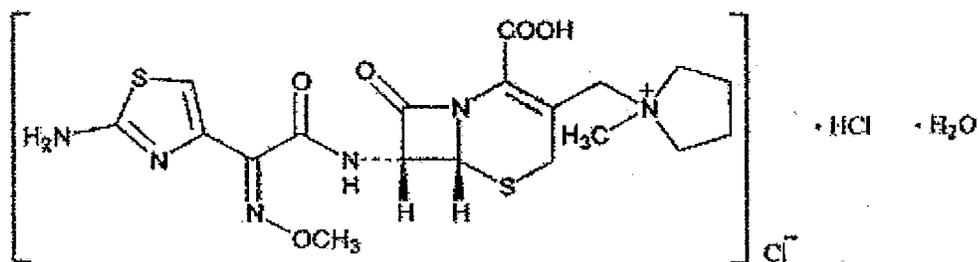


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**50-817**

**CHEMISTRY REVIEW(S)**

**NDA 50-817****Cefepime Injection in GALAXY Container (PL 2040)****Baxter Healthcare Corporation****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 50-817
2. REVIEW #: 3
3. REVIEW DATE: 27-March-2008
4. REVIEWER: Milton J. Sloan, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Chemistry Review #2	09-Jan-2008 (signed into DFS)
Chemistry Review #1	20-Dec-2007 (signed into DFS)
Amendment (BL)	13-Jul-2007
Original	01-Mar-2007
PIND 73,452	10-Feb-2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Re-Submission (AZ)	01-Feb-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Baxter Healthcare Corporation  
Address: 1620 Waukegan Road  
McGaw Park, IL 60084  
Representative: Vicki L. Drews  
Telephone:

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cefepime Injection in Galaxy® Container (PL 2040 Plastic)
- b) Non-Proprietary Name (USAN): Cefepime Injection
- c) Code Name/# (ONDQA only):

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1g/50mL and 2g/100mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:   X   Rx          OTC

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

     SPOTS product – Form Completed

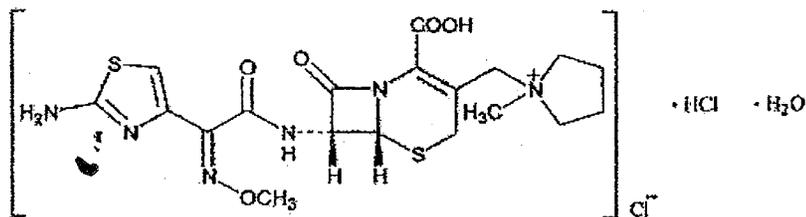
  X   Not a SPOTS product

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

Chemical name for cefepime hydrochloride:

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

Structural formula:



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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
		[ ]			Adequate	12-Dec-2007	
6344	III	Baxter	Manufacture of container/closure system and _____ of final dosage form	1	Adequate	26-Feb-2008 (Stephen E Langille, Ph.D.)	Product quality microbiology Review #1 found DMF inadequate on 18-Dec-2007
		[ ]	[ ]		Adequate	21-Aug-2007	Responses to deficiencies found adequate

<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
Maxipime	50-679	Reference label drug

**18. STATUS:**

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	21-May-2007	Shirnette Ferguson
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Not needed per ONDQA policy		



Chemistry Review Data Sheet

DMETS	Acceptable with revision to label (see review)	24- Aug-2007	Richard Abate
EA	Request for Categorical Exclusion-Acceptable	N/A	N/A
Quality Microbiology	Approval	26-Feb-2008	Stephen Langille, Ph.D.

# The Chemistry Review for NDA 50-817

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This application is recommended for approval (AP).

#### 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, USP is the drug substance used in manufacture of the proposed Cefepime Injection drug product. Cefepime Hydrochloride, USP is supplied by \_\_\_\_\_ (DMF \_\_\_\_\_). The Drug Master File (DMF) was reviewed and is adequate for support of this NDA. The active ingredient in the proposed product is the same as that in referenced listed MAXIPIME manufactured by Bristol-Myers Squibb Co. (BMS). Cefepime Hydrochloride is highly soluble in water and readily dissolves in the formulation vehicle. No known incompatibility issues exist with the drug substance and the excipients.

b(4)

##### Drug Product

Baxter's premixed Cefepime Injection product is a sterile, injectable, iso-osmotic solution of Cefepime Hydrochloride, USP, Dextrose \_\_\_\_\_ USP, L-Arginine, USP, and Water for Injection, USP packaged in Baxter's PL 2040 Plastic (GALAXY) Container-Closure System. Baxter is proposing two presentations: 1 g per 50 mL (1 g of cefepime in a 50 mL container) and 2 g per 100 mL (2 g of cefepime in a 100 mL container). As with other commercially available products packaged in GALAXY (PL 2040 Plastic), the product is manufactured for frozen storage at or below -20°C and is thawed prior to intravenous administration.

b(4)

The concentration of cefepime in the solution formulation is \_\_\_\_\_

b(4)

Dextrose is not an excipient in MAXIPIME, but several dextrose-containing solutions, including 5 and 10% Dextrose Injection, are listed in MAXIPIME's labeling as compatible IV fluids for reconstitution. The use of an \_\_\_\_\_

b(4)



Chemistry Assessment Section

for the safety and effectiveness of Baxter's premixed products and a waiver of in vivo bioavailability studies was granted during the pre-NDA process.

The applicant has demonstrated via CMC data submitted in the applicant that this new dosage form can be manufactured pre mixed in a compatible diluent to meet quality standards. The drug product is stable throughout the proposed shelf life of \_\_\_\_\_ frozen at or below -20°C plus 7 days under refrigeration (5°C) or 24 hours at room temperature (25°C). Container/closure compatibility for the drug product has been demonstrated. The results of the biological reactivity tests, toxicological data from mixtures of the extractables in animal studies, and the hazard potential of each individual chemical indicates there is negligible risk of adverse biological effects from the GALAXY (PL 2040 Plastic) container closure system. The additional studies to qualify impurities were completed as agreed. The levels proposed were found acceptable. The manufacturing sites were all found acceptable by the Office of Compliance. The applicant request for a categorical exclusion from the preparation of an Environmental Assessment provided under 21 CFR § 25.31(a) is acceptable. The proposed specifications have been found adequate and suitable for a quality drug product. Labeling concerns including those expressed by the Office of Drug Safety's Division of Medication Errors and Technical Support were communicated to the sponsor. Revised labeling has been submitted in the NDA resubmission. There are no outstanding concerns with labeling in the NDA.

b(4)

The responses to the quality microbiology deficiencies have been reviewed and the reviewer concurs with the conclusions of Stephen Langille, Ph.D, product quality microbiology reviewer, that the responses are adequate to support approval. The assessment identified no deficiencies in the application. DMF # 6344 was found adequate to support the manufacture of Cefepime Injection at the Round Lake facility. The sponsor's responses provided the identity of the equipment used for \_\_\_\_\_ of the drug product and its location within the manufacturing facility. The sponsor also provided the methodology and acceptance criteria for filter integrity testing.

b(4)

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

Chemist: Milton J. Sloan, Ph.D.

Date: April 09, 2008

Branch Chief: Norman Schmuff, Ph.D.

Date:

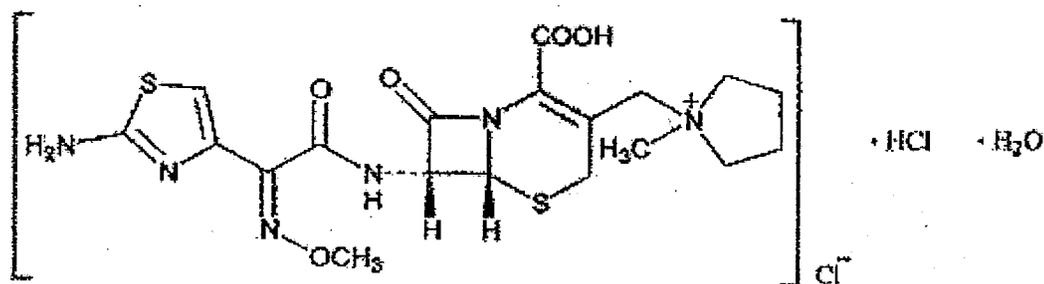
**C. CC Block**

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this page is the manifestation of the electronic signature.**  
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/s/

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Milton Sloan  
4/9/2008 05:35:15 PM  
CHEMIST  
Recommend for AP

Norman Schmuff  
4/10/2008 07:47:35 AM  
CHEMIST

**NDA/ANDA 50-817****Cefepime Injection in GALAXY Container (PL 2040)****Baxter Healthcare Corporation****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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<b>III. Administrative.....</b>	<b>8</b>
A. Reviewer's Signature.....	8
B. Endorsement Block.....	9
C. CC Block .....	9

# Chemistry Review Data Sheet

1. NDA 50-817
2. REVIEW #: 2
3. REVIEW DATE: 07-Jan 2008
4. REVIEWER: Milton J. Sloan, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Chemistry Review #1  
PIND 73,452

Document Date

20-Dec-2007 (signed into DFS)  
10-Feb-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Document Date

01-Mar-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Baxter Healthcare Corporation  
Address: 1620 Waukegan Road  
McGaw Park, IL 60084  
Representative: Vicki L. Drews  
Telephone:

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cefepime Injection in Galaxy® Container (PL 2040 Plastic)
- b) Non-Proprietary Name (USAN): Cefepime Injection
- c) Code Name/# (ONDQA only):
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type:
  - Submission Priority: S

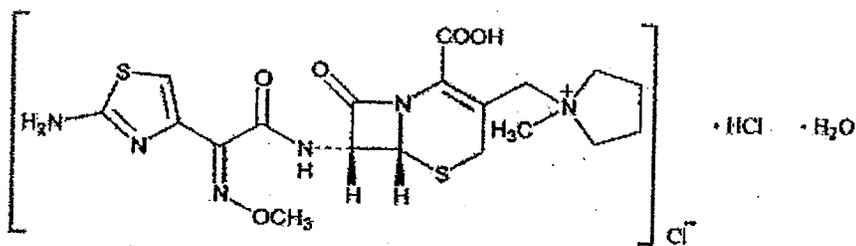
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: Antibacterial
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 1g/50mL and 2g/100mL
13. ROUTE OF ADMINISTRATION: Intravenous
14. Rx/OTC DISPENSED:   X   Rx        OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
       SPOTS product – Form Completed  
  X   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, 7<sup>2</sup>-(Z)-(O-methyloxime), monohydrochloride, monohydrate

Structural formula:



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

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

					Adequate	12-Dec-2007	
6344	III	Baxter	Manufacture of container/closure system and _____ of final dosage form	1	Inadequate	18-Dec-2007 (Stephen E Langille, Ph.D.)	Consulted review to product quality microbiology
					Adequate	21-Aug-2007	Responses to deficiencies found adequate

<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
Maxipime	50-679	Reference label drug

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	21-May-2007	Shirnette Ferguson
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	To be done per ONDQA policy		
DMETS	Acceptable with revises to label (see review)	24- Aug-2007	Richard Abate
EA	Request for Categorical Exclusion-Acceptable	N/A	N/A
Quality Microbiology	Approvable	21-Dec-2007	Stephen Langille, Ph.D.

# The Chemistry Review for NDA 50-817

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This application is recommended for approvable (AE) pending resolution of product quality microbiology deficiencies.

#### 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, USP is the drug substance used in manufacture of the proposed Cefepime Injection drug product. Cefepime Hydrochloride, USP is supplied by \_\_\_\_\_ (DMF \_\_\_\_\_). The Drug Master File (DMF) was reviewed and is adequate for support of this NDA. The active ingredient in the proposed product is the same as that in referenced listed MAXIPIME manufactured by Bristol-Myers Squibb Co. (BMS). Cefepime Hydrochloride is highly soluble in water and readily dissolves in the formulation vehicle. No known incompatibility issues exist with the drug substance and the excipients.

b(4)

##### Drug Product

Baxter's premixed Cefepime Injection product is a sterile, injectable, iso-osmotic solution of Cefepime Hydrochloride, USP, Dextrose \_\_\_\_\_, USP, L-Arginine, USP, and Water for Injection, USP packaged in Baxter's PL 2040 Plastic (GALAXY) Container-Closure System. Baxter is proposing two presentations: 1 g per 50 mL (1 g of cefepime in a 50 mL container) and 2 g per 100 mL (2 g of cefepime in a 100 mL container). As with other commercially available products packaged in GALAXY (PL 2040 Plastic), the product is manufactured for frozen storage at or below -20°C and is thawed prior to intravenous administration.

b(4)

The concentration of cefepime in the solution formulation is \_\_\_\_\_

b(4)

Dextrose is not an excipient in MAXIPIME, but several dextrose-containing solutions, including 5 and 10% Dextrose Injection, are listed in MAXIPIME's labeling as

## Chemistry Assessment Section

compatible IV fluids for reconstitution. The use of an \_\_\_\_\_  
\_\_\_\_\_ in Baxter's premixed products provides an increased assurance of compatibility. b(4)  
Baxter's premixed Cefepime Injection products have the same labeled ratio of L-  
arginine as MAXIPIME. Approximately 725 mg of L-arginine is added as a pH  
adjuster per gram of cefepime, consistent with MAXIPIME. However, Baxter's  
premixed Cefepime Injection products include hydrochloric acid, NF, additionally for  
pH adjustment. During the formulation procedure, \_\_\_\_\_ hydrochloric acid is used to b(4)  
adjust the solution pH to the optimum target pH of 4.0-6.0, consistent with  
reconstituted MAXIPIME. \_\_\_\_\_ b(4)

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

Independent of BMS, Baxter has developed a ready-to-use, iso-osmotic formulation of Cefepime Injection intended for IV administration only. Baxter's frozen drug products in GALAXY container require only thawing prior to IV administration. The potential for medication errors may be reduced with the increased convenience as compared to manually reconstituted drug products that must be prepared with a suitable diluent prior to IV administration. This new dosage form is a ready to use version of MAXIPIME, the referenced listed drug manufactured by BMS with labeling for safety and effectiveness established for 4 indications in pediatric patients 2 months up to 16 years. However, safety and effectiveness have not established in pediatric patients less than 2 months of age. The pediatric rule (PREA) requires pediatric assessment study. The review division will decide this indication via consideration of a waiver or deferred study.

Baxter's premixed frozen drug products are stored long term at -20°C to ensure product stability. Prior to administration, the frozen container is thawed at room temperature or under refrigeration. Once thawed, the solution is stable for additional storage under refrigeration (5°C) or at room temperature (25°C). The recommended expiration dating period is the same as the proposed period for long-term frozen plus short-term thawed stability for a drug product in the GALAXY (PL 2040 Plastic) container is \_\_\_\_\_ b(4)  
frozen at or below -20°C plus 7 days under refrigeration (5°C) or 24 hours at room temperature (25°C). The submitted data confirms the stability under these conditions.

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

Baxter has submitted this NDA for Cefepime Injection in Galaxy® Container (PL 2040 Plastic) in accordance with section 505(b)(2) of the Federal Food Drug and Cosmetic Act. The NDA submission describes a new dosage form and is presented in the Common Technical Document (CTD) format. The reference listed drug (RLD) for Baxter's NDA submission is MAXIPIME, BMS's NDA 50-679 approved on 01/18/96.

## Chemistry Assessment Section

In contrast to the RLD, Baxter's proposed drug product is designed to be a ready-to-use version of MAXIPIME for IV administration only. Therefore Baxter 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 Review Division found the clinical studies described in NDA 50-679 provided adequate support for the safety and effectiveness of Baxter's premixed products and a waiver of in vivo bioavailability studies was granted during the pre-NDA process.

The applicant has demonstrated via CMC data submitted in the applicant that this new dosage form can be manufactured pre mixed in a compatible diluent to meet quality standards. The drug product is stable throughout the proposed shelf life of \_\_\_\_\_ frozen at or below -20°C plus 7 days under refrigeration (5°C) or 24 hours at room temperature (25°C). Container/closure compatibility for the drug product has been demonstrated. The results of the biological reactivity tests, toxicological data from mixtures of the extractables in animal studies, and the hazard potential of each individual chemical indicates there is negligible risk of adverse biological effects from the GALAXY (PL 2040 Plastic) container closure system. The additional studies to qualify impurities were completed as agreed. The levels proposed were found acceptable. The manufacturing sites were all found acceptable by the Office of Compliance. The applicant request for a categorical exclusion from the preparation of an Environmental Assessment provided under 21 CFR § 25.31(a) is acceptable. The proposed specifications have been found adequate and suitable for a quality drug product. The Office of Drug Safety's Division of Medication Errors and Technical Support has no outstanding concern with labeling in the NDA.

b(4)

The quality microbiology consult has been reviewed and the reviewer concurs with the conclusions of Stephen Langille, Ph.D, product quality microbiology reviewer. The assessment identified several deficiencies in the application and also found DMF #6344 inadequate to support this NDA. The identified deficiencies are given below.

- The applicant failed to identify the equipment to be used for \_\_\_\_\_ of the drug product and its location within the manufacturing facility
- The applicant failed to provide the methodology and acceptance criteria for filter integrity testing

b(4)

DMF # 6344 was found inadequate to support the manufacture of Cefepime Injection at the Round Lake facility. The comments were forwarded to the DMF Holder (also Baxter) and is expected to be addressed in the DMF for adequate support of the NDA.

### III. Administrative

#### A. Reviewer's Signature



Chemistry Assessment Section

**B. Endorsement Block**

Chemist: Milton J. Sloan, Ph.D.

Date: January 09, 2008

Branch Chief: Norman Schmuff, Ph.D.

Date:

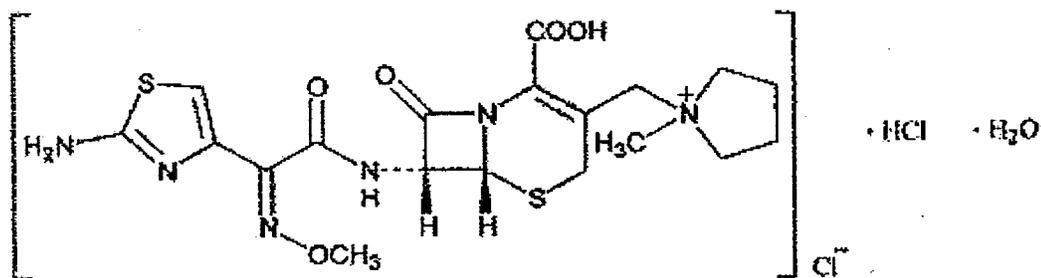
**C. CC Block**

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this page is the manifestation of the electronic signature.**  
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/s/

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Milton Sloan  
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CHEMIST

Norman Schmuff  
1/10/2008 06:29:05 AM  
CHEMIST

**NDA/ANDA 50-817****Cefepime Injection in GALAXY Container (PL 2040)****Baxter Healthcare Corporation****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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C. CC Block .....	9
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**b(4)**

# Chemistry Review Data Sheet

1. NDA 50-817
2. REVIEW #: 1
3. REVIEW DATE: 11-June 2007
4. REVIEWER: Milton J. Sloan, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

PIND 73,452

Document Date

10-Feb-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Document Date

01-Mar-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Baxter Healthcare Corporation

Address: 1620 Waukegan Road  
McGaw Park, IL 60084

Representative:

Telephone:

8. DRUG PRODUCT NAME/CODE/TYPE:

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

- a) Proprietary Name: Cefepime Injection in Galaxy® Container (PL 2040 Plastic)
- b) Non-Proprietary Name (USAN): Cefepime Injection
- c) Code Name/# (ONDQA only):
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type:
  - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1g/50mL and 2g/100mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  X  Rx      OTC

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

        SPOTS product – Form Completed

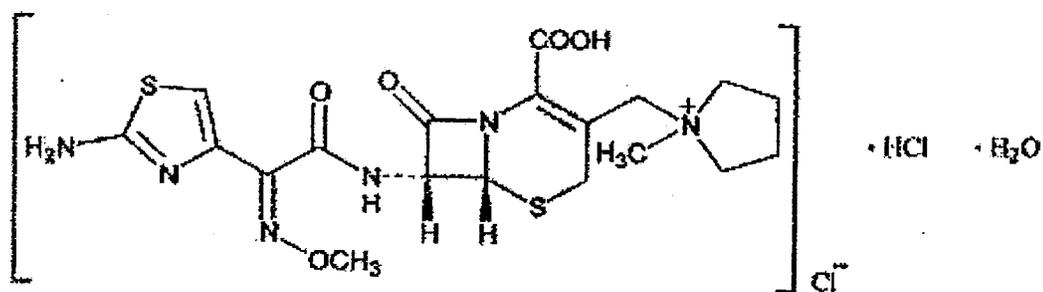
        Not a SPOTS product

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, 7<sup>2</sup>-(Z)-(O-methyloxime), monohydrochloride, monohydrate

Structural formula:



Cefepime hydrochloride (monohydrate) has a molecular mass of 571.50 and a molecular formula of C<sub>19</sub>H<sub>25</sub>ClN<sub>6</sub>O<sub>5</sub>S<sub>2</sub> · HCl · H<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
					Adequate		
6344	III	Baxter	Manufacture of container/closure system and _____ of final dosage form				
					Adequate	21-Aug-2007	Responses to deficiencies found adequate

<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)

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

**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	Acceptable	21-May-2007	Shirnette Ferguson
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	To be done per ONDQA policy		
DMETS	Acceptable with revises to label (see review)	24- Aug-2007	Richard Abate
EA	Request for Categorical Exclusion-Acceptable	N/A	N/A
Quality Microbiology	Pending		Stephen Langille

# The Chemistry Review for NDA 50-817

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This application is recommended for approval (AP) from the Chemistry, Manufacturing, and Controls perspective.

#### 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, USP is the drug substance used in manufacture of the proposed Cefepime Injection drug product. Cefepime Hydrochloride, USP is supplied by \_\_\_\_\_ (DMF, \_\_\_\_\_). The DMF was reviewed and is adequate for support of this NDA. The active ingredient in the proposed product is the same as that in referenced listed MAXIPIME manufactured by Bristol-Myers Squibb Co. (BMS). Cefepime Hydrochloride is highly soluble in water and readily dissolves in the formulation vehicle. No known incompatibility issues exist with the drug substance and the excipients. b(4)

##### Drug Product

Baxter's premixed Cefepime Injection product is a sterile, injectable, iso-osmotic solution of Cefepime Hydrochloride, USP, Dextrose \_\_\_\_\_, L-Arginine, USP, and Water for Injection, USP packaged in Baxter's PL 2040 Plastic (GALAXY) Container-Closure System. Baxter is proposing two presentations: 1 g per 50 mL (1 g of cefepime in a 50 mL container) and 2 g per 100 mL (2 g of cefepime in a 100 mL container). As with other commercially available products packaged in GALAXY (PL 2040 Plastic), the product is manufactured for frozen storage at or below -20°C and is thawed prior to intravenous administration. b(4)

The concentration of cefepime in the solution formulation is \_\_\_\_\_ b(4)

Dextrose is not an excipient in MAXIPIME, but several dextrose-containing solutions, including 5 and 10% Dextrose Injection, are listed in MAXIPIME's labeling as

## Executive Summary Section

compatible IV fluids for reconstitution. The use of an \_\_\_\_\_  
in Baxter's premixed products provides an increased assurance of compatibility. Baxter's premixed Cefepime Injection products have the same labeled ratio of L-arginine as MAXIPIME. Approximately 725 mg of L-arginine is added as a pH adjuster per gram of cefepime, consistent with MAXIPIME. However, Baxter's premixed Cefepime Injection products include hydrochloric acid, NF, additionally for pH adjustment. During the formulation procedure, \_\_\_\_\_ hydrochloric acid is used to adjust the solution pH to the optimum target pH of 4.0-6.0, consistent with reconstituted MAXIPIME.

b(4)

b(4)

b(4)

b(4)

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

Independent of BMS, Baxter has developed a ready-to-use, iso-osmotic formulation of Cefepime Injection intended for IV administration only. Baxter's frozen drug products in GALAXY container require only thawing prior to IV administration. The potential for medication errors may be reduced with the increased convenience as compared to manually reconstituted drug products that must be prepared with a suitable diluent prior to IV administration. This new dosage form is a ready to use version of MAXIPIME, the referenced listed drug manufactured by BMS with labeling for safety and effectiveness established for 4 indications in pediatric patients 2 months up to 16 years. However, safety and effectiveness have not established in pediatric patients less than 2 months of age. The pediatric rule (PREA) requires pediatric assessment study. The review division will decide this indication via consideration of a wavier or deferred study.

Baxter's premixed frozen drug products are stored long term at -20°C to ensure product stability. Prior to administration, the frozen container is thawed at room temperature or under refrigeration. Once thawed, the solution is stable for additional storage under refrigeration (5°C) or at room temperature (25°C). The recommended expiration dating period is the same as the proposed period for long-term frozen plus short-term thawed stability for a drug product in the GALAXY (PL 2040 Plastic) container is \_\_\_\_\_ frozen at or below -20°C plus 7 days under refrigeration (5°C) or 24 hours at room temperature (25°C). The submitted data confirms the stability under these conditions.

b(4)

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

Baxter has submitted this NDA for Cefepime Injection in Galaxy® Container (PL 2040 Plastic) in accordance with section 505(b)(2) of the Federal Food Drug and Cosmetic Act. The NDA submission describes a new dosage form and is presented in the Common Technical Document (CTD) format. The reference listed drug (RLD) for Baxter's NDA submission is MAXIPIME, BMS's NDA 50-679 approved on 01/18/96.

## Executive Summary Section

In contrast to the RLD, Baxter's proposed drug product is designed to be a ready-to-use version of MAXIPIME for IV administration only. Therefore Baxter 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 Review Division found the clinical studies described in NDA 50-679 provided adequate support for the safety and effectiveness of Baxter's premixed products and a waiver of in vivo bioavailability studies was granted during the pre-NDA process.

The applicant has demonstrated via CMC data submitted in the applicant that this new dosage form can be manufactured pre mixed in a compatible diluent to meet quality standards. The drug product is stable throughout the proposed shelf life of \_\_\_\_\_ frozen at or below -20°C plus 7 days under refrigeration (5°C) or 24 hours at room temperature (25°C). Container/closure compatibility for the drug product has been demonstrated. The results of the biological reactivity tests, toxicological data from mixtures of the extractables in animal studies, and the hazard potential of each individual chemical indicates there is negligible risk of adverse biological effects from the GALAXY (PL 2040 Plastic) container closure system. The additional studies to qualify impurities were completed as agreed. The levels proposed have been found acceptable. The manufacturing sites have all been found acceptable by the Office of Compliance. The applicant request for a categorical exclusion from the preparation of an Environmental Assessment provided under 21 CFR § 25.31(a) is acceptable. The proposed specifications have been found adequate and suitable for a quality drug product. The Office of Drug Safety's Division of Medication Errors and Technical Support has no outstanding concern with labeling in the NDA. The supporting DMF 6344 status is currently adequate for the support of this NDA. However, the quality microbiology consult is still pending.

b(4)

It should be noted that there are recent safety concerns regarding cefepime. Based on published meta-analysis, evidence of increased mortality have been reported among patients treated with cefepime. This issue is currently being reviewed further by the Division of Anti-Infective and Ophthalmology Drug Products.

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

Chemist: Milton J. Sloan, Ph.D.

Date: October 15, 2007

Final Draft: December 11, 2007

Branch Chief: Norman Schmuff, Ph.D.

Date:

**C. CC Block**

55 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Chemistry Assessment Section

Attachment 1

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of 2

10-DEC-2007

FDA CDER EES

Page 1

ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Application : NDA 50817/000      Sponsor: BAXTER HLTHCARE  
Org Code : 520      1 BAXTER PKY  
Priority : S      DEERFIELD, IL 60015

Stamp Date : 01-MAR-2007      Brand Name : CEFEPIME INJECTION  
PDUFA Date : 01-JAN-2008      Estab. Name:  
Action Goal :      Generic Name: CEFEPIME INJECTION  
District Goal: 02-NOV-2007      Dosage Form: (INJECTION)  
Strength : 1G/50ML AND 2G/100ML

FDA Contacts:      L. MULLINS ATHEY      Project Manager (HFD-800)      301-796-2096  
                         M. SLOAN      Review Chemist      301-796-1464  
                         R. MADURAWA      Team Leader      301-796-1408

Overall Recommendation:      ACCEPTABLE on 21-MAY-2007 by S. FERGUSON (HFD-322) 301-827-9009

Establishment :      CFN : \_\_\_\_\_      FEI : \_\_\_\_\_

b(4)

DMF No: \_\_\_\_\_      AADA: \_\_\_\_\_

Responsibilities: \_\_\_\_\_

b(4)

Profile : \_\_\_\_\_      OAI Status: NONE

Last Milestone:      OC RECOMMENDATION

Milestone Date:      16-APR-07

Decision :      ACCEPTABLE

Reason :      DISTRICT RECOMMENDATION

Establishment :      CFN : 1025114      FEI : 1025114

BAXTER HEALTHCARE CORP

HWY 221 NORTH

Chemistry Assessment Section

Attachment 1 cont'd

MARION, NC 28752

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile : CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 28-MAR-07  
Decision : ACCEPTABLE  
Reason : BASED ON PROFILE

-----  
Establishment : CPN : 1416980 FEI : 1416980  
BAXTER HEALTHCARE CORP  
RT. 120 & WILSON RD  
ROUND LAKE, IL 60073

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Chemistry Assessment Section

Attachment 1 cont'd

10-DEC-2007

FDA CDER EES

Page 2 of 2

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

- DRUG SUBSTANCE STABILITY TESTER
- FINISHED DOSAGE LABELER
- FINISHED DOSAGE MANUFACTURER
- FINISHED DOSAGE PACKAGER
- FINISHED DOSAGE RELEASE TESTER
- FINISHED DOSAGE STABILITY TESTER

Profile : LIQ OAI Status: NONE  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 21-MAY-07  
 Decision : ACCEPTABLE  
 Reason : DISTRICT RECOMMENDATION

Establishment : CFN : \_\_\_\_\_ FEI : \_\_\_\_\_

\_\_\_\_\_  
 \_\_\_\_\_ b(4)  
 \_\_\_\_\_

DMF No: \_\_\_\_\_ AADA: \_\_\_\_\_

Responsibilities: \_\_\_\_\_

b(4)

Profile : CTL OAI Status: NONE  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 28-MAR-07  
 Decision : ACCEPTABLE  
 Reason : BASED ON PROFILE

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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 Sloan  
12/11/2007 09:25:02 AM  
CHEMIST

Norman Schmuff  
12/12/2007 06:41:24 AM  
CHEMIST

Initial Quality Assessment  
Branch IV  
Pre-Marketing Assessment Division II

**OND Division:** DAIOP  
**NDA:** 50-817  
**Applicant:** Baxter Healthcare Corporation  
**Stamp Date:** 01-Mar-07  
**PDUFA Date:** 01-Jan-08  
**Trademark:** Cefepime Injection in GALAXY container (PL 2040 Plastic)  
**Established Name:** Cefepime Injection  
**Dosage Form:** Injection  
**Route of Administration:** Intravenous  
**Indication:** Treatment of various infections caused by susceptible strains of microorganisms (same indications are proposed as MAXIPIME)  
**PAL:** Rapti D. Madurawe  
YES NO  
**ONDQA Fileability:**   To be determined by the reviewer. Did not see any significant fileability issues based on the QOS.  
**Comments for 74-Day Letter**

## Summary and Critical Issues:

### A: Summary

#### Application Description

NDA 50-817 is a 505(b)(2) application submitted by Baxter Healthcare for Cefepime Injection in a GALAXY container. The drug substance is cefepime hydrochloride, USP, a broad spectrum fourth generation cephalosporin antibacterial agent. The drug product is a sterile, premixed, ready-to-use, iso-osmotic, intravenous solution. It is stored frozen and thawed before use. The drug product is supplied 1 g cefepime in 50 mL and 2 g cefepime in 100 mL containers. The referenced drug product is MAXIPIME (Cefepime Hydrochloride) for Injection by Bristol-Myers Squibb. MAXIPIME needs to be reconstituted with a suitable diluent prior to use and is for both intravenous and intramuscular use. The applicant's NDA is developed independently of Bristol-Myers Squibb.

The corresponding IND number is 73,452. The pre-IND/pre-NDA meeting package dated Feb-2006 contains all the CMC information provided to the IND. CMC review comments are available in DFS under Telecon Minutes and Chemistry Advice Letter.

#### Drug Substance

The drug substance (DS), cefepime hydrochloride, USP, is manufactured by \_\_\_\_\_ in \_\_\_\_\_ All DS information is referenced to \_\_\_\_\_ DMF \_\_\_\_\_ for \_\_\_\_\_ A letter of authorization is provided. This is a new DMF and has not been reviewed. The DMF is not reviewed in this Initial Quality Assessment.

b(4)

Proposed DS specifications are provided in the NDA. They include the USP monograph specifications for cefepime hydrochloride with \_\_\_\_\_

b(4)

The proposed acceptance criterion for \_\_\_\_\_ is NMT \_\_\_\_\_%, the ICH Q3C recommended limit for Class 3 solvents. Although the impurity acceptance criteria listed in the DS specifications are the same as USP requirements, the applicant states that impurities are subjected to tighter control due to the criticality of impurities in the finished drug product.

b(4)

**Drug Product**

The drug product (DP) is described in page 1. The DP is manufactured at Baxter Healthcare, Round Lake, IL. The DP formulation is given in Table 1. All excipients are USP/NF standard, not novel and not of animal origin. The same formula is used for both the 1 g and 2 g drug product configurations. The DP contains \_\_\_\_\_ DS in \_\_\_\_\_. The DP pH is 4.0-6.0. L-Arginine at ~ 725 mg/g cefepime is said to control the pH to this range. The DP has both \_\_\_\_\_ of DS in the formulation and an \_\_\_\_\_. The two \_\_\_\_\_ for the 50 mL and \_\_\_\_\_ for the 100 mL presentation) are not proportionate.

b(4)

**Table 1: Drug Product Composition**

Component	Quality Standard	Function	Component Quantity		
			Per mL	Per 50 mL <sup>a</sup>	Per 100 mL <sup>b</sup>
Cefepime (added as Cefepime Hydrochloride)	USP	Active Ingredient	20 mg <sup>c</sup>	1 g <sup>c</sup>	2 g <sup>c</sup>
Dextrose Hydrus (added as _____)	USP	Osmolality Adjuster	20.6 mg (Approximate)	1.03 g (Approximate)	2.06 g (Approximate)
L-Arginine	USP	pH Adjuster	14.5 mg <sup>d</sup> (Approximate)	0.725 g <sup>d</sup> (Approximate)	1.45 g <sup>d</sup> (Approximate)
L-Arginine	USP	pH Adjuster	As needed	As needed	As needed
Hydrochloric Acid <sup>e</sup>	NF	pH Adjuster	As needed	As needed	As needed
Water for Injection	USP	Vehicle	Q.S.	Q.S.	Q.S.

b(4)

Temperature and pH are identified as physicochemical properties impacting manufacturability and stability of the DP. The maximum commercial batch size is stated to be \_\_\_\_\_. The batch formula provided is for \_\_\_\_\_. Key manufacturing operations are \_\_\_\_\_

b(4)

\_\_\_\_\_ DP is packaged in 50 or 100 mL in GALAXY (PL 2040 Plastic) containers \_\_\_\_\_ containers per pack. \_\_\_\_\_ The cartons are placed in the freezer. Critical steps and controls identified are: (a) \_\_\_\_\_

\_\_\_\_\_, (b) \_\_\_\_\_  
\_\_\_\_\_ and (c) \_\_\_\_\_

b(4)

The GALAXY (PL 2040) plastic container closure system is referenced to Baxter's DMF 6344, Production of Sterile SVP injections in \_\_\_\_\_ Plastic Containers. The DMF has been reviewed before and found adequate. Material extractable studies show the presence of two \_\_\_\_\_ of \_\_\_\_\_ and \_\_\_\_\_ arising from the \_\_\_\_\_. The \_\_\_\_\_ are said to be non toxic based on animal toxicology studies levels \_\_\_\_\_ and below the qualified level at the maximum daily dose of Cefepime Injection.

b(4)

DMF 6344 was last reviewed in Nov-2000 and was found adequate. This was a limited review (i.e. review of a specific change) and several amendments have been submitted since then.

DP specifications are given in Table 2. The NMT specification limit for \_\_\_\_\_ is higher than the USP specification of NMT 1.0% for Cefepime Injection. Applicant states the proposed limit of NMT \_\_\_\_\_ has been qualified.

b(4)

**Table 2: Proposed DP Specifications**

Test	Method Type	Method Procedure	Acceptance Criteria
Visual Appearance	Visual Inspection	D1-21-10-895	Clear and colorless to amber solution, essentially free of particles.
Cefepime Identification (UV)	UV Spectroscopy	D1-20-11-034	Positive (Exhibits two maxima and one minimum at the similar wavelengths as a USP Reference Standard, and ratio of absorbance for the two maxima of the sample is within the acceptable range)
Cefepime Identification (HPLC)	HPLC	D1-25-10-981	Positive (Retention time of major peak in sample chromatogram corresponds to that in the chromatogram of the Standard preparation)
Arginine Identification	TLC	D1-20-11-037	Positive (Arginine appears as a dark red spot and RF values match)
Cefepime Assay	HPLC	D1-25-10-981	_____
Related Compounds	HPLC	D1-25-10-974	Related Compound A: NMT 0.5% Related Compound B: NMT 0.5% Peaks _____, NMT _____ Peak _____ NMT _____ Peak _____ NMT _____ Peak _____ NMT _____ Peak _____ NMT _____ Other Individual Peak: NMT _____ Total Related Compounds: NMT _____
	HPLC	D1-25-10-979	NMT _____
pH at 25°C	pH	USP <791> (11-21-16-003)	4.0 – 6.0
Osmolality <sup>a</sup>	Freezing Point Depression	USP <785> (11-25-15-005)	_____ mOsm/kg
Volume in Container <sup>b</sup>	Volume in Container	USP <1> (16-08-06-223)	50 mL bag: NLT _____ nL 100 mL bag: NLT _____ mL
Particulate Matter	Instrumental Particle Counts	USP <788> (20-03-07-006)	50 mL bag 1) NMT _____ particles/mL = _____ 2) NMT _____ particles/mL = _____ 100 mL bag 1) NMT _____ particles/mL = _____ 2) NMT _____ particles/mL = _____
Bacterial Endotoxins	_____	USP <85> (13-01-R)	NMT _____ IU/mg of cefepime
Sterility	_____	USP <71> (12-08-A)	Pass (No evidence of microbial growth)

b(4)

b(4)

b(4)

b(4)

b(4)

No clinical studies of Cefepime Injection were conducted. The DP pharmaceutical development centers on the comparison of the applicant's DP (after thawing) to reconstituted MAXIPIME, the referenced drug. The concentration of cefepime, pH range and amount of arginine per gram cefepime are said to be consistent for both drug products in the solution form. The HPLC chromatograms of frozen DP after thawing are compared with that of the reconstituted MAXIPIME. Studies are conducted with DP formulated at different pH, but within the 4-6 pH range specified in the formulation. The chromatographic profiles for the 2 drug products are said to be generally comparable with no new impurity peaks above \_\_\_\_\_ observed in the applicant's DP. The impurity profile of the applicant's DP formulated at a higher pH is said to be the most similar to MAXIPIME. The applicant's impurity profile (including the \_\_\_\_\_ impurities discussed below) has been qualified. \_\_\_\_\_

b(4)

b(4)

In a communication dated 09-May-06, the Agency agreed to accept primary stability data from 2 batches for each 1g and 2g DP configurations. Six months long-term ( $-20^{\circ}\pm 2^{\circ}\text{C}$ ) primary stability data are provided for batches manufactured at the \_\_\_\_\_ scale. Short-term thawed storage stability data (14 days at  $5\pm 2^{\circ}\text{C}$ , 2 days at  $25\pm 2^{\circ}\text{C}$ ) are provided for 0-months and 4-months frozen DP batches. Supportive stability data are provided for three \_\_\_\_\_ scale DP batches formulated at pH 4.2, 4.5 and 4.8. Stability tests are: Cefepime, \_\_\_\_\_ Related Compounds, pH, Osmolality, Visual Appearance, Visual Inspection, Total \_\_\_\_\_ Particulate Matter, Sterility, and Bacterial Endotoxins. All stability batches were within the proposed specification over the test periods. No statistical data analysis is done. General stability trends are an increase in the amount of \_\_\_\_\_ and related compounds and a \_\_\_\_\_

b(4)

b(4)

\_\_\_\_\_ Color, particulate matter and osmolality do not change significantly over storage.

b(4)

The proposed shelf life for  $-20^{\circ}\text{C}$  long-term storage is \_\_\_\_\_ while that for short term-storage is 7 days at  $5^{\circ}\text{C}$  or 24 hours at  $25^{\circ}\text{C}$ .

b(4)

## **B: Review, Comments and Recommendations**

1. DMF \_\_\_\_\_ is a new DMF filed in Oct-2006. It has not been reviewed before. Early review of the DMF is recommended to address any potential deficiencies.
2. Although the drug substance manufacturing facility at \_\_\_\_\_ was last inspected in Mar-2006 and found acceptable, the inspection history does not indicate a prior inspection for cefepime manufacture. As the DMF is new, Cefepime manufacture may be a new process at the facility. The drug product manufacturing facility at Baxter Healthcare, Round Lake, IL was last inspected and found acceptable for sterile filled small volume

b(4)

b(4)

parenteral manufacture (SVS profile) in Oct-1997. Last cGMP inspection was in Nov-2004 for control testing (CTX profile). If the reviewer determines that facility inspections are desirable for NDA approval, EES comments section need to be updated to reflect the reviewer recommendation.

3.  b(4)
4. The maximum drug product batch size is ~~is~~ It appears from the submitted Master Batch Records that the commercial-scale drug product manufacturing batch size is either variable or not defined as of yet. Is the commercial process described in the application a hypothetical description of the intended process? Although a variable scale process may be acceptable under the current QbD paradigm, it does not appear as if much QbD or process development has occurred. The minimum scale, applicability of the process parameters, controls, etc for a range of batch sizes, equipment changes (if any), applicability of the submitted Master Batch Records to the actual commercial process, etc would need to be established. b(4)
5. It appears that the applicant has not yet established the actual time and temperature conditions for the ~~step.~~ b(4)
6. No clinical studies of Cefepime Injection were conducted. Comparison of the applicant's product to MAXIPIME is important and data requires careful review.
7. A shelf-life of 7 days at 5°C ~~is~~ is proposed for the thawed drug product. There are no preservatives in the DP formulation. Has sufficient container-closure integrity and sterility data been provided to justify the proposed shelf-life? b(4)
8.  b(4)
9. The specification limit for ~~is~~ is set at a ~~is~~ than the USP limit. The QOS did not adequately discuss why the applicant's product ~~is~~ than monograph Cefepime Injection. More substantial justification is required. The Pharmacology/Toxicology reviewer should be consulted. b(4)
10. New amendments to DMF 6344 need to be reviewed. ~~is~~ extractable levels and safety should be consulted with the Pharmacology/Toxicology reviewer. b(4)
11. In the drug product specifications, the language for related compounds should be revised to indicate 'specified', 'unspecified' and 'total' degradants.

**C: Critical issues for review**

1. Comparison of the applicant's drug product to the referenced drug product
2. Definition of the commercial manufacturing process and scale

**D: Comments for 74-Day Letter**

None

Rapti D. Madurawe  
Pharmaceutical Assessment Lead

\_\_\_\_\_  
Date

Norman R. Schmuff  
Branch Chief

\_\_\_\_\_  
Date

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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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Rapti Madurawe  
4/18/2007 03:35:09 PM  
CHEMIST

Norman Schmuff  
4/19/2007 03:00:42 PM  
CHEMIST