

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 50-792**

**Chemistry Review(s)**



**NDA 50-792**

**Cefotaxime/Dextrose injection in Duplex container®**

**B Braun Inc.**

**Andrew Yu  
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS,  
HFD-520**



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# Chemistry Review Data Sheet

1. NDA 50-792

2. REVIEW #:1

3. REVIEW DATE: 7/20/04

4. REVIEWER: Andrew Yu

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 67178	<u>6/9/03</u>
Pre-IND (NDA) 67178 meeting minute	<u>8/19/03</u>
NDA checklist review	<u>9/29/04</u>
Deficiency list fax to B. Braun	<u>5/6/04</u>

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA 50-792 (Original Submission)	9/30/03
NDA 50-792 BC (Update of stability data)	5/10/04
NDA 50-792 BC (Response to deficiency)	6/7/04
NDA 50-792 BC (Amendment –Chromatogram)	6/18/04
NDA 50-792 BZ	6/26/04
NDA 50-792 BC (Amendment – Impurity Specification/commitment)	7/1/04
NDA 50-792 BC	7/12/04

7. NAME & ADDRESS OF APPLICANT:



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

Name: B Braun Inc

Address: B. Braun Medical Inc.  
2525 McGaw Avenue,  
P.O. Box 19791,  
Irvine, CA 92623-9791

Representative: Qansy Salako, Director, Regulatory Affairs

Telephone: (949) 660-2176

8. DRUG PRODUCT NAME/CODE/TYPE: Injection

- a) Proprietary Name: Cefotaxime/Dextrose injection in Duplex container®
- b) Non-Proprietary Name (USAN): Cefotaxime sodium
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 5
  - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-infective

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1 and 2 g

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

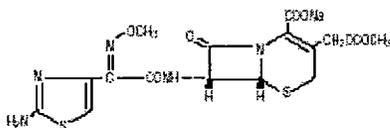
\_\_\_\_\_ SPOTS product – Form Completed

X  Not a SPOTS product

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

Cefotaxime sodium C<sub>16</sub>H<sub>16</sub> N<sub>5</sub>NaO<sub>7</sub>S<sub>2</sub>

Sodium (6R,7R)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0.]oct-2-ene-2-carboxylate<sup>7-</sup>-(Z)-(0-methyloxime), acetate (ester) 64485-93-4  
M.W. 477.45



### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
<u>        </u>	II	( )	Cefotaxime sodium	1	Adequate	3/27/04 (Rev#6) 7/21/04 (Rev#7)	Deficiency letter sent and responded. Both reviewed by A. Yu
<u>        </u>	III	( )	DUPLEX	1	Adequate	1/13/97	<u>        </u> was reviewed by RO. Riggleman and reviewed 6/1/04 by A. Yu



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

	III		DUPLEX Container	1	Adequate	6/1/04	Deficiency letter issued in 6/2/94 by R. M. Patel and responded by DMF holder. Reviewed by A. Yu for [ ]
	III		DUPLEX Container	4	Adequate		Not in contact with drug diluent. See review for 50-780 on 10/25/00 by S. Pagay on the same duplex container
	III		DUPLEX Container	4	Adequate		Not in contact with drug diluent. Reviewed for 50-780 on 10/25/00 by S. Pagay on the same duplex container
	III			4	Adequate	6/25/02	Not in contact with drug diluent. See review for 50-780 on 10/25/00 by S. Pagay on the same duplex container
	III			3	Adequate	3/10/03	E. Chikhale HFD-510. Fasson adhesive is adequate.
	III		DUPLEX	4	Adequate		Not in contact with drug diluent



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

	III		DUPLEX Container	3	Adequate	2/05/01	Adequate by
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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:** None

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION STATUS	DATE	REVIEWER
EES	Acceptable	12/16/04	Janine D Ambrogio
Pharm/Tox	None	2/13/04	Terry Peters
Biopharm	None		Paul Buehler/V. Jarugula
LNC	None (not new drug)		
Methods Validation	Sent to M. Folkendt	1/12/04	Method validated by FDA lab not recommended, reviewed by A. Yu
EA	Categoric exclusion waiver found acceptable	6/12/04	Andrew Yu
Microbiology	Acceptable	6/30/04	Vinnie Pawar



# The Chemistry Review for NDA 50-792

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Recommend approval from CMC view point. The label is pending final revision; all other CMC deficiencies are resolved, and all facility inspections are acceptable.

#### 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)

Cefotaxime sodium is a semi-synthetic broadspectrum, cephalosporin antibiotic for parenteral administration. Its molecular formula is  $C_{16}H_{16}N_5NaO_7S_2$ . Cefotaxime sodium drug substance is available as the sodium salt, and is a white crystalline powder with a molecular weight of 477.45. Cefotaxime sodium contains approximately 50.5 mg (2.2 mEq) of sodium per gram of Cefotaxime activity.

Cefotaxime for Injection USP and Dextrose Injection is a sterile, nonpyrogenic, single use, packaged combination of Cefotaxime Sodium and Dextrose Injection (diluent) in the DUPLEX sterile container. The DUPLEX Container is a flexible dual chamber container.

Excessive moisture and heat can cause decomposition of Cefotaxime sodium. Under the dry storage conditions employed in manufacturing by both process A & B Cefotaxime sodium is stable and several known and unknown impurities are adequately controlled by specification in the DMF. B Braun has developed and validated analytical methods for related impurities, including decomposition products. Cefotaxime/Dextrose injection in Duplex™ are injections each containing 1 and 2 g Cefotaxime sodium after reconstitution. Dextrose hydrous USP has been added to the diluent to adjust the product to be iso-osmotic (approximately 1.95 g and 1.2 g to 1 g and 2 g dosages, respectively). Dextrose Injection was 3.9% and 2.4% for the 1 g and 2 g doses, respectively. The product is packaged in Duplex container containing 50 mL of final solution after reconstitution.

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

Cefotaxime for Injection USP and Dextrose Injection is indicated for the treatment of patients with serious infections caused by susceptible strains of the designated microorganisms in the diseases listed including: Lower respiratory tract infections, gynecologic infections, bacteremia/septicemia and other infections indicated in the package insert. Cefotaxime for Injection USP and Dextrose Injection is a sterile, injection for single use. The 1 and 2 g injections are available in 50 mL injection in Duplex and provides an approximately iso-osmotic solution after reconstitution. The proposed storage condition is: Store the unactivated unit at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). Following reconstitution (activation), the product must be used within 12 hours if stored at room temperature or within 5 days if stored under refrigeration.

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

The basis for approval from a CMC perspective is that Cefotaxime sodium is documented to be consistently prepared by synthesis from an intermediate. All by-products and reactants formed during synthesis were adequately removed, and the purity of the final drug substance is assured [ ] The quality of the drug substance is similar to the commercial product (Claforan) in the market and meet or exceed USP specification. The Duplex container was demonstrated to be an appropriate sterile container for dispensing iso-osmotic Cefotaxime in dextrose solution in a single sterile IV container. Stability was demonstrated by evaluation of the three batches of drug substance produced with a primary and a secondary source of drug supply. Long-term stability data from pilot and batches were presented for up to [ ] with both primary and alternate drug source in the submission. The long-term stability data prepared from both sources support the expiry of Cefotaxime/ Dextrose injection in Duplex container for 24 months.

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

ChemistName/Date: Same date as draft review  
ChemistryTeamLeaderName/Date



# CHEMISTRY REVIEW



## Executive Summary Section

ProjectManagerName/Date

**C. CC Block**

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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



# CHEMISTRY REVIEW



## Chemistry Assessment Section

08-JUN-2004  
Page 1 of 1

FDA CDER EES

### ESTABLISHMENT EVALUATION REQUEST

#### SUMMARY REPORT

Application	: NDA 50792/000	Sponsor:	B BRAUN
Org Code	: 520		2525 MCGAW AVE
Priority	: 5S		IRVINE, CA 92714

Stamp Date : 30-SEP-2003  
CONTAINER (CEFOTAXIME)

Brand Name : DUPLEX

PDUFA Date : 31-OCT-2004

1.0/2.0G/DEX

Action Goal :

Estab. Name:

District Goal: 01-JUN-2004  
1.0/2.0G/DEXTROXE

Generic Name: CEFOTAXINE

INJECTION

Dosage Form: (FOR INJECTION)

Strength : 1 & 2 G

FDA Contacts: A. YU  
301-827-2143

Review Chemist (HFD-520)

J. VIDRA  
301-827-2184

Team Leader (HFD-540)

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Overall Recommendation: ACCEPTABLE on 20-FEB-2004 by S.  
FERGUSON (HFD-322) 301-827-

9009

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Establishment : CFN : 2021236 FEI : 2021236

B BRAUN MEDICAL INC



# CHEMISTRY REVIEW



## Chemistry Assessment Section

2525 MCGAW AVE  
IRVINE, CA 92614

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER  
FINISHED DOSAGE STERILITY TESTER

Profile : SVS OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 20-FEB-04  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

-----  
Establishment : CFN : [ ] FEI : [ ]  
[ ]

DMF No: [ ] AADA:

Responsibilities: [ ]

Profile : CSS OAI Status: NONE



## CHEMISTRY REVIEW



### Chemistry Assessment Section

Last Milestone: OC RECOMMENDATION  
Milestone Date: 22-OCT-03  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

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/s/

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Andy Yu  
7/22/04 09:09:00 AM  
CHEMIST

Jim Vidra  
7/22/04 10:06:20 AM  
CHEMIST