	30-July-2010
Amendment (BC)	10-Sep-2010
Amendment (BC)	12-Oct-2010
Amendment (BC)	17-Feb-2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC)	27-April-2011

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: Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex<sup>®</sup> Container
- b) Non-Proprietary Name (USAN): Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex<sup>®</sup> Container
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 4
  - Submission Priority: S

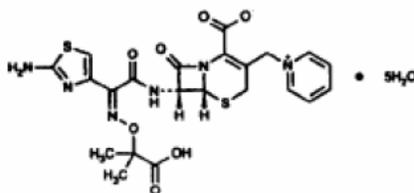
## Chemistry Review Data Sheet

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 ceftazidime pentahydrate and sodium carbonate: 1-[[[(6R,7R)-7-[2-Amino-4-thiazolyl]glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]pyridinium hydroxide, inner salt, 7 $\alpha$ -(Z)-[0-(1-carboxy-1-methylethyl)oxime], pentahydrate.

Structural formula:



Ceftazidime pentahydrate has a molecular mass of 636.6<sup>(b)(4)</sup> and a molecular formula of C<sub>22</sub>H<sub>22</sub>N<sub>6</sub>O<sub>7</sub>S<sub>2</sub>·5H<sub>2</sub>O.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS

Chemistry Review Data Sheet

(b) (4)	(b) (4)	II	Sterile Bulk Drug Product (b) (4)	1	Adequate	April 14, 2011 (S. Fong) (M.Sloan)	
	(b) (4)	II	Sterile Sodium Carbonate	1, 7	Adequate	April 14, 2011 (S. Fong)	No CMC; refer to Quality Micro for Review
	(b) (4)	II	Ceftazidime (b) (4)	1	Adequate	April 14, 2011 (M.Sloan)	
(b) (4)	(b) (4)	III	(b) (4)	4	N/A		
		III	(b) (4)	4	N/A		
		III	(b) (4)	4	N/A		
		III	(b) (4)	4	N/A		
		III	(b) (4)	4	N/A		
		III	(b) (4)	4	N/A		
		III	(b) (4)	4	N/A		
		III	(b) (4)	4	N/A		

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	4	N/A		
	III		4	N/A		

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

1 – DMF Reviewed.

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

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Fortaz	50-578	Reference label drug

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	02/10/2011	M. Stock
Pharm/Tox	Acceptable	09/29/2010	Amy Ellis, Ph.D.
Biopharm	Request for bioequivalence/bioavailability waiver acceptable		
LNC	N/A		
Methods Validation	Not requested per ONDQA policy		
DDMAC	See comments in this Review	05/04/2011	Lubna Merchant
EA	Request for Categorical Exclusion-Acceptable		Milton Sloan, Ph.D.
Quality Microbiology	Acceptable	04/18/2011	Stephen Fong, Ph. D.

## Executive Summary Section

# The Chemistry Review for NDA 50-823

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the Chemistry, Manufacturing, and Controls (CMC) perspective. The applicant responded to deficiencies related to the Comparability Protocol. An amendment was submitted to withdraw the Comparability Protocol (April 27, 2011) and found acceptable. All sites remain acceptable as reported in the Establishment Evaluation Request from the Office of Compliance. The labels have adequate information as required. Assessment of sterility assurance from the Product Quality Microbiology perspective found no deficiencies. This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

#### 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

Ceftazidime (pentahydrate) is the drug substance and has an USP monograph.

Ceftazidime pentahydrate is synthesized (b) (4)

(b) (4) to produce Ceftazidime for Injection, USP.

Ceftazidime for Injection, USP (sterile bulk) is the subject of DMF (b) (4). The manufacture of sodium carbonate is covered under (b) (4) DMF (b) (4). All three DMFs have been reviewed and found to be adequate to support this NDA. DMFs (b) (4) and (b) (4) both for Quality Micro and DMFs (b) (4) and (b) (4) for CMC.

##### Drug Product

Ceftazidime for Injection, USP (sterile bulk) manufactured by (b) (4), is a sterile (b) (4) mixture of ceftazidime pentahydrate, USP and (b) (4), sodium carbonate, USP. Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex<sup>®</sup> (b) (4) Container is sterile, nonpyrogenic and packaged in a single use, dual chamber container. The finished drug product consists of sterile

## Executive Summary Section

Ceftazidime 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 Ceftazidime for Injection USP, is referred to in the NDA submission as the sterile bulk API by the sponsor, it is actually the sterile un-reconstituted /un-activated drug product. The sterile dry powder is also referred to in this review as the sterile bulk (b) (4) or sterile bulk. Ceftazidime for Injection USP, sterile bulk (b) (4) ceftazidime pentahydrate USP and sodium carbonate, USP. It contains the equivalent of not less than (b) (4) and not more than (b) (4) of the labeled amount of ceftazidime. This consistent with the USP drug product monograph for Ceftazidime Injection. The patented Duplex<sup>®</sup> (b) (4) dual chamber container drug delivery system is made from a specially formulated material (Review #1). 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 reconstituted in the diluent. The formulation provided was used in the manufacture of the registration stability batches included in the NDA and is 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 reconstitute 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. Ceftazidime 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<sup>®</sup> (b) (4) 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 at controlled 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 Ceftazidime pentahydrate equivalent to either 1 gram or 2 grams of Ceftazidime. Ceftazidime for injection and Dextrose injection should be administered intravenously over approximately 30 minutes. Reconstituted solutions of Ceftazidime for injection and Dextrose injection range in color from (b) (4) to amber. Following reconstitution (activation), product must be used within 12 hours if stored at room temperature or within 3 days if stored under refrigeration.

Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex<sup>®</sup> Container is expected to remain stable on storage throughout the proposed shelf life of 9 months at 25°C; Seven days after removal of foil strip; Twelve hours after

## Executive Summary Section

activation/reconstitution at 25°C or 3 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.].

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

B. Braun has submitted this NDA for Ceftazidime 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® (b) (4) container closure system. The reference listed drug (RLD) for B Braun's NDA is FORTAZ®, GSK's NDA 50-578 approved in 1985. B. Braun relies on FDA's previous determination of the safety and effectiveness of FORTAZ® and no additional clinical studies are provided to support its 505(b)(2) NDA application. B. Braun Medical Inc., requests a waiver of the requirement for the submission of evidence of in-vivo bioequivalence/bioavailability in accordance with 21 CFR 320.22 (b)(1)(i-ii). Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® Container is a parenteral solution intended solely for administration by injection and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application (NDA 50-578).

B. Braun will manufacture this product at its facility located at 2206 Alton Parkway Irvine, California 92614-5895. The Duplex® container used for this finished product is identical to the container used in B. Braun's seven other approved Duplex® NDAs with the latest being NDA 50821, Cefepime for Injection USP and Dextrose Injection USP in the Duplex® Container. B. Braun has demonstrated via CMC data submitted in this NDA that the drug product could be manufactured with a compatible diluent to meet established quality standards (see Review #1). Long-term stability data results demonstrate that the integrity of the product will be maintained throughout its proposed shelf life of 9 months. Data from the studies demonstrated that the drug product, stored at recommended conditions, met all chemical, microbiological, and particulate matter requirements (Review #1).

The Office of Surveillance and Epidemiology's Division of Medication Errors and Prevention Analysis (DMEPA) and The Office of Medical Policy's Division of Drug Marketing Advertising and Communications (DDMAC) have no major outstanding concern with labeling in the NDA. Some concerns that may affect previous approved container labels are recommended. The request for a categorical exclusion from the preparation of an Environmental Assessment provided under 21 CFR § 25.31(a) is acceptable. The Office of Compliance has issued an acceptable recommendation on this NDA. An assessment of the sterility assurance from the Product Quality Microbiology perspective found no deficiencies.

Comments and recommendations were sent to the applicant on April 8, 2011, regarding the comparability protocol (Review #1). B. Braun response was to withdraw the

### Executive Summary Section

comparability protocol enclosed in Module 3.2.R.2 of the NDA submission along with any additional information that was submitted to support the change in manufacturing process [REDACTED] <sup>(b) (4)</sup>. B. Braun reports they will submit a post approval supplement (Prior Approval Supplement) for the change to the manufacturing process and include the additional information requested by the Agency in the April 8, 2011 email along with the relevant information that was submitted with the comparability protocol in this future Prior Approval Supplement. The applicant's amendment response is acceptable and there are no outstanding issues or concerns. Approval is recommended.

See Review #1 (April 18, 2011) for aspects not covered in this Review.

### **III. Administrative**

#### **A. Reviewer's Signature**

#### **B. Endorsement Block**

Chemist: Milton J. Sloan, Ph.D.

Date: 18-May-11

CMC Lead: Stephen Miller, Ph.D.

For

Branch Chief: Rapti Madurawe, Ph. D.

#### **C. CC Block**

Attachments:

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MILTON J SLOAN  
05/18/2011

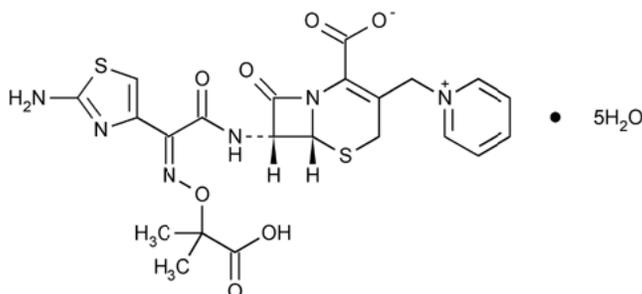
STEPHEN P MILLER  
05/19/2011

I concur, this NDA is recommended for approval from the CMC perspective

## NDA 50-823

### Ceftazidime for Injection USP and Dextrose Injection USP in Duplex® Container

**B Braun**



**Milton J. Sloan, Ph.D.**

**ONDQA Pre-Marketing Assessment Division II Branch V**

**For Division of Anti-Infective and Ophthalmology Drug  
Products**

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## Chemistry Review Data Sheet

# Chemistry Review Data Sheet

1. NDA 50-823
2. REVIEW #: 1
3. REVIEW DATE: 04-March-2011
4. REVIEWER: Milton J. Sloan, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	30-July-2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC)	17-Feb-2011
Amendment (BC)	12-Oct-2010
Amendment (BC)	10-Sep-2010

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

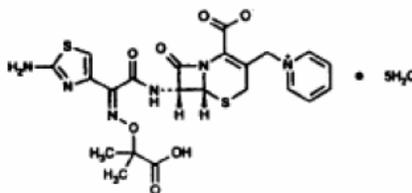
## Chemistry Review Data Sheet

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 ceftazidime pentahydrate and sodium carbonate: 1-[[[(6R,7R)-7-[2-Amino-4-thiazolyl]glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]pyridinium hydroxide, inner salt, 7 $\alpha$ -(Z)-[0-(1-carboxy-1-methylethyl)oxime], pentahydrate.

Structural formula:



Ceftazidime pentahydrate has a molecular mass of 636.6<sup>(b) (4)</sup> and a molecular formula of C<sub>22</sub>H<sub>22</sub>N<sub>6</sub>O<sub>7</sub>S<sub>2</sub>·5H<sub>2</sub>O.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Sterile Bulk Drug	1	Adequate	April 14,	

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(b) (4)	(b) (4)	Product (b) (4)			2011 (S. Fong) (M.Sloan)	
II		Sterile Sodium Carbonate	1, 7	Adequate	April 14, 2011 (S. Fong)	No CMC; refer to Quality Micro for Review
II		Ceftazidime Dihydrochloride	1	Adequate	April 14, 2011 (M.Sloan)	
III		(b) (4)	4	N/A		
III		(b) (4)	4	N/A		
III		(b) (4)	4	N/A		
III		(b) (4)	4	N/A		
III		(b) (4)	4	N/A		
III		(b) (4)	4	N/A		
III		(b) (4)	4	N/A		
III		(b) (4)	4	N/A		

Chemistry Review Data Sheet

(b) (4)	III	Corporation	(b) (4)	4	N/A		
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<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

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

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Fortaz	50-578	Reference label drug

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	02/10/2011	M. Stock
Pharm/Tox	Acceptable	09/29/2010	Amy Ellis, Ph.D.
Biopharm	Request for bioequivalence/bioavailability waiver acceptable		
LNC	N/A		
Methods Validation	Not requested per ONDQA policy		
DDMAC	No outstanding issues		
EA	Request for Categorical Exclusion-Acceptable		Milton Sloan, Ph.D.
Quality Microbiology	Acceptable	04/18/2011	Stephen Fong, Ph. D.

# The Chemistry Review for NDA 50-823

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The labels have adequate information as required. All sites have an “Acceptable” recommendation reported in the Establishment Evaluation Request from the Office of Compliance. An assessment of the sterility assurance from the Product Quality Microbiology perspective found no deficiencies but is not yet complete. The applicant has not responded to deficiencies related to the Comparability Protocol (IR communication of April 8, 2011). Therefore, from the Chemistry, Manufacturing, and Controls (CMC) perspective, this NDA cannot be recommended for approval until these two issues are resolved.

#### 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

Ceftazidime (pentahydrate) is the drug substance and has an USP monograph.

Ceftazidime pentahydrate is synthesized (b) (4)

(b) (4)

to produce Ceftazidime for Injection, USP.

Ceftazidime for Injection, USP (sterile bulk) is the subject of DMF (b) (4). The manufacture of sodium carbonate is covered under (b) (4) DMF (b) (4). All three DMFs have been reviewed and found to be adequate to support this NDA. DMFs (b) (4) and (b) (4) both for Quality Micro and DMFs (b) (4) and (b) (4) for CMC.

##### Drug Product

Ceftazidime for Injection, USP (sterile bulk) manufactured by (b) (4), is a sterile (b) (4) mixture of ceftazidime pentahydrate, USP and a buffer, sodium carbonate, USP. Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex<sup>®</sup> (b) (4) Container is sterile, nonpyrogenic and packaged in a single use, dual chamber container. The finished drug product consists of sterile

## Executive Summary Section

Ceftazidime 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 Ceftazidime for Injection USP, is referred to in the NDA submission as the sterile bulk API by the sponsor, it is actually the sterile un-reconstituted /un-activated drug product. The sterile dry powder is also referred to in this review as the sterile bulk (b) (4) or sterile bulk. Ceftazidime for Injection USP, sterile bulk (b) (4) ceftazidime pentahydrate USP and sodium carbonate, USP. It contains the equivalent of not less than (b) (4) and not more than (b) (4) of the labeled amount of ceftazidime. This consistent with the USP drug product monograph for Ceftazidime Injection. The patented Duplex<sup>®</sup> (b) (4) 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 reconstituted in the diluent. The formulation provided was used in the manufacture of the registration stability batches included in the NDA and is 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 reconstitute 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. Ceftazidime 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<sup>®</sup> (b) (4) 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 Ceftazidime pentahydrate equivalent to either 1 gram or 2 grams of Ceftazidime. Ceftazidime for injection and Dextrose injection should be administered intravenously over approximately 30 minutes. Reconstituted solutions of Ceftazidime for injection and Dextrose injection range in color from (b) (4) to amber. Following reconstitution (activation), product must be used within 12 hours if stored at room temperature or within 3 days if stored under refrigeration.

Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex<sup>®</sup> Container is expected to remain stable on storage throughout the proposed shelf life of 9 months at 25°C; Seven days after removal of foil strip; Twelve hours after

## Executive Summary Section

activation/reconstitution at 25°C or 3 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.].

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

B. Braun has submitted this NDA for Ceftazidime 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® (b) (4) container closure system. The reference listed drug (RLD) for B Braun's NDA is FORTAZ®, GSK's NDA 50-578 approved in 1985. B. Braun relies on FDA's previous determination of the safety and effectiveness of FORTAZ® and no additional clinical studies are provided to support its 505(b)(2) NDA application. B. Braun Medical Inc., requests a waiver of the requirement for the submission of evidence of in-vivo bioequivalence/bioavailability in accordance with 21 CFR 320.22 (b)(1)(i-ii). Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® Container is a parenteral solution intended solely for administration by injection and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application (NDA 50-578).

B. Braun will manufacture this product at its facility located at 2206 Alton Parkway Irvine, California 92614-5895. The Duplex® container used for this finished product is identical to the container used in B. Braun's seven other approved Duplex® NDAs with the latest being NDA 50821, Cefepime for Injection USP and Dextrose Injection USP in the Duplex® Container. B. Braun is proposing a 9-month expiration date for Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® Container.

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 reconstituted solution of Ceftazidime for Injection USP and Dextrose Injection USP appear to have the same quality and stability as the final reconstituted solution of FORTAZ® and is consistent with the USP monograph for Ceftazidime for Injection. It contains ceftazidime pentahydrate and sodium carbonate to produce the active drug substance, equivalent to 1 g and 2 g ceftazidime. 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 Ceftazidime 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. Long-term stability data results demonstrate that the integrity of the product will be

## Executive Summary Section

maintained throughout its proposed shelf life of 9 months. The Office of Surveillance and Epidemiology's Division of Medication Errors and Prevention Analysis (DMEPA) and The Office of Medical Policy's Division of Drug Marketing Advertising and Communications (DDMAC) have no outstanding concern with labeling in the NDA. The request for a categorical exclusion from the preparation of an Environmental Assessment provided under 21 CFR § 25.31(a) is acceptable. The Office of Compliance has issued an acceptable recommendation on this NDA. An assessment of the sterility assurance from the Product Quality Microbiology perspective found no deficiencies but is not yet complete.

(b) (4)

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

Chemist: Milton J. Sloan, Ph.D.

Date: 06-March-11

Final Draft: 12-April-11

CMC Lead: Stephen Miller, Ph.D. Date: 04-April-11

Date: 18-April-11

**C. CC Block**

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/s/  
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MILTON J SLOAN  
04/18/2011

STEPHEN P MILLER  
04/18/2011

I concur - this NDA cannot be recommended for approval until the concerns about the Comparability Protocol have been resolved. No other CMC issues that would prevent approval have been identified.

Initial Quality Assessment  
Branch IV  
Pre-Marketing Assessment Division II

<b>OND Division:</b>	Division of Anti-Infective and Ophthalmology Products	
<b>NDA:</b>	50-823	
<b>Applicant:</b>	B. Braun Medical Inc.	
<b>Stamp Date:</b>	13-Aug-2010	
<b>PDUFA Date:</b>	13-June-2011	
<b>Trademark:</b>	Not given	
<b>Established Name:</b>	Ceftazidime for Injection and Dextrose Injection in the Duplex Container, 1 g and 2 g	
<b>Dosage Form:</b>	For Injection (in the Duplex container)	
<b>Route of Administration:</b>	IV	
<b>Indication:</b>	For treatment of patients with infections caused by susceptible strains of designated microorganisms	
<b>PAL:</b>	Rapti D. Madurawe	
	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

## Summary and Critical Issues:

### A: Summary

#### General Introduction

NDA 50-823, a 505(b)(2) application, is submitted by B. Braun Medical Inc. (B. Braun) for the drug product (DP) Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex Container, 1 g and 2 g. The DP is stated to be bioequivalent to the reference listed drug (RLD), Fortaz (Ceftazidime for Injection), 1 g and 2 g in the ADD-Vantage vials approved under NDA 50-578. NDA 50-823 is not a generic submission, due to the Duplex container, which has separate compartments for holding the DP and the diluent.

The NDA is an eCTD submission located in the Electronic Document Room. The NDA consists of the CMC modules, administrative information and labeling. There are no clinical modules and no IND number is associated with this NDA. CMC is the primary review discipline for this submission.

#### Issues Identified During Filing Review

There is no Table of Contents (TOC) with hyperlinks in the NDA. This makes it difficult for the reviewer to navigate through the submission. All modules, folders and files in the NDA are organized according to the "comprehensive TOC headings and hierarchy" given in the 7/7/2005 FDA eCTD specification document, "FDA eCTD Table of Contents

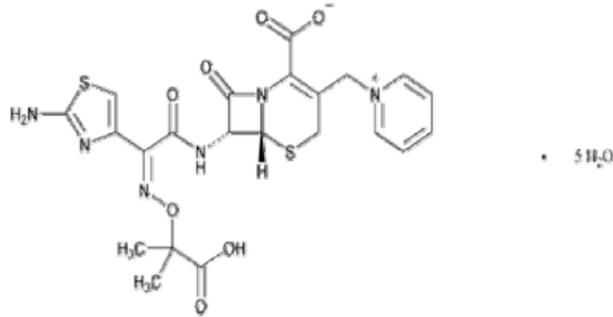
Headings and Hierarchy.” As there appears to be no requirement for the inclusion of a TOC in an eCTD NDA, I have not identified this as a refuse-to-file (RTF) issue.

The NDA identifies Ceftazidime for Injection, USP (Sterile Bulk) as the substance (DS). This is incorrect. Ceftazidime for Injection, according to the USP monograph, is a sterile mixture of sterile ceftazidime and sodium carbonate or arginine. Ceftazidime for Injection, USP, referred to in this NDA is the sterile bulk drug product (b)(4), not the DS. The DS in this 505(b)(2) NDA is sterile Ceftazidime. The USP monograph for Ceftazidime DS is for the pentahydrate form of ceftazidime as shown in Figure 1 below. During filing review, the CMC review team agreed on the above nomenclature.

Although the NDA cites three Type II DMFs for the requisite CMC information and provides letters of authorization to access the DMFs, the incorrect identification of DS makes it difficult for the reviewer to distinguish DS information from DP information. In addition, this error has caused the following problems.

- (a) The NDA incorrectly identifies the DS and DP manufacturing facilities. The NDA states the DS manufacturer is (b)(4) the manufacturer of the sterile bulk DP (b)(4) not the DS manufacturer. During filing review, this error was resolved after discussion with the applicant, the Office of Compliance/EES staff, and the CMC review team. An additional site for DS manufacture was submitted and all facilities are now entered in EES.
- (b) Information submitted under Section 3.2.S in the quality module, such as, description, specification, expiration date, registration lots, etc., is for the sterile bulk DP (b)(4) and not for the DS. NDA should contain certain DS information even when DMF's are referenced for the DS. The lack of DS information in the NDA could be considered an RTF issue. However, in a similar situation, B. Braun's NDA 50-821 for Cefepime for Injection and Dextrose Injection in the Duplex Container submitted in September 2008 incorrectly identified the bulk DP as the DS. Although the problems discussed above were noted at that time, ONDQA filed NDA 50-821 and the NDA was subsequently approved in May 2010. Due to the Cefepime precedence and the availability of all information necessary for complete review in the referenced DMF's and the NDA, I have not identified the lack of DS information in the NDA as an RTF issue.

The following sections contain an overview of the DS and DP information in the NDA and briefly discuss some of the review issues identified during the initial quality assessment. The lack of meaningful commentary in the summary sections of this NDA make it difficult to evaluate the information without a thorough review of Module 3.

**Drug Substance (DS)****Figure 1: Structure of Ceftazidime**

The DS is ceftazidime. Ceftazidime has a pentahydrate structure as shown above. In NDA 50-823.

(b) (4)

CMC information related to the ceftazidime manufacture is referenced to three Type II DMFs. The NDA contains letters of authorization (LOA) to access the DMFs. Each DMF and its status are briefly described below.

(b) (4)



(b) (4)

As the Quality reviews of the three DMFs are adequate, significant review issues relating to the DS seem unlikely. Since the NDA incorrectly identifies the sterile bulk DP (b) (4) as the DS, the applicant should submit to the NDA the specifications, a Certificate of Analysis, storage conditions, expiry period, and characterization information for the ceftazidime dihydrochloride (b) (4). Characterization information may not be readily available to the NDA applicant. Additionally, lot numbers of the Ceftazidime dichloride lots used to manufacturer bulk DP Lots #13121, 131122 and 13127 (i.e., the registration lots) should also be provided.

### **Drug Product (DP)**

The DP in NDA 50-823 is Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® Container, 1 g and 2g strengths. For ease of review, I have broken down DP manufacturing into three stages for the manufacture of, (A) sterile bulk DP (b) (4) (B) sterile diluent, and (C) finished DP (in Duplex containers). Each stage is discussed below.

#### **A. Sterile Bulk DP (b) (4)**



(b) (4)

**D. Review, Comments and Recommendation**

If the following information is not in the NDA (or DMF), the reviewer may wish to get additional information on the following.

- The commercial manufacturing scale is identified as (b) (4)  
Can commercial manufacturing occur at lower scales?
- The number of (b) (4) used in the 1g and 2g Duplex manufacturing process (b) (4)
- (b) (4)

Rapti D. Madurawe, Ph. D.  
CMC Lead

\_\_\_\_\_  
Date

Stephen R. Miller, Ph. D.  
Branch Chief

\_\_\_\_\_  
Date

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RAPTI D MADURAWA  
10/14/2010

STEPHEN P MILLER  
10/21/2010

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

**NDA Number: 50-823**

**Supplement Number and Type:  
N-000**

**Established/Proper Name:  
Ceftazidime for Injection USP  
and Dextrose Injection ISP in  
the Duplex® Container**

**Applicant: B. Braun  
Medical Inc.**

**Letter Date: 12-Aug-2010**

**Stamp Date: 13-Aug-2010**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Is the CMC section organized adequately?			There is no overall TOC in the quality module for easy location of the subject topics.
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		Individual files are organized per eCTD
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			Not applicable.

<b>B. FACILITIES*</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		List needs further clarification
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>	X		DS information is referenced to DMFs

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		Some FAX #s are not included. But all phone numbers are included.

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	X		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	<p>Has an environmental assessment report or categorical exclusion been provided?</p>	X		

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?			DS manufacturing is referenced to a DMF. See IQA
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			As above
14.	Does the section contain information regarding the characterization of the DS?			As above
15.	Does the section contain controls for the DS?			As above
16.	Has stability data and analysis been provided for the drug substance?			As above
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		(b) (4) control and environmental control procedures, in-process tests, etc., are given
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		X	Not applicable
23.	Have any biowaivers been requested?		X	Not applicable
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?	X		

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		

<b>H. MASTER FILES (DMF/MAF)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		DMFs are referenced. LOAs are provided. Completeness of information is a review issue.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
<b>DS DMFs</b>					
(b) (4)	II	(b) (4)	Ceftazidime for Injection (Sterile Bulk)	April 9, 2010	DS (in situ) and sterile bulk DP mfg
	II		Sterile Sodium Carbonate	April 9, 2010	Sterile excipient mfg
	II		Ceftazidime (b) (4)	April 9, 2010	(b) (4)
<b>Packaging DMFs</b>					
(b) (4)	III	(b) (4)		February 4, 2009	
	III			March 8, 2010	
	III			July 12, 2010	
	III			June 1, 2008	

**PRODUCT QUALITY (Small Molecule)  
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		(b) (4)		
(b) (4)	III		July 19, 2010	
	III		November 19, 2009	
	III		August 12, 2009	
	III		July 13, 2010	
	III		July 21, 2010	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	X		Applicant should submit a comprehensive TOC to facilitate review

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

*Rapti D. Madurawe {See appended electronic signature page}*

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Name of Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer Division of Pre-Marketing Assessment V Office of New Drug Quality Assessment	Date
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*Stephen Miller {See appended electronic signature page}*

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Name of Branch Chief Division of Pre-Marketing Assessment V Office of New Drug Quality Assessment	Date
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/s/

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RAPTI D MADURAWA  
10/04/2010

STEPHEN P MILLER  
10/06/2010