

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-817

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

26-February-2008

NDA: 50-817-N-000-AZ

Drug Product Name

Proprietary: Cefepime Injection in GALAXY Container

Non-proprietary: Cefepime Injection

Drug Product Priority Classification: Standard

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
2/1/08	2/4/08	N/A	2/22/08

Submission History (for amendments only): Not applicable

Submission Date(s)	Microbiology Review #	Review Date(s)
2/28/07	1	12/18/07

Applicant/Sponsor

Name: Baxter Healthcare Corporation

Address: 1620 Waukeegan Rd.
McGaw Park, IL, 60085

Representative: Vicki Drews

Telephone: 847-473-6296

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA
 2. **SUBMISSION PROVIDES FOR:** New Drug product
 3. **MANUFACTURING SITE:** Baxter Healthcare Corporation
Round Lake, Illinois Facility
Route 120 and Wilson Rd.
Round Lake, IL 60073
CFN # 1416980
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Injection
 - Intravenous and intramuscular
 - 1g/50 mL and 2g/100 mL
 - GALAXY flexible plastic containers
 5. **METHOD(S) OF STERILIZATION:** _____ **b(4)**
 6. **PHARMACOLOGICAL CATEGORY:** Antibiotic
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF 6344
- C. **REMARKS:** NDA 50-817 was submitted electronically and arranged in CTD format. An Initial Quality Assessment was entered into DFS on 4/19/07. The applicant states in the cover letter that a Microbiology Review Copy (white binders) was submitted to facilitate the microbiology review. These binders were not provided for review and the submission was not available for review in the EDR. However, a CD containing the entire submission was provided by the project manager.

The initial product quality microbiology review was completed on December 18, 2007. The microbiology deficiencies were conveyed to the applicant in an approvable letter dated December 21, 2007.

filename: N050817R2.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability -**
NDA 50-817 is recommended for approval from the standpoint of product quality microbiology.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -**
Not applicable.

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -**
The drug product will be _____ in GALAXY containers using a _____ process. Filling will take place within a _____ b(4)
- B. **Brief Description of Microbiology Deficiencies -**
No deficiencies were identified based upon the information provided.
- C. **Assessment of Risk Due to Microbiology Deficiencies -**
Not applicable

III. Administrative

- A. **Reviewer's Signature** _____
Stephen E. Langille, Ph.D.
- B. **Endorsement Block** _____
James McVey
Team Leader
- C. **CC Block**
N/A

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Stephen Langille
2/29/2008 08:41:58 AM
MICROBIOLOGIST

James McVey
3/3/2008 10:46:39 AM
MICROBIOLOGIST

MEMORANDUM



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 12/28/07

TO: DFS file for NDA 50-817

FROM: Stephen E. Langille, Ph.D.

THROUGH: N/A

cc: Kyong Hyon

SUBJECT: NDA 50-817 Product Quality Microbiology Review

The product Quality Microbiology review for NDA 50-817 (completed on December, 21, 2007) contains a typographical error in section II.B. of the Executive Summary. This section states that microbiology deficiencies in "DMF 6433 should be addressed prior to approval of the application". The statement should state that microbiology deficiencies in "DMF 6344 should be addressed prior to approval of the application".

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/s/

Stephen Langille
12/28/2007 12:10:46 PM
MICROBIOLOGIST

Product Quality Microbiology Review

18-DEC-2007

NDA: 50-817

Drug Product Name

Proprietary: Cefepime Injection in GALAXY Container

Non-proprietary: Cefepime Injection

Drug Product Priority Classification: Standard

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
2/28/07	3/1/07	5/17/07	5/18/07

Submission History (for amendments only): Not applicable

Applicant/Sponsor

Name: Baxter Healthcare Corporation

Address: 1620 Waukeegan Rd.
McGaw Park, IL, 60085

Representative: Vicki Drews

Telephone: 847-473-6296

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Approvable Pending Revision

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA
 2. **SUBMISSION PROVIDES FOR:** New Drug product
 3. **MANUFACTURING SITE:** Baxter Healthcare Corporation
Round Lake, Illinois Facility
Route 120 and Wilson Rd.
Round Lake, IL 60073
CFN # 1416980
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Injection
 - Intravenous and intramuscular
 - 1g/50 mL and 2g/100 mL
 - GALAXY flexible plastic containers
 5. **METHOD(S) OF STERILIZATION:** **b(4)**
 6. **PHARMACOLOGICAL CATEGORY:** Antibiotic
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF 6344
- C. **REMARKS:** NDA 50-817 was submitted electronically and arranged in CTD format. An Initial Quality Assessment was entered into DFS on 4/19/07. The applicant states in the cover letter that a Microbiology Review Copy (white binders) was submitted to facilitate the microbiology review. These binders were not provided for review the submission was not available for review in the EDR. However, a CD containing the entire submission was provided by the project manager.

filename: N050817R1.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability -**
NDA 50-817 is approvable pending the resolution of product quality microbiology deficiencies.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -**
Not applicable.

II. Summary of Microbiology Assessments

A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -**

The drug product will be _____ in GALAXY containers using a _____ process. Filling will take place within a _____

b(4)

B. **Brief Description of Microbiology Deficiencies -**

The applicant failed to:

- Identify the equipment to be used for _____ of the drug product and its location within the manufacturing facility
- Provide the methodology and acceptance criteria for filter integrity testing.

b(4)

In addition, the microbiology deficiencies identified during the review of DMF 6433 should be addressed prior to the approval of this application.

C. **Assessment of Risk Due to Microbiology Deficiencies -**

Failure to address the product quality microbiology deficiencies could result in microbial contamination of the drug product.

III. Administrative

- A. Reviewer's Signature** _____
Stephen E. Langille, Ph.D.
- B. Endorsement Block** _____
David Hussong, Ph.D.
Associate Director –
New Drug Microbiology Staff
- C. CC Block**
N/A

8 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Stephen Langille

12/21/2007 09:34:27 AM

MICROBIOLOGIST

Baxter application for Cefepime injection in GALAXY containers. Linked
to DMF 6344.

David Hussong

12/21/2007 09:42:01 AM

MICROBIOLOGIST

I concur with the reviewer's recommendation of Approvable. Deficiencies
were provided.

DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA: 50-817

DATE REVIEW COMPLETED: 11/26/07

Date Company Submitted: March 19th, 2007

Date received by CDER: March 19th, 2007

Date Assigned: March 19th, 2007

Reviewer: Avery Goodwin, Ph.D

NAME AND ADDRESS OF APPLICANT:

Baxter Healthcare Corporation

Global Regulatory Affairs

1620 Waukegan Rd.

McGraw Park, Illinois 60085

CONTACT PERSON:

Vicki L. Drews

Tel No: 847-473-6296

Fax No: 847-785-5107

DRUG PRODUCT NAMES:

Proprietary Name: Cefepime Hydrochloride

Established Name: Maxipime, Cefepime

Chemical Name: Pyrrolidinium _____

b(4)

Structural Formula:

b(4)

Molecular Formula:

$C_{19}H_{25}ClN_6O_5S_2 \cdot HCl \cdot H_2O$

Molecular Mass:

571.50

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

NDA: 50-817

DATE REVIEW COMPLETED: 11/26/07

PROPOSED DOSAGE FORM AND STRENGTH:

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

ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:

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

INDICATION:

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

RELATED SUBMISSION REVIEWED:

NDA 50-679

TYPE OF SUBMISSION:

505(b)(2).

PURPOSE OF SUBMISSION:

Due to the difference in dosage form and formulation composition, this application is being submitted under Section 505(b)(2) of the FD&C Act. Baxter is relying on the Agency's previous finding of safety and effectiveness of MAXIPIME to support the safety and effectiveness of Baxter's premixed drug products, precluding the need to conduct any clinical trials to support this application. Baxter has conducted nonclinical studies to qualify the safety of the impurity profile of the premixed drug products.

REMARKS:

MICROBIOLOGY SUBSECTION OF THE LABEL:

The microbiology section of the label was revised to reflect the current CLSI guidelines. Additionally, the organism _____ was omitted from the second list since the genus *Enterobacter* is present in the first list. Disk diffusion testing of *S. pneumoniae* can be unreliable when conducted with a _____, therefore, disk diffusion susceptibility testing should be done with an oxacillin disk.

b(4)

SUMMARY AND RECOMMENDATIONS:

From the microbiology perspective, based on analysis of the information provided by the applicant, the Reviewer recommends approval of this NDA under Section 505(b)(2) of the FD&C Act. The Agency recommends that that Applicant update the microbiology section of the label to reflect the current CLSI guidelines.

6 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

NDA: 50-817

DATE REVIEW COMPLETED: 11/26/07

INTRODUCTION AND BACKGROUND:

Baxter Healthcare Corporation has submitted a New Drug Application for the approval of cefepime injection in Galaxy Container. They are not proposing to change the microbiology section of the label. However, the Applicant has proposed to change the formulation of the product proposes two presentations: 1 g/50 mL (1 g of cefepime in a 50 mL container) and g/100 mL (2 g of cefepime in a 100 mL container). The formulation of the two presentations is identical; only the container volume (50 mL or 100 mL) is different. The formulation contains _____ and the _____ . Approximately 725 mg of L-Arginine is added per gram of cefepime as a pH adjuster. The pH may be adjusted with hydrochloric acid and/or additional LArginine. The pH is 4.0 – 6.0. b(4)

According to the Applicants description, Cefepime Injection is a premixed IV formulation of the Reference Listed Drug, MAXIPIME (Cefepime Hydrochloride) for Injection (NDA 50-679, held by Bristol-Myers Squibb, approved on 01/18/96). MAXIPIME is for IV or IM use and must be reconstituted with a suitable diluent prior to use. Baxter's proposed 1 g/50 mL and 2 g/100 mL premixed products are for IV use only and are stored frozen (at or below -20°C) for long-term storage and thawed prior to intravenous administration. The proposed indications, route of administration, and dosage regimen (dose, frequency, and duration) for Baxter's 1 g/50 mL and 2 g/100 mL Cefepime Injection products will be identical to the approved indications, route of administration, and dosage regimen (dose, frequency, and duration) for the 1 g and 2 g IV doses of MAXIPIME.

Cephalosporins are known to inhibit the penicillin binding proteins (PBPs), enzymes involved in bacterial cell wall synthesis, resulting in abnormal cell wall thereby promoting cell lysis. However, the development of bacterial resistance to antibiotics is a major issue throughout the healthcare system; and resistant organism may emerge due to a myriad of factors some of which involves widespread usage of antibiotics. There are three ways in which bacteria avoid the bactericidal effect of β -lactams¹:

(a) *Production of beta-lactamases.* Beta-lactamases are bacterial enzymes that hydrolyze the beta-lactam ring and render the antibiotic inactive before it reaches the PBP target. The underlying structural kinship that beta-lactamases share with PBPs allows these enzymes to bind, acylate, and use a strategically located water molecule to hydrolyze and thereby inactivate the beta-lactam².

(b) *Altered PBPs that exhibit low affinity for beta-lactam antibiotics.* Examples are PBP 2x of *Streptococcus pneumoniae* and PBP 2' (PBP2a) of *Staphylococcus aureus*³. These PBPs are relatively resistant to inactivation by penicillins and are able to assume the functions of other PBPs when the latter are inactivated.

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

NDA: 50-817

DATE REVIEW COMPLETED: 11/26/07

(c) *Lack or diminished expression of outer membrane proteins (OMPs) in gram-negative bacteria.* The loss of OMPs restricts the entry of certain beta-lactams into the periplasmic space of gram-negative bacteria and hence access to PBPs on the inner membrane. Imipenem resistance in *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* can arise from the loss of OMP D2 and of OmpK36, respectively^{4,5,6}.

Cefepime is a semi-synthetic, fourth generation broad-spectrum cephalosporin that is active against a variety of Gram negative and Gram positive bacteria due to improved β -lactamase stability; thereby resulting in increased antibacterial stability⁷.

Antimicrobial Spectrum of Activity:

The Applicant has not proposed any changes to the microbiology section of the label. The current interpretive criteria for MAXIPIME® are listed in Table 1. Standardized procedures are based on a dilution method¹ (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefepime powder. The minimum inhibitory concentration against control microorganisms are listed in Table 2.

Table 1: The current interpretive criteria for MAXIPIME®

Microorganism	MIC ($\mu\text{g/mL}$)		
	Susceptible (S)	Intermediate (I)	Resistant (R)
Microorganisms other than <i>Haemophilus</i> spp. * and <i>S. pneumoniae</i>	≤ 8	16	≥ 32
<i>Haemophilus</i> spp. *	≤ 2	-- *	-- *
<i>Streptococcus pneumoniae</i> *	≤ 0.5	1	≥ 2

* NOTE: Isolates from these species should be tested for susceptibility using specialized dilution testing methods. ¹ Also, strains of *Haemophilus* spp. with MICs greater than 2 $\mu\text{g/mL}$ should be considered equivocal and should be further evaluated.

Table 2: The minimum inhibitory concentration range against control microorganisms.

Microorganism	ATCC	MIC ($\mu\text{g/mL}$)
<i>Escherichia coli</i>	25922	0.016-0.12
<i>Staphylococcus aureus</i>	29213	1-4
<i>Pseudomonas aeruginosa</i>	27853	1-4
<i>Haemophilus influenzae</i>	49247	0.5-2
<i>Streptococcus pneumoniae</i>	49619	0.06-0.25

This review will attempt to analyze susceptibility/resistance rates of cefepime since its approval. In 2005, Bijie et al. conducted a literature review of the in vitro activity of ceftriaxone compared to third and fourth generation cephalosporins (including cefepime). It is unclear if all MIC studies were conducted in accordance with the CLSI guidelines. Table 3 shows the result of the study that compared the in vitro activity of third

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

NDA: 50-817

DATE REVIEW COMPLETED: 11/26/07

generation cephalosporins (ceftriaxone, cefoperazone/sulbactam (sulpreazone) with cephalosporins (cefpime and cefpirome)⁷.

Table 3: Comparative in vitro activity (MIC₅₀ and MIC₉₀)* of third generation cephalosporins and 4th generation cephalosporins.

	Ceftriaxone		Cefoperazone		Sulperazone		Cefpime		Cefpirome	
	MIC ₅₀	MIC ₉₀								
Gram-positive bacteria										
Methicillin-susceptible										
<i>Staphylococcus aureus</i>	4	4			2	32	2	4	0.5-1	0.5-1
Coagulase-negative staphylococci	2-8	6->32			1.5-2	3-8	1-4	1.5->16	0.5	2
β-haemolytic streptococci	≤0.25	≤0.25			≤0.5	≤0.5	≤0.12	≤0.12		
Viridans group streptococci	≤0.25	1					≤0.12	1		
<i>Streptococcus pneumoniae</i>	0.12-0.5	1			≤1	≤1	≤0.12-0.5	1-2	0.03	0.25
<i>S. pneumoniae</i> Pen-S†	0.03	0.06					≤0.12	≤0.12	0.016-0.032	0.03-0.125
<i>S. pneumoniae</i> Pen-‡	0.12-0.25	1					0.25	1	0.06	0.5
<i>S. pneumoniae</i> Pen-R**	1	2					1	2	0.5	0.5-1
Anaerobic cocci	1	8			1	32				
<i>Clostridium</i> spp.	0.5	64			2	16				
Enterobacteriaceae										
<i>Citrobacter</i> spp.	≤2	16-64	≤4	≥32	≤1	16	0.25	1	0.032	0.063
<i>Klebsiella</i> spp.	≤0.06-≤2	≤0.25-≤2	≤4	8	≤1*	≤4	≤0.06-≤0.12	0.25	0.03	0.03-0.063
<i>Enterobacter</i> spp.	0.12-≤2	1->64	≤4	≥32	2	≥32	≤0.06	1	0.063	4
<i>Escherichia coli</i>	≤0.06-≤2	≤0.06-≤2	≤4	≥32	≤1	2	≤0.06	0.12	0.032	0.063
<i>Morganella</i> spp.	≤0.06-≤2	0.5-8	≤4	16	≤1	≤4	≤0.06	≤0.06	0.032	0.125
<i>Proteus</i> spp.	≤0.06-≤2	≤0.06->64	≤4	≥32	≤1	≤1	≤0.06	0.12	0.125-0.25	0.125-1
<i>Serratia</i> spp.	0.25-≤2	0.25-≤2	≤4	8	≤1	2	0.12	0.25		
Other Gram-negative bacteria										
<i>Haemophilus influenzae</i>	≤0.25	≤0.25					≤0.12	≤0.12	0.008	0.01
<i>Pseudomonas aeruginosa</i>	≥32	>32->256			4	32-64	3-4	16-64	4	16
<i>Acinetobacter</i> spp.	16	>16->256			2	64	4->16	>16-96		
<i>Fusobacterium</i> spp.	0.12	4			4	16				
<i>Prevotella</i> spp.	0.5	32			1	32				
<i>Bacteroides fragilis</i>	8	64			8	64			25	>200

*Minimum inhibition concentration; †bold values indicate MIC's ≥8μg/ml; ‡Penicillin susceptible (MIC≤0.06 μg/ml); §Penicillin intermediate (MIC 0.012-1 μg/ml); **Penicillin resistant (MIC ≥2μg/ml).

Cefpirome MIC₉₀ values were 4-8 folds lower than cefepime against *S. aureus* and 8 fold lower against coagulase-negative staphylococci (Table 3). Against penicillin resistant *S. pneumoniae* isolates, cefpirome demonstrated MIC₉₀ values that were 2-4 folds better than cefepime. Generally, the 4th generation cephalosporins (especially cefpirome) exhibited lower MIC activity against the Gram negative and Gram positive isolates examined in the study.

Since approval of cefepime, the SENTRY Antimicrobial Surveillance (established in 1997 to monitor the occurrence of pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections via a network of hospitals distributed by geographic locations) evaluated the in vitro activity of cefepime against a large 6-year collection (1998-2003) of clinical isolates in North America.

A total of 65,746 clinical bacterial isolates were analyzed (Table 4)⁸. All isolates were identified by the participating laboratories and confirmed by the monitoring facility (JMI Laboratories, North Liberty, IA). Each isolate was tested by a reference broth microdilution method against more than 30 antimicrobial agents. All quantitative MIC results were done in accordance with Clinical and Laboratory Standards Institute (CLSI, 2005) methods and criteria. Quality control testing was performed using the following organisms: *Streptococcus pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC

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

NDA: 50-817

DATE REVIEW COMPLETED: 11/26/07

29213, *Escherichia coli* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853. All quality control results were within published ranges as those reported by CLSI, 2005.

Table 4: Frequency of occurrence for bacterial isolates in the SENTRY Antimicrobial Surveillance Program medical centers in North America for the years 1998–2003 (65746 strains)

Organism or group	No. of occurrences	% of all isolates
1. Oxacillin-susceptible <i>S. aureus</i>	10 835	16.5
2. <i>E. coli</i>	10 361	15.8
3. <i>Streptococcus pneumoniae</i>	9244	14.1
4. <i>H. influenzae</i>	7975	12.1
5. <i>P. aeruginosa</i>	5517	8.4
6. <i>Klebsiella spp.</i>	5166	7.9
7. <i>M. catarrhalis</i>	3565	5.4
8. <i>Enterobacter spp.</i>	2836	4.3
9. β -Hemolytic streptococci	2703	4.1
10. <i>Serratia spp.</i>	1412	2.2
11. <i>Proteus mirabilis</i>	1225	1.9
12. Oxacillin-susceptible coagulase-negative staphylococci	1177	1.8
13. <i>Acinetobacter spp.</i>	1046	1.6
14. Viridans group streptococci	783	1.2
15. <i>Citrobacter spp.</i>	717	1.1
16. Indole-positive <i>Proteus spp.</i>	433	0.7
17. <i>Salmonella spp.</i>	405	0.6
18. <i>Shigella spp.</i>	106	0.2
19. Other species	240	0.4

Oxacillin-resistant *Staphylococcus spp.* and *Enterococcus spp.* isolates were not included.

Tables 5-9 shows a comparative analysis of the in vitro activity of antibacterial agents currently used in the hospital environment. The data was taken from studies published by Sader et al⁸.

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

NDA: 50-817

DATE REVIEW COMPLETED: 11/26/07

Table 5: In vitro activity of cefepime and selected comparators against Enterobacteriaceae collected in North America (SENTRY Program, 1998–2003)

Organism/antimicrobial agent (no. tested)	MIC (µg/mL)			Category ^a	
	50%	90%	Range	% Susceptible	% Resistant
<i>Citrobacter</i> spp. (717) ^b					
Cefepime	≤0.12	0.5	≤0.12 to >16	99.6	0.3
Ceftazidime	≤2	>16	≤2 to >16	84.1	13.4
Ceftriaxone	≤0.25	32	≤0.25 to >32	86.5	6.4
Aztreonam	≤0.12	>16	≤0.12 to >16	85.4	11.0
Piperacillin/tazobactam	2	32	≤0.5 to 128	87.9	4.2
Imipenem	0.25	1	≤0.5 to >8	99.9	0.1
Ciprofloxacin	0.12	0.5	≤0.016 to >4	92.3	5.7
Gatifloxacin	≤0.03	1	≤0.03 to >4	92.7	4.3
Amikacin	1	2	≤0.25 to 32	99.7	0.0
Gentamicin	≤2	≤2	≤2 to >16	94.1	4.6
<i>Enterobacter</i> spp. (2836) ^c					
Cefepime	≤0.12	2	≤0.12 to >16	99.0	0.4
Ceftazidime	≤2	>16	≤2 to >16	79.2	17.5
Ceftriaxone	≤0.25	32	≤0.25 to >32	82.3	9.3
Aztreonam	≤0.12	>16	≤0.12 to >16	81.1	14.6
Piperacillin/tazobactam	2	64	0.25 to 256	83.0	6.5
Imipenem	0.5	1	≤0.5 to >8	99.8	0.1
Ciprofloxacin	0.06	0.5	≤0.016 to >4	93.6	4.6
Gatifloxacin	≤0.03	0.5	≤0.03 to >4	95.5	2.9
Amikacin	2	4	≤0.25 to >32	99.2	0.2
Gentamicin	≤2	≤2	≤2 to >16	93.7	5.0
<i>E. coli</i> (10361)					
Cefepime	≤0.12	≤0.12	≤0.12 to >16	99.7	0.2
Ceftazidime	≤2	≤2	≤2 to >16	98.5	1.0
Ceftriaxone	≤0.25	≤0.25	≤0.25 to >32	98.9	0.4
Aztreonam	≤0.12	0.25	≤0.12 to >16	98.9	0.7
Piperacillin/tazobactam	2	4	≤0.12 to >256	96.6	1.1
Imipenem	≤0.5	≤0.5	≤0.5 to 4	100.0	0.0
Ciprofloxacin	≤0.25	≤0.25	≤0.25 to >4	93.1	6.7
Gatifloxacin	≤0.03	0.12	≤0.03 to >4	93.4	5.2
Amikacin	2	4	≤0.25 to >32	99.7	0.0
Gentamicin	≤2	≤2	≤2 to >16	95.8	3.3
<i>E. coli</i> (ESBL-producing, 386)					
Cefepime	0.25	4	≤0.12 to >16	93.8	4.1
Ceftazidime	8	>16	≤2 to >16	60.6	27.2
Ceftriaxone	1	>32	≤0.25 to >32	71.8	11.4
Cefoxitin	>32	>32	≤0.25 to >32	29.8	56.7
Aztreonam	4	>16	≤0.12 to >16	71.2	19.4
Piperacillin/tazobactam	4	64	≤0.5 to >64	86.2	6.5
Imipenem	≤0.5	≤0.5	≤0.5 to 4	100.0	0.0
Ciprofloxacin	≤0.25	>2	≤0.25 to >2	68.7	29.3
Gatifloxacin	0.06	>4	≤0.03 to >4	71.2	24.4
Amikacin	2	8	0.5 to >32	97.2	0.3
Gentamicin	≤2	>8	≤2 to >8	72.8	21.2
<i>Klebsiella</i> spp. (5166) ^d					
Cefepime	≤0.12	0.25	≤0.12 to >16	99.3	0.3
Ceftazidime	≤2	≤2	≤2 to >16	94.6	4.9
Ceftriaxone	≤0.25	≤0.25	≤0.25 to >32	96.1	1.2
Aztreonam	≤0.12	0.5	≤0.12 to >16	94.5	5.0
Piperacillin/tazobactam	2	8	≤0.12 to >256	94.0	3.4
Imipenem	≤0.5	≤0.5	≤0.5 to >8	99.9	0.1
Ciprofloxacin	0.06	0.5	≤0.016 to >4	94.0	4.7
Gatifloxacin	0.06	0.5	≤0.03 to >4	95.5	2.8
Amikacin	1	2	≤0.25 to >32	98.4	0.9
Gentamicin	≤2	≤2	≤2 to >16	94.4	4.2
<i>Klebsiella</i> spp. (ESBL-producing, 442)					
Cefepime	1	8	≤0.12 to >16	92.5	3.6
Ceftazidime	>16	>16	≤2 to >16	36.9	57.0
Ceftriaxone	8	>32	≤0.25 to >32	53.8	13.8
Cefoxitin	16	>32	≤0.25 to >32	49.5	35.1

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Table 5 (continued)

Organism/antimicrobial agent (no. tested)	MIC ($\mu\text{g/mL}$)		Range	Category ^a	
	50%	90%		% Susceptible	% Resistant
<i>Klebsiella</i> spp. (ESBL-producing, 442)					
Aztreonam	>16	>16	≤ 0.12 to >16	35.7	58.6
Piperacillin/tazobactam	16	>64	≤ 0.5 to >64	51.2	28.6
Imipenem	≤ 0.5	≤ 0.5	≤ 0.5 to >8	99.3	0.5
Ciprofloxacin	1	>2	≤ 0.25 to >2	60.2	32.1
Gatifloxacin	1	>4	≤ 0.03 to >4	69.0	20.4
Amikacin	2	>32	≤ 0.25 to >32	81.4	11.1
Gentamicin	≤ 2	>8	≤ 2 to >8	47.3	40.5
<i>Proteus mirabilis</i> (1225)					
Cefepime	≤ 0.12	≤ 0.12	≤ 0.12 to >16	99.5	0.3
Ceftazidime	≤ 2	≤ 2	≤ 2 to >16	99.2	0.5
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 to >32	99.3	0.4
Aztreonam	≤ 0.12	≤ 0.12	≤ 0.12 to >16	99.2	0.6
Piperacillin/tazobactam	≤ 0.5	1	≤ 0.12 to >64	99.6	0.2
Imipenem	1	2	≤ 0.06 to 8	99.5	0.0
Ciprofloxacin	0.12	>2	≤ 0.016 to >2	86.0	11.3
Gatifloxacin	0.12	4	≤ 0.03 to >4	86.0	9.7
Amikacin	4	8	0.5 to >32	99.7	0.2
Gentamicin	≤ 2	4	≤ 2 to >16	93.7	5.1
<i>Indole-positive Proteae</i> spp. (433)					
Cefepime	≤ 0.12	0.25	≤ 0.12 to >16	98.6	0.5
Ceftazidime	≤ 2	16	≤ 2 to >16	89.1	5.3
Ceftriaxone	≤ 0.25	2	≤ 0.25 to >32	96.1	1.4
Aztreonam	≤ 0.12	2	≤ 0.12 to >16	96.1	2.5
Piperacillin/tazobactam	≤ 0.5	4	≤ 0.5 to >64	96.8	0.9
Imipenem	2	4	≤ 0.5 to 8	98.6	0.0
Ciprofloxacin	≤ 0.25	>2	≤ 0.25 to >2	74.1	22.9
Gatifloxacin	0.12	>4	≤ 0.03 to >4	76.2	20.1
Amikacin	2	4	≤ 0.25 to >32	98.4	0.9
Gentamicin	≤ 2	8	≤ 2 to >8	85.9	9.2
<i>Salmonella</i> spp. (405) ^e					
Cefepime	≤ 0.12	≤ 0.12	≤ 0.12 to 2	100.0	0.0
Ceftazidime	≤ 2	≤ 2	≤ 2 to >16	96.0	2.5
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 to 32	96.8	0.0
Aztreonam	≤ 0.12	0.25	≤ 0.12 to >16	97.3	0.7
Piperacillin/tazobactam	2	4	≤ 0.5 to >64	98.3	0.7
Imipenem	≤ 0.5	≤ 0.5	≤ 0.5 to 2	100.0	0.0
Ciprofloxacin	≤ 0.25	≤ 0.25	≤ 0.25 to 2	99.8	0.0
Gatifloxacin	≤ 0.03	0.06	≤ 0.03 to 2	100.0	0.0
Amikacin	2	2	≤ 0.25 to 16	100.0	0.0
Gentamicin	≤ 2	≤ 2	≤ 2 to >16	98.0	1.0
<i>Serratia</i> spp. (1412 strains) ^f					
Cefepime	≤ 0.12	0.25	≤ 0.12 to >16	99.3	0.4
Ceftazidime	≤ 2	≤ 2	≤ 2 to >16	97.5	1.7
Ceftriaxone	≤ 0.25	1	≤ 0.25 to >32	96.4	0.8
Aztreonam	≤ 0.12	0.5	≤ 0.12 to >16	97.7	2.1
Piperacillin/tazobactam	2	4	≤ 0.5 to >256	95.5	0.6
Imipenem	0.5	2	≤ 0.5 to >8	99.6	0.2
Ciprofloxacin	≤ 0.25	1	≤ 0.25 to >4	92.8	4.1
Gatifloxacin	0.25	2	≤ 0.03 to >4	94.4	2.9
Amikacin	2	4	≤ 0.25 to >32	99.8	0.1
Gentamicin	≤ 2	≤ 2	≤ 2 to >16	96.3	2.3
<i>Shigella</i> spp. (106) ^g					
Cefepime	≤ 0.12	0.25	≤ 0.12 to 1	100.0	0.0
Ceftazidime	≤ 2	≤ 2	≤ 2 to 4	100.0	0.0
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 to 0.5	100.0	0.0
Aztreonam	≤ 0.12	≤ 0.12	≤ 0.12 to 0.25	100.0	0.0
Piperacillin/tazobactam	2	4	≤ 0.5 to >64	99.1	0.9
Imipenem	≤ 0.5	≤ 0.5	≤ 0.5	100.0	0.0
Ciprofloxacin	≤ 0.03	≤ 0.03	≤ 0.03 to 0.5	100.0	0.0
Gatifloxacin	≤ 0.03	≤ 0.03	≤ 0.03 to 0.5	100.0	0.0
Amikacin	4	8	2 to 8	100.0	0.0
Gentamicin	≤ 2	≤ 2	≤ 2	100.0	0.0

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Organism/antimicrobial agent (no. tested)	MIC (µg/mL)			Category ^a	
	50%	90%	Range	% Susceptible	% Resistant
All enteric bacilli (22 860)					
Cefepime	≤0.12	0.25	≤0.12 to >16	99.5	0.3
Cefazidime	≤2	≤2	≤2 to >16	94.5	4.5
Ceftriaxone	≤0.25	0.5	≤0.25 to >32	95.6	1.9
Aztreonam	≤0.12	0.5	≤0.12 to >16	95.1	3.9
Piperacillin/tazobactam	2	8	≤0.12 to >256	94.2	2.3
Imipenem	0.25	1	≤0.06 to >8	99.9	0.0
Ciprofloxacin	0.06	0.5	≤0.016 to >4	92.8	6.1
Gatifloxacin	≤0.03	0.5	≤0.03 to >4	93.7	4.6
Amikacin	2	4	≤0.25 to >32	99.4	0.3
Gentamicin	≤2	≤2	≤2 to >16	95.0	3.8

^a According to the criteria published by the CLSI (2005).

^b Includes *Citrobacter amalonaticus* (27 strains), *C. braaki* (25 strains), *C. diversus* (4 strains), *C. farmeri* (4 strains), *C. freundii* (382 strains), *C. koseri* (232 strains), and *Citrobacter* spp. (43 strains).

^c Includes *Enterobacter aerogenes* (719 strains), *E. amnigenus* (4 strains), *E. asburiae* (5 strains), *E. cancerogenus* (6 strains), *E. cloacae* (1975 strains), *E. gergoviae* (12 strains), *E. hormaechei* (3 strains), *E. intermedium* (3 strains), *E. sakazakii* (13 strains), *E. taylorae* (6 strains), and *Enterobacter* spp. (90 strains).

^d Includes *Klebsiella ornithinolytica* (11 strains), *K. oxytoca* (801 strains), *K. ozaenae* (8 strains), *K. pneumoniae* (4249 strains), *K. terrigena* (1 strain), and *Klebsiella* spp. (96 strains).

^e Includes *Salmonella agona* (4 strains), *S. arizonae* (1 strain), *S. berulley* (1 strain), *S. enterica* (4 strains), *S. enteritidis* (23 strains), *Salmonella* group B (61 strains), *Salmonella* group C (20 strains), *Salmonella* group D (44 strains), *S. hadar* (2 strains), *S. heidelberg* (19 strains), *S. infantis* (2 strains), *S. litchfield* (1 strain), *S. montevideo* (1 strain), *S. muenchen* (3 strains), *S. newport* (5 strains), *S. panama* (1 strain), *S. paratyphi* (11 strains), *S. schwarzengrund* (1 strain), *S. stanley* (2 strains), *S. StPaul* (1 strain), *S. thompson* (1 strain), *S. typhi* (15 strains), *S. typhinarium* (28 strains), *S. virchow* (1 strain), and *Salmonella* spp. (153 strains).

^f Includes *Serratia fonticola* (9 strains), *Serratia liquefaciens* (27 strains), *Serratia marcescens* (1345 strains), *Serratia odorifera* (3 strains), *Serratia plymuthica* (3 strains), *Serratia rubidaea* (13 strains), and *Serratia* spp. (12 strains).

^g Includes *Shigella boydii* (5 strains), *S. dysenteriae* (4 strains), *S. flexneri* (18 strains), *S. sonnei* (65 strains), and *Shigella* spp. (14 strains).

Table 6 shows the in vitro activity of cefepime and selected comparators against non-fermentative Gram negative bacilli collected in North America (SENTRY program, 1998-2003).

Table 6: In vitro activity of cefepime and selected comparators against nonfermentative Gram-negative bacilli

Organism/antimicrobial agent (no. tested)	MIC (µg/mL)			Category ^a	
	50%	90%	Range	% Susceptible	% Resistant
<i>P. aeruginosa</i> (5517)					
Cefepime	4	16	≤0.12 to >16	85.2	5.5
Ceftazidime	2	>16	≤2 to >16	82.8	12.8
Aztreonam	8	>16	≤0.12 to >16	63.7	21.5
Piperacillin/tazobactam	8	>64	≤0.5 to >64	89.0	11.0
Imipenem	1	8	≤0.5 to >8	86.9	7.6
Ciprofloxacin	0.25	>2	≤0.25 to >2	75.2	19.0
Gatifloxacin	1	>4	≤0.03 to >4	69.1	21.6
Amikacin	4	8	≤0.25 to >32	96.2	2.0
Gentamicin	≤2	8	≤2 to >16	85.9	9.4
<i>Acinetobacter</i> spp. (1046) ^b					
Cefepime	4	>16	≤0.12 to >16	63.0	22.7
Ceftazidime	8	>16	≤2 to >16	62.0	28.2
Ceftriaxone	16	>32	≤0.25 to >32	32.2	29.3
Aztreonam	>16	>16	≤0.12 to >16	9.6	73.1
Piperacillin/tazobactam	8	>64	≤0.5 to >64	62.7	20.3
Imipenem	0.25	4	≤0.5 to >8	92.5	4.6
Ciprofloxacin	0.25	>4	≤0.25 to >4	60.6	37.9
Gatifloxacin	0.12	>4	≤0.03 to >4	64.6	28.8
Amikacin	4	32	≤0.25 to >32	85.2	9.6
Gentamicin	≤2	>8	≤2 to >8	64.1	31.1

^a Criteria as published by the CLSI (2005).

^b Includes *Acinetobacter haemolyticus* (3 strains), *A. anitratus* (59 strains), *A. calcoaceticus* (80 strains), *A. baumannii* (747 strains), *A. lwoffii* (113 strains), *A. junii* (3 strains), and *Acinetobacter* spp. (41 strains).

Table 7 shows the in vitro activity of cefepime and selected comparators against Gram-negative bacilli collected from community-acquired respiratory tract infections in North America (SENTRY Program, 1998–2003).

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Table 7: In vitro activity of cefepime and selected comparators against Gram-negative bacilli collected from community-acquired respiratory tract infections in North America

Organism/antimicrobial agent (no. tested)	MIC ($\mu\text{g/mL}$)			Category ^a	
	50%	90%	Range	% Susceptible	% Resistant
<i>H. influenzae</i> (7975)					
Cefepime	≤ 0.06	0.12	≤ 0.06 to 2	100.0	- ^b
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 to 2	100.0	-
Cefuroxime	1	2	≤ 0.06 to >16	98.7	0.2
Ampicillin	≤ 0.5	> 4	≤ 0.5 to >4	68.5 ^c	31.5 ^c
Amoxicillin/clavulanate	≤ 2	≤ 2	≤ 2 to >8	99.9	0.1
Azithromycin	1	2	≤ 0.06 to >16	86.8	-
Levofloxacin	≤ 0.5	≤ 0.5	≤ 0.5 to 2	100.0	-
Gatifloxacin	≤ 0.03	≤ 0.03	≤ 0.03 to 1	100.0	-
Tetracycline	≤ 4	≤ 4	≤ 4 to >16	86.9	0.5
Trimethoprim/sulfamethoxazole	≤ 0.5	> 4	≤ 0.5 to >4	79.5	15.9
<i>M. catarrhalis</i> (3565)					
Cefepime	0.5	2	≤ 0.06 to 8	-	-
Ceftriaxone	0.25	0.5	≤ 0.008 to 8	-	-
Cefuroxime	1	2	≤ 0.06 to 8	-	-
Ampicillin	≤ 2	4	≤ 2 to 16	4.4 ^c	95.6 ^c
Amoxicillin/clavulanate	≤ 0.25	0.5	≤ 0.25 to 8	-	-
Azithromycin	≤ 0.12	≤ 0.12	≤ 0.12 to 1	-	-
Levofloxacin	≤ 0.5	≤ 0.5	≤ 0.5 to >4	-	-
Gatifloxacin	≤ 0.03	≤ 0.03	≤ 0.03 to >4	-	-
Tetracycline	≤ 2	≤ 2	≤ 2 to 16	-	-
Trimethoprim/sulfamethoxazole	≤ 0.5	≤ 0.5	≤ 0.5 to 8	-	-

^a Criteria as published by the CLSI (2005) for *Haemophilus* spp.

^b - = no criteria have been established by the CLSI (2005).

^c Isolates were categorized as susceptible or resistant to ampicillin based on the β -lactamase test result (CLSI, 2005).

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Table 8: In vitro activity of cefepime and selected comparators against Gram-positive cocci collected in North America (SENTRY Program, 1998–2003)

Organism/antimicrobial agent (no. tested)	MIC (µg/mL)			Category ^a	
	50%	90%	Range	% Susceptible	% Resistant
<i>Staphylococcus aureus</i> (10835) ^b					
Cefepime	2	4	≤0.12 to 8	100.0	0.0
Ceftazidime	8	16	≤0.12 to >16	86.4	0.4
Ceftriaxone	4	4	≤0.25 to 16	99.7	0.0
Piperacillin/tazobactam	1	2	≤0.12 to 64	99.8	0.2
Imipenem	≤0.5	≤0.5	≤0.5 to >8	100.0	0.0
Ciprofloxacin	0.25	1	≤0.016 to >4	93.2	5.4
Gatifloxacin	0.06	0.12	≤0.03 to >4	95.0	4.6
Clindamycin	0.12	0.25	≤0.06 to >8	95.8	4.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >2	98.7	1.3
Vancomycin	1	1	≤0.12 to 4	100.0	0.0
Coagulase-negative staphylococci (1177) ^{b,c}					
Cefepime	0.5	2	≤0.12 to 8	100.0	0.0
Ceftazidime	4	8	0.25 to >16	94.1	0.6
Ceftriaxone	2	4	≤0.25 to >32	99.2	0.1
Piperacillin/tazobactam	≤0.5	1	≤0.5 to 8	100.0	0.0
Imipenem	≤0.5	≤0.5	≤0.5 to >8	99.8	0.2
Ciprofloxacin	≤0.25	>2	0.06 to >2	86.5	12.4
Gatifloxacin	0.12	2	≤0.03 to >4	87.3	10.7
Clindamycin	0.12	0.25	≤0.06 to >8	90.7	9.0
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 to >2	89.7	10.3
Vancomycin	1	2	≤0.12 to 4	100.0	0.0
<i>Streptococcus pneumoniae</i> (9244)					
Cefepime	≤0.06	1	≤0.06 to >8	97.4	0.3
Ceftriaxone	0.06	1	≤0.008 to >16	96.5	1.4
Penicillin	≤0.03	2	≤0.03 to 8	69.9	15.2
Amoxicillin/clavulanate	≤0.25	2	≤0.25 to >16	95.2	2.5
Erythromycin	≤0.25	8	≤0.25 to >32	76.6	22.5
Clindamycin	≤0.25	≤0.25	≤0.25 to >16	92.2	7.0
Levofloxacin	1	1	≤0.03 to >4	99.2	0.7
Gatifloxacin	0.25	0.5	≤0.03 to >4	99.2	0.7
Tetracycline	≤2	>16	≤2 to >16	67.0	14.1
Trimethoprim/sulfamethoxazole	≤0.5	4	≤0.5 to >8	70.0	22.5
β-Hemolytic streptococci (2703) ^d					
Cefepime	≤0.12	≤0.12	≤0.12 to 0.5	100.0	– ^e
Ceftriaxone	0.06	0.06	≤0.008 to 0.5	100.0	–
Penicillin	0.03	0.06	≤0.016 to 0.25	>99.9	–
Amoxicillin/clavulanate	≤2	≤2	≤2 to 4	–	–
Erythromycin	≤0.06	2	≤0.06 to >32	80.3	18.8
Clindamycin	≤0.06	≤0.06	≤0.06 to >8	93.2	6.6
Levofloxacin	0.5	1	≤0.03 to >4	99.6	0.3
Gatifloxacin	0.25	0.25	≤0.03 to >4	99.7	0.1
Tetracycline	>8	>8	≤2 to >8	43.7	54.1
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >8	–	–
Viridans group streptococci (783)					
Cefepime	≤0.12	1	≤0.12 to >8	94.1	2.3
Ceftriaxone	0.12	0.5	≤0.008 to 16	93.6	2.7
Penicillin	0.06	1	≤0.016 to 8	75.7	4.2
Amoxicillin/clavulanate	≤2	≤2	≤2 to 16	–	–
Erythromycin	≤0.25	8	≤0.25 to >32	58.0	38.2
Clindamycin	≤0.06	0.12	≤0.06 to >8	92.2	7.8
Levofloxacin	1	2	≤0.03 to >4	96.9	2.1
Gatifloxacin	0.25	0.5	≤0.03 to >4	97.2	2.4
Tetracycline	≤4	>8	≤4 to >8	68.3	31.7
Trimethoprim/sulfamethoxazole	≤0.5	2	≤0.5 to >8	–	–

^a Criteria as published by the CLSI (2005).

^b Includes only oxacillin-susceptible staphylococci.

^c Includes *Staphylococcus auricularis* (9 strains), *S. capitis* (30 strains), *S. caprae* (1 strain), coagulase-negative staphylococci (745 strains), *S. cohnii* (1 strain), *S. epidermidis* (267 strains), *S. haemolyticus* (20 strains), *S. hominis* (46 strains), *S. intermedius* (7 strains), *S. lugdunensis* (6 strains), *S. saprophyticus* (1 strain), *S. sciuri* (2 strains), *S. simulans* (17 strains), *S. warnerii* (14 strains), and *Staphylococcus* spp. (11 strains).

^d Includes β-hemolytic streptococci (52 strains), *S. dysgalactiae* (1 strain), *S. equisimilis* (2 strains), group A β-hemolytic streptococci (900 strains), group B β-hemolytic streptococci (1328 strains), group C β-hemolytic streptococci (77 strains), group F β-hemolytic streptococci (31 strains), group G β-hemolytic streptococci (301 strains), and *Streptococcus* spp. (11 strains).

^e – = no breakpoint has been established by the CLSI (2005).

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Table 9: Antimicrobial spectrum of cefepime and selected comparators by year

Organism	% Susceptible/resistant by year (no. of isolates tested)					
	1998	1999	2000	2001	2002	2003
<i>P. aeruginosa</i>	(1099)	(1041)	(1107)	(815)	(1058)	(397)
Cefepime	85.6/4.6	84.5/6.1	84.4/5.8	84.9/6.3	85.1/5.6	88.4/3.5
Ceftazidime	81.1/13.5	79.5/14.8	82.5/12.6	83.4/13.4	86.0/11.4	87.2/8.3
Piperacillin/tazobactam	89.9/10.0	88.4/11.6	88.3/11.6	88.6/11.4	88.8/11.2	91.4/8.6
Imipenem	84.7/10.2	88.4/7.2	87.7/7.0	86.6/8.5	86.4/5.7	89.4/6.5
Ciprofloxacin	77.3/17.2	76.1/17.1	73.8/21.1	75.7/18.9	73.3/20.0	75.3/20.2
Gentamicin	86.6/8.8	86.7/9.1	83.4/11.3	85.0/9.6	85.9/8.9	90.4/7.3
<i>Klebsiella</i> spp.	(918)	(876)	(944)	(757)	(915)	(756)
Cefepime	99.3/0.3	99.2/0.2	99.7/0.2	99.6/0.4	99.2/0.2	98.9/0.7
Ceftazidime	95.8/4.0	86.1/3.8	96.4/3.3	94.2/5.0	92.0/7.2	92.7/6.2
Piperacillin/tazobactam	93.0/3.2	95.9/2.6	93.2/2.1	94.5/3.3	93.4/5.4	94.0/3.7
Imipenem	99.9/0.1	100.0/0.0	100.0/0.0	99.7/0.0	99.9/0.1	99.9/0.1
Ciprofloxacin	95.1/4.0	95.3/3.4	95.8/3.4	83.5/5.0	93.4/4.0	89.8/9.1
Gentamicin	95.1/2.7	96.3/2.2	96.3/2.6	93.9/4.4	91.6/7.7	93.0/5.8
<i>Enterobacter</i> spp.	(511)	(526)	(520)	(475)	(475)	(329)
Cefepime	99.4/0.2	98.7/1.0	99.4/0.0	99.2/0.6	99.2/0.6	97.3/0.3
Ceftazidime	77.1/19.8	73.8/21.9	80.8/16.7	78.9/17.5	78.9/17.5	83.6/14.0
Piperacillin/tazobactam	79.5/8.2	79.7/10.5	82.1/4.8	84.4/4.8	84.4/4.8	87.8/4.9
Imipenem	100.0/0.0	99.8/0.0	100.0/0.0	99.4/0.6	99.4/0.6	99.7/0.0
Ciprofloxacin	93.9/3.9	94.5/3.2	95.4/3.3	92.4/6.5	92.4/6.5	90.9/7.3
Gentamicin	94.1/4.5	93.3/5.3	95.2/3.5	93.5/5.9	93.5/5.9	91.5/5.8
All enteric bacilli	(4307)	(3751)	(4188)	(3518)	(3682)	(3414)
Cefepime	99.4/0.3	99.4/0.3	99.8/0.1	99.5/0.3	99.5/0.3	99.3/0.3
Ceftazidime	94.6/4.6	94.1/4.8	95.4/3.9	93.9/4.7	93.8/5.0	95.1/3.7
Piperacillin/tazobactam	92.7/2.5	94.4/2.6	92.9/1.6	94.8/2.1	95.0/2.7	95.7/2.3
Imipenem	99.7/0.0	100.0/0.0	100.0/0.0	99.8/0.1	99.9/0.1	99.9/0.1
Ciprofloxacin	95.1/3.9	94.3/4.6	94.6/4.6	92.7/6.4	90.9/7.5	88.2/10.8
Gentamicin	95.6/3.2	95.7/3.3	96.3/2.8	94.9/3.9	93.4/5.3	93.9/4.9

The results of the SENTRY study found that all Enterobacteriaceae species evaluated were highly susceptible to cefepime, with susceptibility rates ranging from 98.6% (indole-positive *Proteae*) to 100.0% (*Salmonella* and *Shigella*). Cefepime was also very active against ESBL-producing *E. coli* (MIC₉₀ = 4 µg/mL, 93.8% susceptible at ≤ 8 µg/mL) (CLSI, 2005) and *Klebsiella pneumoniae* (MIC₉₀ = 8 µg/mL, 92.5% susceptibility). However, cefepime demonstrated relatively low activity against *Acinetobacter* spp., with susceptibility rates of 63% (MIC range ≤ 0.12 to >16 µg/mL). All *H. influenzae* isolates tested (7975) were susceptible to cefepime (MIC₉₀ = 0.12 µg/mL); and of the 7975 *H. influenzae* tested, 31.5% were β-lactamase produces and all were reported to be susceptible to cefepime.

Cefepime continues to demonstrated activity against methicillin susceptible *S. aureus* (MSSA) (MIC₅₀ = 2 µg/mL; MIC₉₀ = 4 µg/mL) with 100% of isolates being susceptible (Table 8). Cefepime was slightly more active against methicillin susceptible CoNS (MIC₅₀ = 0.5 µg/mL; MIC₉₀ = 2 µg/mL) when compared with the MSSA results. Against *Streptococcus pneumoniae*, 97.4% of the isolates were susceptible to cefepime (MIC₉₀ = 1 µg/mL). The data showed that only 0.3% of *Streptococcus pneumoniae* isolates were resistant to cefepime (MIC ≥ 4 µg/mL). Cefepime continues to show good activity against β-hemolytic (MIC₉₀ ≤ 0.12 µg/mL) and viridans group streptococci (MIC₉₀ = 1 µg/mL).

Table 6 shows the susceptibility and resistance rates for *P. aeruginosa*, *Klebsiella* spp., *Enterobacter* spp., and the entire Enterobacteriaceae group when tested against the major representatives for antimicrobial agent classes evaluated. Cefepime activity remained

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constant between 1998–2003. Against *P. aeruginosa*, susceptibility/resistance rates varied from 85.6%/4.6% in 1998 to 88.4%/3.5% in 2003. Against Enterobacteriaceae, susceptibility/resistance rates remained basically unchanged. The results from the 1998-2003 SENTRY analysis showed that cefepime continues to demonstrate activity against Enterobacteriaceae, *P. aeruginosa*, and the most prevalent Gram-positive cocci (except methicillin-resistant staphylococci and enterococci) isolated in North American medical centers.

In a similar study, the activity of cefepime was tested against isolates from pediatric patients⁹, the results of which were published in 2007. The study examined 12,737 isolates from pediatric patients (< 18 years of age) isolated over a 7-year period (1998-2004) from 52 hospitals in North America. All isolates were identified by the participating laboratories and confirmed by the monitoring facility (JMI Laboratories, North Liberty, IA). The strains were predominantly isolated from blood (4876, 38.3%), community-acquired respiratory tract infections (4223, 33.2%), respiratory tract specimens of patients with nosocomial pneumonia (1609, 12.6%), documented skin and soft tissue infections (589, 4.6%), and urine (472, 3.7%).

MICs of 14 antimicrobials were determined according to CLSI broth microdilution methods, and interpretive criteria. β -Lactamase characterization was determined using nitrocefin disks (Remel, Lenexa, KS). Extended spectrum β -lactamase production was screened and confirmed in accordance with CLSI methods. Concurrent quality control testing was performed using the following organisms: *Escherichia coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49247, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619. Table 10 shows the antimicrobial activity of cefepime and selected comparators tested against isolated pathogens.

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Table 10: Antimicrobial activity of cefepime and selected comparator agents tested against the 11 most frequently isolated pathogens (excluding *Enterococcus* spp.) from pediatric patients (SENTRY Antimicrobial Surveillance Program, 1998–2004)

Organism/antimicrobial agent (no. tested)	MIC ($\mu\text{g/mL}$)			% Category ^a	
	50%	90%	Range	Susceptible	Resistant
<i>S. pneumoniae</i> (1975)					
Cefepime	≤ 0.12	1	≤ 0.12 to 8	93.9	0.9
Ceftriaxone	≤ 0.25	1	≤ 0.25 to 16	93.7	3.1
Penicillin	≤ 0.03	2	≤ 0.03 to 8	56.6 ^b	24.2 ^b
Erythromycin	≤ 0.25	32	≤ 0.25 to >32	66.2	33.3
Clindamycin	≤ 0.25	>2	≤ 0.25 to >2	89.4	10.4
Levofloxacin	1	1	≤ 0.03 to >4	99.9	0.1
Tetracycline	≤ 2	>16	≤ 2 to >16	71.4	18.9
Trimethoprim-sulfamethoxazole	≤ 0.5	>4	≤ 0.5 to >4	57.1	33.9
<i>H. influenzae</i> (1862)					
Cefepime	≤ 0.06	0.12	≤ 0.06 to 2	100.0	- ^c
Ceftriaxone	≤ 0.008	0.016	≤ 0.008 to 0.5	100.0	-
Ceftazidime	≤ 0.25	≤ 0.25	≤ 0.25 to 8	99.9	-
Ampicillin ^d	≤ 2	>4	≤ 1 to >4	66.0	34.0
Clarithromycin	8	16	≤ 0.25 to >32	87.0	0.5
Levofloxacin	≤ 0.5	≤ 0.5	≤ 0.5	100.0	-
Tetracycline	≤ 2	≤ 2	≤ 2 to >16	94.0	0.4
Trimethoprim-sulfamethoxazole	≤ 0.5	>4	≤ 0.5 to >4	79.1	16.1
<i>S. aureus, oxacillin-susceptible</i> (1313)					
Cefepime	2	4	0.25 to 8	100.0	0.0
Ceftriaxone	4	4	≤ 0.25 to 16	99.8	0.0
Ceftazidime	8	16	0.25 to >16	86.7	0.5
Erythromycin	0.5	>8	≤ 0.06 to >8	71.5	25.5
Clindamycin	0.12	0.25	≤ 0.06 to >8	97.2	2.3
Levofloxacin	0.12	0.25	≤ 0.03 to >4	98.4	1.4
Tetracycline	≤ 4	≤ 4	≤ 4 to >8	95.7	3.6
Trimethoprim-sulfamethoxazole	≤ 0.5	≤ 0.5	≤ 0.5 to >2	99.5	0.5
<i>M. catarrhalis</i> (1022)					
Cefepime	0.5	2	≤ 0.06 to 4	-	-
Ceftriaxone	0.25	1	≤ 0.008 to 2	-	-
Ceftazidime	≤ 0.25	0.5	≤ 0.25 to 8	-	-
Ampicillin ^d	2	>4	≤ 1 to >4	0.8	99.2
Clarithromycin	≤ 0.25	≤ 0.25	≤ 0.25 to 0.5	-	-
Levofloxacin	≤ 0.5	≤ 0.5	≤ 0.5	-	-
Tetracycline	≤ 2	≤ 2	≤ 2 to 16	-	-
Trimethoprim-sulfamethoxazole	≤ 0.5	≤ 0.5	≤ 0.5 to 8	-	-
<i>E. coli</i> (988)					
Cefepime	≤ 0.12	≤ 0.12	≤ 0.12 to >16	99.6	0.3
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 to >32	98.9	0.7
Ceftazidime	≤ 2	≤ 2	≤ 2 to >16	98.6	0.7
Piperacillin-tazobactam	2	4	≤ 0.12 to >64	97.1	1.3
Imipenem	≤ 0.5	≤ 0.5	≤ 0.5 to 4	100.0	0.0
Levofloxacin	≤ 0.5	≤ 0.5	≤ 0.5 to >4	97.4	2.0
Ciprofloxacin	≤ 0.25	≤ 0.25	≤ 0.25 to >4	97.3	2.7
Gentamicin	≤ 2	≤ 2	≤ 2 to >16	95.7	3.2
<i>P. aeruginosa</i> (661)					
Cefepime	2	8	≤ 0.12 to >16	90.8	2.3
Ceftriaxone	>32	>32	0.5 to >32	11.0	62.8
Ceftazidime	2	16	0.5 to >16	87.3	8.8
Piperacillin-tazobactam	4	64	≤ 0.5 to >64	93.3	6.7
Imipenem	1	2	≤ 0.5 to >8	94.4	1.4
Levofloxacin	0.5	2	≤ 0.5 to >4	91.4	3.9
Ciprofloxacin	≤ 0.25	1	≤ 0.25 to >4	92.9	4.2
Gentamicin	≤ 2	4	≤ 2 to >16	91.4	4.4

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Table 10 (continued)

Organism/antimicrobial agent (no. tested)	MIC ($\mu\text{g/mL}$)			% Category ^a	
	50%	90%	Range	Susceptible	Resistant
<i>Klebsiella</i> spp. (615)					
Cefepime	≤ 0.12	0.25	≤ 0.12 to > 16	99.0	0.5
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 to > 32	96.4	1.6
Ceftazidime	≤ 2	≤ 2	≤ 2 to > 16	95.1	4.1
Piperacillin-tazobactam	2	8	≤ 0.5 to > 256	94.6	2.6
Imipenem	≤ 0.5	≤ 0.5	≤ 0.5 to > 8	99.7	0.2
Levofloxacin	≤ 0.5	≤ 0.5	≤ 0.5 to > 4	99.0	0.2
Ciprofloxacin	≤ 0.25	≤ 0.25	≤ 0.25 to > 4	98.7	1.0
Gentamicin	≤ 2	≤ 2	≤ 2 to 16	94.1	3.9
<i>β-hemolytic streptococci</i> ^b (556)					
Cefepime	≤ 0.12	≤ 0.12	≤ 0.12 to 0.5	100.0	-
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 to 0.5	100.0	-
Penicillin	≤ 0.016	0.06	≤ 0.016 to 0.12	100.0	-
Erythromycin	≤ 0.06	2	≤ 0.06 to > 32	84.4	15.5
Clindamycin	≤ 0.25	≤ 0.25	≤ 0.25 to > 8	93.7	6.1
Levofloxacin	0.5	1	≤ 0.03 to > 4	99.8	0.2
Tetracycline	≤ 4	> 8	≤ 4 to > 8	9.3	42.8
<i>Enterobacter</i> spp. (459)					
Cefepime	≤ 0.12	2	≤ 0.12 to > 16	99.3	0.4
Ceftriaxone	≤ 0.25	> 32	≤ 0.25 to > 32	81.0	10.7
Ceftazidime	≤ 1	> 16	≤ 1 to > 16	78.4	18.1
Piperacillin-tazobactam	2	64	≤ 0.5 to 128	81.5	8.4
Imipenem	≤ 0.5	1	≤ 0.5 to 4	100.0	0.0
Levofloxacin	≤ 0.5	≤ 0.5	≤ 0.5 to > 4	99.3	0.4
Ciprofloxacin	≤ 0.25	≤ 0.25	≤ 0.25 to > 4	98.9	0.7
Gentamicin	≤ 2	≤ 2	≤ 2 to > 16	93.7	5.0
<i>CoNS, oxacillin-susceptible</i> (182)					
Cefepime	1	2	≤ 0.12 to 4	100.0	0.0
Ceftriaxone	2	4	≤ 0.25 to > 32	98.3	0.6
Ceftazidime	8	8	≤ 1 to > 16	94.0	1.1
Erythromycin	> 8	> 8	≤ 4 to > 8	47.3	51.1
Clindamycin	0.12	> 8	≤ 0.06 to > 8	86.8	12.6
Levofloxacin	0.12	0.25	0.06 to > 4	98.3	0.8
Tetracycline	≤ 4	> 8	≤ 4 to > 8	86.8	13.2
Trimethoprim-sulfamethoxazole	≤ 0.5	≤ 0.5	≤ 0.5 to > 2	94.5	5.5

^a Criteria as published by the CLSI (2006a, 2006b).

^b Penicillin results used to predict susceptibility to ceftazidime.

^c - = no breakpoints have been established by the CLSI (2006a, 2006b).

^d Susceptibility and resistance rates based on β -lactamase test results.

^e Includes β -hemolytic streptococci (2 strains), group A streptococci (300 strains), group B streptococci (228), group C streptococci (6 strains), group F streptococci (5 strains), and group G streptococci (15 strains).

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The susceptibility rates of *S. pneumoniae* to cefepime are shown in Table 10. The results showed that 93.9% of the *S. pneumoniae* pediatric isolates were susceptible to cefepime compared with 97.4% of those isolates reported above by Sader et al⁸. The MIC ranged also differed in the pediatric study (≤ 0.06 to > 8 $\mu\text{g/ml}$) compared to (≤ 0.12 to 8 $\mu\text{g/ml}$). The trend shows a slight increase in the frequency of resistant isolates. *H. influenzae* isolates showed absolute susceptibility (100.0%) to cefepime (MIC_{90} , ≤ 0.12 $\mu\text{g/ml}$), and ceftriaxone (MIC_{90} , 0.016 $\mu\text{g/ml}$). Cefepime also demonstrated excellent activity against *Klebsiella spp.* (MIC_{90} , ≤ 0.5 $\mu\text{g/ml}$; 99.0% susceptible); these results were similar to those published by Sader et al⁸. Overall, there were no significant changes observed for *S. aureus* and *E. coli* with respect to antimicrobial susceptibility between the pediatric study and the isolates collected from North American medical centers⁸. In the pediatric study, lower susceptibility rates were observed for *P. aeruginosa* 85.2% compared to 90.8% in the Sader et al study.

Streptococcus pneumoniae is the leading cause of community-acquired respiratory tract infection and the medical community has been faced with reduced penicillin susceptibility ($\text{MIC} \geq 0.12$ - 1 $\mu\text{g/ml}$, intermediate susceptibility; $\text{MIC} \geq 2$ $\mu\text{g/ml}$, resistant) which has increased worldwide. The SENTRY Antimicrobial Surveillance Program analyzed a collection of 21,605 *S. pneumoniae* isolates from a large international collection to determine the comparative activity of cefuroxime, cefpodoxime, ceftriaxone and cefepime (Table 11)⁹. Isolates were obtained from blood stream infection; community acquired respiratory tract infections, hospitalized patients with pneumoniae, wound or skin and soft tissue infections, urinary tract infections and from various body sites in patients located the intensive care unit. MIC values were determined using the reference broth microdilution test as described in the CLSI-approved standard and interpreted by CLSI guidelines for *S. pneumoniae*.

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Table 11: Activity of selected cephalosporins tested by reference methods against MDR *S. pneumoniae* phenotypes

MDR phenotype (no. tested) ^a	Antimicrobial agent	MIC (µg/mL)		Percentage by category ^b		
		Mode	90%	Susceptible	Intermediate	Resistant
PEN (6907)	Cefepime	1	2	88.1	10.7	1.2
	Ceftriaxone	1	2	89.1	8.2	2.7
	Cefpodoxime	2	4	35.0	12.5	52.5
	Cefuroxime	4	8	33.4	8.9	57.7
PEN, ER (3798)	Cefepime	1	2	85.0	13.7	1.3
	Ceftriaxone	1	2	86.9	10.0	3.0
	Cefpodoxime	2	4	22.7	12.3	65.0
	Cefuroxime	4	8	21.2	8.6	70.2
PEN, ER, CM (1863)	Cefepime	1	2	83.8	14.6	1.6
	Ceftriaxone	1	2	85.0	11.6	3.4
	Cefpodoxime	2	4	24.5	11.1	64.4
	Cefuroxime	4	8	23.0	7.6	69.4
PEN, ER, CM, TET (1633)	Cefepime	1	2	84.0	14.5	1.5
	Ceftriaxone	1	2	83.2	11.2	3.6
	Cefpodoxime	2	4	24.8	10.8	64.4
	Cefuroxime	4	8	23.6	7.1	69.3
PEN, ER, CM, TS (1410)	Cefepime	1	2	80.8	17.3	1.9
	Ceftriaxone	1	2	82.4	13.4	4.2
	Cefpodoxime	2	4	15.6	10.3	74.1
	Cefuroxime	4	8	13.9	7.0	79.1
PEN, ER, CM, TET, TS (1232)	Cefepime	1	2	80.8	17.3	1.9
	Ceftriaxone	1	2	82.7	12.9	4.4
	Cefpodoxime	2	4	16.1	10.3	73.6
	Cefuroxime	4,8	8	14.5	6.7	78.8
All strains (21 605)	Cefepime	≤0.12	1	96.2	3.5	0.3
	Ceftriaxone	≤0.25	1	96.5	2.6	0.9
	Cefpodoxime	≤0.03	2	77.6	4.4	18.0
	Cefuroxime	≤0.06	4	77.3	3.2	19.5

^a PEN, penicillin-resistant (MIC ≥ 0.12 µg/mL); ER, erythromycin-resistant (MIC ≥ 0.5 µg/mL); CM, clindamycin-resistant (MIC ≥ 0.5 µg/mL); TET, tetracycline-resistant (MIC ≥ 4 µg/mL); TS, trimethoprim/sulfamethoxazole-resistant (MIC ≥ 1/19 µg/mL) (NCCLS, 2004).

^b Interpretive criteria of the NCCLS (2004) for respiratory tract infection isolates of *S. pneumoniae*.

The data showed that while overall susceptibility rates were lower for cefpodoxime and cefuroxime, high susceptibility rates were observed for cefepime and ceftriaxone (96.2 and 96.5 %, respectively). Similar trends were also observed with isolates that were resistant to 4-5 drugs. This is consistent with other SENTRY findings reported above in that cefepime demonstrated good in vitro compared when tested against Gram-positive and Gram-negative bacteria.

Summary:

Based on the studies reviewed, the data indicated that cefepime continue to have broad coverage in both a pediatric and none pediatric environments. Cefepime was shown to have good activity against some multi drug resistance pneumococci isolates associated with respiratory tract infections. Cefepime continues to demonstrate good activity against methicillin susceptible *S. aureus* isolates and coagulase negative staphylococci. Cefepime also demonstrated good activity some Gram negative isolates. No significant shift in the MIC was observed for Gram negative and Gram positive isolates. However, like with other antimicrobial of its class, the potential for a shift in the susceptibility patterns remains with the increasing use of Cefepime.

Pharmacokinetics/Pharmacodynamics:

In another study, the activity of cefepime, ceftriaxone, and ceftazidime was assessed by CLSI broth microdilution methods against 41,644 oxacillin-susceptible *S. aureus* and 14,266 oxacillin-susceptible coagulase negative staphylococci isolates. Briefly, the authors used the data obtained from SENTRY program MIC database from 1998-2004 to assess the effectiveness of cefepime, ceftriaxone, and ceftazidime. They also used PK/PD

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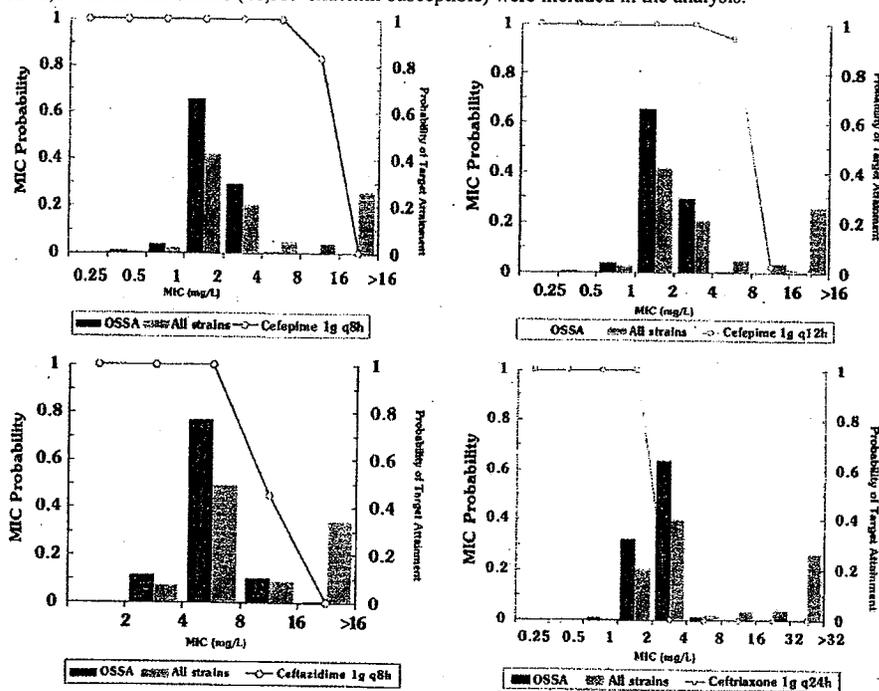
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relationships for staphylococci, normal volunteer PK data and Monte Carlo simulation to evaluate probabilities of target attainment for the three agents and different dosing regimens¹⁰.

Serum pharmacokinetic parameters for intravenous dosing of cefepime, ceftriaxone, and ceftazidime were obtained from the medical literature. The fraction of unbound drug for cefepime, ceftazidime and ceftriaxone was assumed to be 84%, 84%, and 7%, respectively. Using a linear intermittent intravenous infusion model and Monte Carlo simulation, PK-PD target attainment analyses were carried out. Dosing regimens modeled included cefepime (1 g i.v. Administered every 8 hours and every 12 hours), ceftazidime (1 g i.v. administered every 8 hours) and ceftriaxone (1 g i.v. administered every 24 hours). Ten thousand patient simulations were carried out in order to estimate the probability of attaining free drug % T > MIC targets of $\geq 40\%$ by fixed MIC values ranging from 0.12-32 mg/L for each drug regimen-organism combination.

The probabilities for attaining the PK-PD target of free-drug % T > MIC of $\geq 40\%$ stratified by dosing regimen, and overlaid by MIC distributions of either *S. aureus* or CoNS strains, are presented in Figures 1 and 2.

Figure 1 - Probability of PK-PD target attainment for three cephalosporins versus *S. aureus*. Panel A, cefepime at 1 g i.v. every 8 h; Panel B, cefepime at 1 g every 12 h; Panel C, ceftazidime at 1 g i.v. every 8 h; Panel D, ceftriaxone at 1 g i.v. every 24 hours. A total of 41,644 *S. aureus* strains (26,339 oxacillin-susceptible) were included in the analysis.

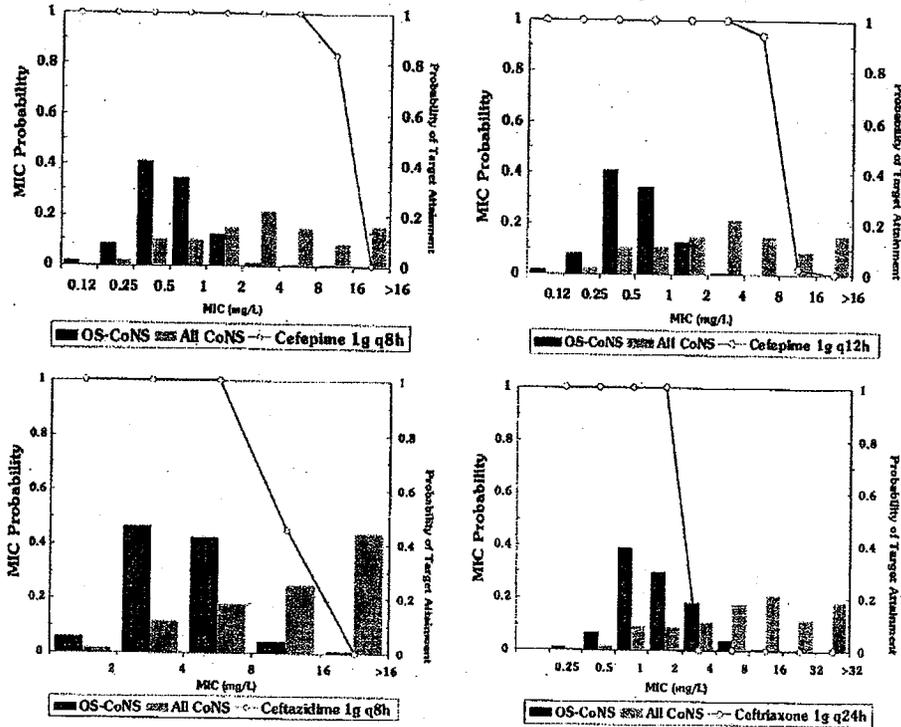


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Figure 2 - Probability of PK-PD target attainment for three cephalosporins versus coagulase-negative staphylococci (CoNS). Panel A, cefepime at 1 g i.v. every 8 h; Panel B, cefepime at 1 g i.v. every 12 h; Panel C, ceftazidime at 1 g i.v. every 8 h; Panel D, ceftriaxone at 1 g i.v. every 24 h. A total of 14,266 CoNS strains (3,166 oxacillin-susceptible) were included in the analysis.



The authors showed that when examined using Monte Carlo simulation, the probabilities of attaining a PK-PD target of free drug %T>MIC of $\geq 40\%$ were higher for cefepime and ceftazidime compared to ceftriaxone.

This is due to the inherently high protein binding characteristics of ceftriaxone (Figures 1 and 2).

In summary, the data presented in the simulation PK/PD study does not appear to support a change in staphylococcal breakpoint for cefepime at the time the study was published. Please note that this summation was not based on clinical data.

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REMARKS:

MICROBIOLOGY SUBSECTION OF THE LABEL:

The microbiology section of the label was revised to reflect the current CLSI guidelines. Additionally, the organism _____ was omitted from the second list since the genus *Enterobacter* is present in the first list. Disk diffusion testing of *S. pneumoniae* can be unreliable when conducted with a _____ therefore, disk diffusion susceptibility testing should be done with an oxacillin disk.

b(4)

SUMMARY AND RECOMMENDATIONS:

From the microbiology perspective, based on analysis of the information provided by the applicant, the Reviewer recommends approval of this NDA under Section 505(b)(2) of the FD&C Act. The Agency recommends that that Applicant update the microbiology section of the label to reflect the current CLSI guidelines.

PACKAGE INSERT:

The package insert that was submitted to the Applicant contained the updated version of the microbiology section of the label.

b(4)

5 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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DATE REVIEW COMPLETED: 11/26/07

Review Reference:

1. M. Babic et al. What's new I antibiotic resistance? Focus on beta-lactamases. *Drug Resistance Updates* **9** (2006) pp. 142-156.
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4. Gootz et al. Global dissemination of beta-lactamases mediating resistance to cephalosporins and carbapenems, *Expert Rev. Anti. Infect. Ther.* **2** (2004), pp. 317-327.
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7. Bijie H. et al., In vitro activity pharmacokinetics, clinical efficacy, safety and pharmacoeconomics of ceftriazone compared with third and fourth generation cephalosporins: review. *Journal of Chemotherapy* **17**(1) (2005) pp. 3-24.
8. Sader H.S. et al., Potency and spectrum trends for cefepime tested against 65746 clinical bacterial isolates collected in North American medical centers: Results from the SENTRY Antimicrobial Surveillance Program (1998-2003). *Diagnostic Microbiology and Infectious Disease* **52** (2005) 265-273.
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10. Sader H.S. Bhavnani S.M et al. Re-evaluation of the role of broad-spectrum cephalosporins against staphylococci by applying contemporary in-vitro results and pharmacokinetic-pharmacodynamic principles. *Journal of Chemotherapy* Vol **19**:1 (2007) 38-43.

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

NDA: 50-817

DATE REVIEW COMPLETED: 11/26/07

Avery Goodwin, Ph.D.
Microbiology Reviewer
HFD-520

Fred Marsik, Ph.D.
Microbiology Team Leader
HFD-520
21 Dec 07 FIN FJM

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

/s/

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12/21/2007 12:27:25 PM
MICROBIOLOGIST

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12/21/2007 12:38:03 PM
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**CLINICAL Microbiology: 45-Day Meeting Checklist
NDA 50-817 (formally NDA 22-133) Cefepime injection**

Sponsor: Baxter

Date Submitted: March 19, 2007

On **initial** overview of the NDA application for RTF:

No.	Item	Yes	No	Comments
1	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?		X	Not Applicable
2	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA indexed, paginated, and/or linked in a manner to allow substantive review to begin?		X	Not Applicable
3	Is the clinical microbiology information (preclinical/nonclinical and clinical) in different sections of the NDA legible so that substantive review can begin?		X	Not Applicable
4	On its face, has the applicant <u>submitted</u> <i>in vitro</i> data in necessary quantity, using necessary clinical and non-clinical strains/ isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?		X	Not Applicable
5	Has the applicant <u>submitted</u> draft provisional breakpoint and interpretive criteria, along with quality control (QC) parameters, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?		X	Not Applicable
6	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?		X	Not Applicable
7	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?		X	Not Applicable
8	Has the applicant <u>submitted</u> the clinical microbiology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcomes exhibited by relevant pathogens isolated from test of cure or end of treatment?		X	Not Applicable
9	Has the applicant <u>submitted</u> a clinical microbiology dataset in a format which intends to determine resistance development by correlating changes in the phenotype (such as <i>in vitro</i> susceptibility) and/or genotype (such as mutations) of the baseline relevant		X	Not Applicable

**CLINICAL Microbiology: 45-Day Meeting Checklist
NDA 50-817 (formally NDA 22-133) Cefepime injection**

Sponsor: Baxter

Date Submitted: March 19, 2007

	pathogen with clinical and microbiologic outcome as exhibited by relevant pathogens isolated from test of cure or end of treatment?			
10	Has the applicant used standardized or nonstandardized methods for measuring microbiologic outcome? If nonstandardized methods were used has the applicant included full details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?		X	Not Applicable
11	Is the clinical microbiology draft labeling consistent with 201.56 and 201.57 of the CFR, current Divisional policy.		X	Not Applicable
12	FROM A CLINICAL MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? IF NO, GIVE REASONS BELOW.	X		See comments below

Any Additional Clinical Microbiology Comments:

Baxter proposes to make a new drug product, cefepime injection in GALAXY container. The two proposed presentations are 1g of cefepime in a 50 ml container and 2g of cefepime in a 100 ml container. The proposed products will be premixed and ready to use in flexible plastic containers for IV use only. The products will be kept frozen and thawed prior to use; no reconstitution is necessary.

The Applicant is not proposing any changes to the microbiology section of the package insert.

Avery Goodwin, Ph.D.

Name

Reviewing Clinical Microbiologist

Name: Fred Marsik, Ph.D.

HFD-520

Team Leader Clinical Microbiology

16Apr07 FIN FJM

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

/s/

Avery Goodwin
4/16/2007 11:36:41 AM
MICROBIOLOGIST

Frederic Marsik
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