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NDA 58679

1 OF 13

UD A50-679

Ap Ltr

FPL

AE Ltr

MOR

Pharm-Tox

Bio

Stat

Clin-Micro

Chem

Fonsi+E.A.

Prevnos

AP Ltr

FPL

AE Ltr

—

NDA 50-679

JAN 18 1996

Bristol-Myers Squibb
Attention: Hugh McIlhenny, Ph.D.
Director
Worldwide Regulatory Affairs
Pharmaceutical Research Institute
P.O. Box 5100
Wallingford, Connecticut 06492-7660

520
Smo / Albrecht

Dear Dr. McIlhenny:

Reference is made to your new drug application (NDA) dated June 30, 1992, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for L-arginine formulation of Maxipime[®] (cefepime hydrochloride for injection).

We acknowledge receipt of your amendments dated September-28, and November 6 and December 11, 1995.

We have completed the review of this application as amended, and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the draft final printed labeling submitted on December 11, 1995. Accordingly, the application is approved effective on the date of this letter.

Marketing this product with labeling that is not identical to the enclosed labeling dated December 11, 1995, may render this product an unapproved new drug product.

Please submit fifteen copies of final printed labeling (FPL), identical to the enclosed labeling dated December 11, 1995. Seven copies of the final printed label should be individually mounted on heavy-weight paper or similar material. These submissions should be designated for administrative purposes as "FPL for approved NDA 50-679." Approval of these submissions by the FDA is not required before the labeling may be used.

Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

Please note that any advertising or promotional labeling for Maxipime[®] Injection will be considered false and misleading under Section 502 of the Act if it utilizes *in vitro* microbiologic data to imply clinical efficacy or to imply clinical superiority over other drug products if such indications or clinical superiority have not been established in adequate and well-controlled clinical trials. *In vitro* microbiologic data establish *in vitro* microbiologic activity. Appropriate use of such data in advertising and promotional labeling requires a balanced

presentation of I w such data should be interpreted in view of the human pharmacokinetic properties of and the established clinical efficacy of this drug product.

In addition, any advertising or promotional labeling for Maxipime^R Injection will be considered false and misleading under Section 502 of the Act if it attempts to minimize, by print size or presentation emphasis, the fact that clinical data from adequate and well-controlled trials are not available establishing efficacy of this drug product in treating diseases due to the organisms contained in the "not clinically supported" (i.e., the second) grouping of organisms in the *Microbiology* subsection of the drug products labeling.

This guidance constitutes notice of activities that may be considered to be violations of the Act. Failure to comply with this guidance may result in regulatory action without further notice.

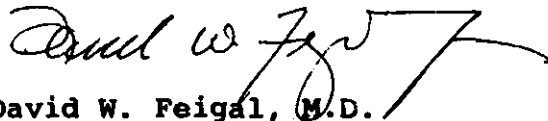
We request that you submit, in triplicate, the advertising and promotional materials you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy of the materials to the Division of Anti-Infective Drug Products and two copies of the materials to the Division of Drug Marketing, Advertising and Communications, HFD-240, Room 17B-05, 5600 Fishers Lane, Rockville, Maryland, 20857. Please submit all proposed promotional and advertising materials in draft or mock-up form, not in final print. Also, please do not use form FDA 2253 for this submission; that form is for routine use, not proposed materials.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions regarding this application, please contact Mr. Carmen DeBellas of the Project Management Staff at 301-827-2159.

Sincerely yours,



David W. Feigal, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

1-16-86

CC: Orig NDA
District Office
HF-2
HFD-104

HFD-85
HFD-240
HFD-500
HFD-683
HFD-735
HFD-100
HFD-230
HFD0520/SMO/Albrecht/RD/init/1/17/96
HFD-520/MO/Girardi *LS-1/18/96*
Hfd-520/micro/King/RD/init/17/96
HFD-520/C30/DeBellas *1/18/96*
HFD-520/Chem/Roy/RDinit/1/17/96
HFD-520/label file
APPROVAL

Concurrence:

HFD-520/DivDir/Fanning *NF 1/18/96*
HFD-520/DepDir/Gavrilovich *1/18/96*
HFD-520/SCSO/Bona *1/18/96*
HFD-520/SMicro/Sheldon
HFD-520/SPharm/Osterberg/RD/init//17/96

MAXIPIME®

(Cefepime Hydrochloride)
For Injection

 Bristol-Myers Squibb Company

CAUTION: Federal law prohibits dispensing without prescription

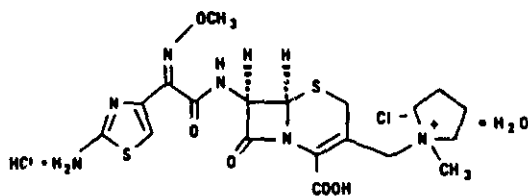
MAXIPIME®

(Cefepime Hydrochloride) for Injection

For Intravenous or Intramuscular Use

DESCRIPTION

Cefepime hydrochloride is a semi-synthetic, broad spectrum, cephalosporin antibiotic for parenteral administration. The chemical name is 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-ylmethyl)-1-methylpyrrolidinium chloride, 7'-[(2'-[O-methylsulfanyl]monohydroxyacetate) monohydrate, which corresponds to the following structural formula:



Cefepime hydrochloride is a white to pale yellow powder with a molecular formula of $C_{22}H_{25}ClN_5O_7S_2 \cdot HCl \cdot H_2O$ and a molecular weight of 571.5. It is highly soluble in water. MAXIPIME® (cefepime hydrochloride) for injection, is supplied for intramuscular or intravenous administration in strengths equivalent to 500 mg, 1 g and 2 g of cefepime. (See DOSAGE AND ADMINISTRATION.) MAXIPIME is a sterile, dry mixture of cefepime hydrochloride and L-arginine. The L-arginine, at an approximate concentration of 725 mg/g of cefepime, is added to control the pH of the constituted solution at 4.0-6.0. Freshly constituted solutions of MAXIPIME will range in color from colorless to amber.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The average plasma concentrations of cefepime observed in healthy adult male volunteers (n=7) at various times following single 30-minute infusions (IV) of cefepime 500 mg, 1 g, and 2 g are summarized in Table 1. Elimination of cefepime is principally via renal excretion with an average ($\pm$ SD) half-life of 2.0 ($\pm$ 0.3) hours and total body clearance of 120.0 ($\pm$ 8.0) mL/min in healthy volunteers. Cefepime pharmacokinetics are linear over the range 250 mg to 2 g. There is no evidence of accumulation in healthy adult male volunteers (n=7) receiving clinically relevant doses for a period of 8 days.

Absorption

The average plasma concentrations of cefepime and its derived pharmacokinetic parameters after intravenous administration are portrayed in Table 1.

TABLE 1

Parameter	Average Plasma Concentrations in μ g/mL of Cefepime and Derived Pharmacokinetic Parameters ($\pm$ SD), Intravenous Administration		
	MAXIPIME		
	500 mg IV	1 g IV	2 g IV
0.5 hr	38.2	78.7	163.1
1.0 hr	21.6	44.5	85.8
2.0 hr	11.6	24.3	44.8
4.0 hr	5.0	10.5	19.2
8.0 hr	1.4	2.4	3.9
12.0 hr	0.2	0.6	1.1
C_{max} , μ g/mL	38.1 (3.9)	81.7 (5.1)	163.9 (23.3)
AUC, hr $\cdot$ μ g/mL	70.8 (6.7)	148.5 (15.1)	284.5 (20.6)
Number of subjects (male)	9	9	9

Following intramuscular (IM) administration, cefepime is completely absorbed. The average plasma concentrations of cefepime at various times following a single IM injection are summarized in Table 2. The pharmacokinetics of cefepime are linear over the range of 500 mg to 2 g IM and do not vary with respect to treatment duration.

TABLE 2

Parameter	Average Plasma Concentrations in μ g/mL of Cefepime and Derived Pharmacokinetic Parameters ($\pm$ SD), Intramuscular Administration		
	MAXIPIME		
	500 mg IM	1 g IM	2 g IM
0.5 hr	8.2	14.8	36.1
1.0 hr	12.5	25.9	49.9
2.0 hr	12.0	26.3	51.3
4.0 hr	6.9	18.0	31.5
8.0 hr	1.9	4.5	8.7
12.0 hr	0.7	1.4	2.3
C_{max} , μ g/mL	13.9 (3.4)	29.6 (4.4)	57.5 (9.5)
T_{max} , hr	1.4 (0.9)	1.6 (0.4)	1.5 (0.4)
AUC, hr $\cdot$ μ g/mL	60.0 (8.0)	137.0 (11.0)	262.0 (23.0)
Number of subjects (male)	6	6	12

Distribution

The average steady state volume of distribution of cefepime is 18.0 ($\pm$ 2.0)L. The serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum.

Cefepime is excreted in human milk. A nursing infant consuming approximately 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per day. (See PRECAUTIONS, Nursing Mothers.)

Concentrations of cefepime achieved in specific tissues and body fluids are listed in Table 3.

TABLE 3

Tissue or Fluid	Dose/Route	# of Patients	Average Concentrations of Cefepime in Specific Body Fluids (μ g/mL) or Tissues (μ g/g)	
			Average Time of Sample Post-Dose (hr)	Average Concentration
Blister Fluid	2 g IV	6	1.5	81.4 μ g/mL
Bronchial Mucosa	2 g IV	20	4.8	24.1 μ g/g
Sputum	2 g IV	5	4.0	7.4 μ g/mL
Urine	500 mg IV	8	0-4	282 μ g/mL
	1 g IV	12	0-4	326 μ g/mL
	2 g IV	12	0-4	3120 μ g/mL

Data suggest that cefepime does cross the inflamed blood-brain barrier. The clinical relevance of these data are uncertain at this time.

Metabolism and Excretion

Cefepime is metabolized to N-methylpyrrolidone (NMP) which is rapidly converted to the N-oxide (NMP-N-oxide). Urinary recovery of unchanged cefepime accounts for approximately 85% of the administered dose. Less than 1% of the administered dose is recovered from urine as NMP, 6.8% as NMP-N-oxide, and 2.5% as an epimer of cefepime. Because renal excretion is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment. (See DOSAGE AND ADMINISTRATION.)

Special Populations

Geriatric patients: Cefepime pharmacokinetics have been investigated in elderly (65 years of age and older) men (n=12) and women (n=12) whose creatinine clearance was 74.0 ($\pm$ 15.0) mL/min. There appeared to be a decrease in cefepime total body clearance as a function of creatinine clearance. Therefore, dosage administration of cefepime in the elderly should be adjusted as appropriate if the patient's creatinine clearance is 60 mL/min or less. (See DOSAGE AND ADMINISTRATION.)

Renal insufficiency: Cefepime pharmacokinetics have been investigated in patients with various degrees of renal insufficiency (n=30). The average half-life in patients requiring

TABLE 6

Microorganism	ATCC	MIC ($\mu\text{g/mL}$)
<i>Escherichia coli</i>	25922	0.015-0.06
<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

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure⁷ requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 μg of cefepime to test the susceptibility of microorganisms to cefepime. Interpretation is identical to that stated above for results using dilution techniques.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30- μg cefepime disk should be interpreted according to the following criteria:

TABLE 6

Microorganism	Zone Diameter (mm)		
	Susceptible (S)	Intermediate (I)	Resistant (R)
Microorganisms other than <i>Haemophilus</i> spp. ^a and <i>S. pneumoniae</i> ^a	≥ 18	15-17	≤ 14
<i>Haemophilus</i> spp. ^a	≥ 26	...	...

^aNOTE: Isolates from these species should be tested for susceptibility using specialized diffusion testing methods.⁷ Isolates of *Haemophilus* spp. with zones smaller than 26 mm should be considered equivocal and should be further evaluated. Isolates of *S. pneumoniae* should be tested against a 1 μg oxacillin disk; isolates with oxacillin zone sizes larger than or equal to 20 mm may be considered susceptible to cefepime.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Laboratory control microorganisms are specific strains of microbiological assay organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains are not clinically significant in their current microbiological status. For the diffusion technique, the 30- μg cefepime disk should provide the following zone diameters in these laboratory test quality control strains (Table 7):

TABLE 7

Microorganism	ATCC	Zone Size Range (mm)
<i>Escherichia coli</i>	25922	29 - 35
<i>Staphylococcus aureus</i>	25923	23 - 29
<i>Pseudomonas aeruginosa</i>	27853	24 - 30
<i>Haemophilus influenzae</i>	49247	25 - 31

INDICATIONS AND USAGE

MAXIPIME is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis) caused by *Escherichia coli* or *Klebsiella pneumoniae*, when the infection is severe, or caused by *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*, when the infection is mild to moderate, including cases associated with concurrent bacteremia with these microorganisms.

Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*.

Pneumonia (moderate to severe) caused by *Streptococcus pneumoniae*, including cases associated with concurrent bacteremia, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or *Enterobacter* species.

Culture and susceptibility studies should be performed where appropriate to determine the susceptibility of the causative microorganism(s) to cefepime.

Therapy with MAXIPIME may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

CONTRAINDICATIONS

MAXIPIME is contraindicated in patients who have shown immediate hypersensitivity reactions to cefepime or the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.

WARNINGS

BEFORE THERAPY WITH MAXIPIME (CEFEPIME HYDROCHLORIDE) FOR INJECTION IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS IMMEDIATE HYPERSENSITIVITY REACTIONS TO CEFEPIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO MAXIPIME OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES INCLUDING OXYGEN, CORTICOSTEROIDS, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including MAXIPIME, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be

PRECAUTIONS

General
As with other antimicrobials, prolonged use of MAXIPIME may result in overgrowth of non-susceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken. Many cephalosporins, including cefepime, have been associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk, and exogenous vitamin K administered as indicated.

Positive direct Coombs' tests have been reported during treatment with MAXIPIME. In hematologic studies or in transfusion cross-matching procedure when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

MAXIPIME should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Arginine has been shown to alter glucose metabolism and elevate serum potassium transiently when administered at 50 times the amount provided by the maximum recommended human dose of MAXIPIME. The effect of lower doses is not presently known.

Drug Interactions

Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with MAXIPIME because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide.

Drug/Laboratory Test Interactions

The administration of cefepime may result in a false-positive reaction for glucose in the urine when using Clinixest[®] tablets. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinixest[®] or Tes-Tape[®]) be used.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No long-term animal carcinogenicity studies have been conducted with cefepime. A battery of *in vivo* and *in vitro* genetic toxicity tests, including the Ames Salmonella reverse mutation assay, CHO/HGPRT mammalian cell forward gene mutation assay, chromosomal aberration and sister chromatid exchange assays in human lymphocytes, CHO fibroblast cytogenetic assay, and cytogenetic and micronucleus assays in mice were conducted. The overall conclusion of these tests indicated no definitive evidence of genotoxic potential. No untoward effects on fertility or reproduction have been observed in rats, mice, and rabbits when cefepime is administered subcutaneously at 1 to 4 times the recommended maximum human dose calculated on a mg/m²/day basis.

Usage in Pregnancy - Teratogenic effects - Pregnancy Category B

Cefepime was not teratogenic or embryocidal when administered during the period of organogenesis to rats at doses up to 1000 mg/kg/day (4 times the recommended maximum human dose calculated on a mg/m²/day basis) or to mice at doses up to 1200 mg/kg/day (2 times the recommended maximum human dose calculated on a mg/m²/day basis) or to rabbits at a dose level of 100 mg/kg/day (approximately equal to the recommended maximum daily human dose calculated on a mg/m²/day basis).

There are, however, no adequate and well-controlled studies of cefepime use in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Cefepime is excreted in human breast milk in very low concentrations (1.5 µg/mL). Caution should be exercised when cefepime is administered to a nursing woman.

Labor and Delivery

Cefepime has not been studied for use during labor and delivery. Treatment should only be given if clearly indicated.

Pediatric Use

The safety and efficacy of MAXIPIME (cefepime hydrochloride) in pediatric patients below the age of 12 years have not been established. This product is intended for use in patients 12 years of age and older.

Geriatric Use

In clinical studies, when geriatric patients received the usual recommended adult dose, clinical efficacy and safety were comparable to clinical efficacy and safety in non-geriatric adult patients.

In elderly patients, dosage and administration of cefepime should be adjusted in the presence of renal insufficiency. (see DOSAGE and ADMINISTRATION.)

ADVERSE REACTIONS

Clinical Trials:

In clinical trials using multiple doses of cefepime, 4,137 patients were treated with the recommended dosages of cefepime (500 mg to 2 g IV q 12h). There were no deaths or permanent disabilities thought related to drug toxicity. Sixty-four (1.5%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. Thirty-three (51%) of these 64 patients who discontinued therapy did so because of rash. The percentage of cefepime-treated patients who discontinued study drug because of drug-related adverse events was very similar at daily doses of 500 mg, 1 g and 2 g q 12h (0.8%, 1.1%, and 2.0%, respectively). However, the incidence of discontinuation due to rash increased with the higher recommended doses.

The following adverse events were thought to be probably related to cefepime during evaluation of the drug in clinical trials conducted in North America (n=3,125 cefepime-treated patients).

TABLE 8

ADVERSE CLINICAL REACTIONS CEPIME MULTIPLE-DOSE DOSING REGIMEN ¹ CLINICAL TRIALS - NORTH AMERICA	
INCIDENCE EQUAL TO OR GREATER THAN 1%	Local reactions (1.0%), including phlebitis (1.3%), pain and/or inflammation (0.6%); rash (1.1%)
INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%	Colitis (including pseudomembranous colitis), diarrhea, fever, headache, nausea, oral mucositis, pruritus, urticaria, vaginitis, vomiting

¹Local reactions, irrespective of relationship to cefepime in those patients who received intravenous infusion (n = 3,048).

TABLE 9

ADVERSE LABORATORY CHANGES CEPIME MULTIPLE-DOSE DOSING REGIMEN ¹ CLINICAL TRIALS - NORTH AMERICA	
INCIDENCE EQUAL TO OR GREATER THAN 1%	Positive Coombs' test (without hemolysis) (1.5 2%); decreased phosphorus (2.8%); increased ALT/SGPT (2.8%); AST/SGOT (2.4%); esophophils (1.7%); abnormal PT (1.8%); PT (1.4%)
INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%	Increased alkaline phosphatase, BUN, calcium, creatinine, phosphorus, potassium, total protein; decreased calcium ² , hematocrit, neutrophils, platelets, WBC

¹Hypocalcemia was more common among elderly patients. Clinical consequences from changes in either calcium or phosphorus were not reported.

In Postmarketing Experience:

In addition to the events reported during North American clinical trials with cefepime, the following adverse experiences have been reported from foreign sources during worldwide postmarketing experience:

Encephalopathy has been reported in renally impaired patients treated with unadjusted dosing regimens of cefepime. Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. (see DOSAGE AND ADMINISTRATION and OVERDOSAGE.) If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Cephalosporin - class adverse reactions:

In addition to the adverse reactions listed above that have been observed in patients treated with cefepime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage and hepatic dysfunction including cholestasis, pancytopenia

OVERDOSAGE

In clinical trials, MAXIPIME (cefepime hydrochloride) overdose occurred in a patient with renal failure (creatinine clearance <11 mL/min) who received 2 g q 24h for seven days. The patient exhibited seizures, encephalopathy, and neuromuscular excitability. Patients who receive an overdose should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis, not peritoneal dialysis, is recommended to aid in the removal of cefepime from the body.

DOSE AND ADMINISTRATION

The recommended adult dosages and routes of administration are outlined in the following table. MAXIPIME should be administered intravenously over approximately 30 minutes.

TABLE 10
Recommended Dosage Schedule for MAXIPIME

Site and Type of Infection	Dose	Frequency	Duration (days)
Mild to Moderate Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis, due to <i>E. coli</i> , <i>K. pneumoniae</i> , or <i>P. mirabilis</i> .	0.5-1g IV/IM*	q12h	7-10
Severe Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis, due to <i>E. coli</i> or <i>K. pneumoniae</i> .	2 g IV	q12h	10
Moderate to Severe Pneumonias due to <i>S. pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Mycobacterium pneumoniae</i> , or <i>Enterobacter</i> species.	1-2 g IV	q12h	10
Moderate to Severe Uncomplicated Skin and Skin Structure Infections due to <i>S. aureus</i> or <i>S. pyogenes</i>	2 g IV	q12h	10

*including cases associated with concurrent bacteremia.

**IM route of administration is indicated only for mild to moderate, uncomplicated or complicated UTIs due to *E. coli* when the IM route is considered to be a more appropriate route of drug administration.

Impaired Hepatic Function - No adjustment is necessary for patients with impaired hepatic function.

Impaired Renal Function - In patients with impaired renal function (creatinine clearance <60 mL/min), the dose of MAXIPIME should be adjusted to compensate for the slower rate of renal elimination. The recommended initial dose of MAXIPIME should be the same as in patients with normal renal function. The recommended maintenance doses of MAXIPIME in patients with renal insufficiency are presented in Table 11.

TABLE 11
Recommended Maintenance Schedule in Patients with Renal Impairment
Relative to Normal Recommended Dosing Schedule

Creatinine Clearance (mL/min)	Recommended Maintenance Schedule		
	500 mg q12h	1 g q12h	2 g q12h
>60	500 mg q24h	1 g q24h	2 g q24h
30-60	500 mg q24h	500 mg q24h	1 g q24h
11-30	250 mg q24h	250 mg q24h	500 mg q24h
≤10	250 mg q24h	250 mg q24h	500 mg q24h

NS = 0.9% Sodium Chloride Injection
DSW = 5% Dextrose Injection
na = not applicable
RTA = Ambient room temperature and light

Solutions of MAXIPIME, like those of most beta-lactam antibiotics, should not be added to solutions of ampicillin at a concentration greater than 40 mg/mL, and should not be added to metronidazole, vancomycin, gentamicin, tobramycin, netilmicin sulfate or aminophylline because of potential interaction. However, if concurrent therapy with MAXIPIME is indicated, each of these antibiotics can be administered separately.

Intramuscular: MAXIPIME (cefepime hydrochloride) constituted as directed is stable for 24 hours at controlled room temperature 20°-25°C (68°-77°F) or for 7 days in a refrigerator 2°-8°C (36°-46°F) with the following diluents: Sterile Water for Injection, 0.9% Sodium Chloride Injection, 5% Dextrose Injection, Bacteriostatic Water for Injection with Parabens or Benzyl Alcohol, or 0.5% or 1% Lidocaine Hydrochloride.

NOTE: PARENTERAL DRUGS SHOULD BE INSPECTED VISUALLY FOR PARTICULATE MATTER BEFORE ADMINISTRATION.

As with other cephalosporins, the color of MAXIPIME powder, as well as its solutions, tend to darken depending on storage conditions; however, when stored as recommended, the product potency is not adversely affected.

HOW SUPPLIED

MAXIPIME® (cefepime hydrochloride) for injection is supplied as follows:

NDC 0003-7731-99	500 mg*	15 mL vial (tray of 10)
NDC 0003-7732-95	1 g*	Piggyback bottle 100 mL (tray of 10)
NDC 0003-7732-89	1 g*	ADD-Vantage® vial (tray of 10)
NDC 0003-7732-89	1 g*	15 mL vial (tray of 10)
NDC 0003-7733-95	2 g*	Piggyback bottle 100 mL (tray of 10)
NDC 0003-7733-99	2 g*	20 mL vial (tray of 10)

*Based on cefepime activity

Storage

MAXIPIME IN THE DRY STATE SHOULD BE STORED BETWEEN 2°-25°C (36°-77°F) AND PROTECTED FROM LIGHT.

U.S. Patent No. 4,408,889; 4,910,361; 4,994,481; and 5,244,881

REFERENCES

- (1) National Committee for Clinical Laboratory Standards.
Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically — Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.
- (2) National Committee for Clinical Laboratory Standards.
Performance Standards for Antimicrobial Disk Susceptibility Tests - 7th Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.
- (3) Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16:31-41.

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Bristol-Myers Squibb Company
Princeton, NJ 08543, USA

Issued: January, 1996

7733DM-02
51-004476-00

NDA 50-679

Food and Drug Administration
Rockville MD 20857

Hugh McIlhenny, Ph.D.
Director
Worldwide Regulatory Affairs
Bristol-Myers Squibb
P.O. Box 5100
Wallingford, Connecticut 06492-7660

JUL 26 1994

Dear Dr. McIlhenny:

Please refer to your new drug application submitted June 30, 1992, pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for the L-arginine formulation of Maxipime[®] (cefepime hydrochloride for injection).

We also acknowledge receipt of your additional communications dated as follows: July 8 and 28, August 20, September 11, 14, 17, 23, 25, and 30, October 6, 16, and 22, November 10, 13, and 19 and December 21, 22 and 31, 1992; January 6, February 12, 17, and 23, March 26, April 22, 23, 26, 28, and 30, May 21 and 26, June 2, 4, 8, 25, 28, and 30, July 9 and 13, August 2, 4, 9, 10, 11, 20, and 30, September 10, 14, 17 and 28, October 13, November 24 and December 15, 22, and 23, 1993; January 13, February 15, 18, and 24, March 21, April 18, and May 9, June 17 and 23, 1994.

We have completed our review of this new drug application, as amended, and it is approvable. However, before this application may be approved, the following nineteen pieces of information must be submitted, reviewed, and found acceptable by the FDA:

- (1) Draft final labeling that is identical to the enclosed proposed tentative labeling, dated July 26, 1994, prepared by the Division of Anti-Infective Drug Products as qualified in the next paragraph.

Please note we request you use the USAN name (USAN 1994, p. 127) as presented in the enclosed Divisional labeling. Please note further that there are several areas in the tentative labeling that have been highlighted. These areas should be completed by Bristol-Myers Squibb with reference in the NDA to where the data that substantiate your completions can be located.

- (2) An examination of whether any relationship exists between the use of cefepime and the incidence of pulmonary and other embolic events, hemorrhagic, and coagulation effects.

It was noted that many patient deaths were reported to be a result of pulmonary emboli, raising the question whether this represents a moribund patient population or whether it represents a drug effect. Your analysis of this observation, especially with reference to the incidence of such occurrences in the control population, would be quite helpful to our final review of this product.

- (3) An explanation for the observed phosphorus and calcium abnormalities in the cefepime-treated patient cohort.

Your explanation in the NDA concerned only the presence of phosphorous abnormalities in cefepime-treated patients. We did not note the same findings in the control arms of the clinical studies. Your analysis of this observation, especially with reference to the incidence of such occurrences in the control population, would be quite helpful to our final review of this product.

- (4) An explanation for the observed decrease in calcium concentrations in the cefepime-treated patient cohort above the age of 65 years.

Your analysis of this observation, especially with reference to the incidence of such occurrences in the control population, would be quite helpful to our final review of this product.

- (5) An evaluation of the incidence of false positive glucose testing with cefepime and recommended appropriate labeling statements.

- (6) An explanation for the lack of blinding, even single-blinding or assessor blinding, in the design of your pivotal clinical trials.

- (7) A description of the conduct of the clinical trials with regard to the time at which the investigator became aware of the product to which his/her patient had been randomized.
- (8) An explanation for the non-sequential numbering of the clinical trial centers in your clinical trials.
- (9) An explanation for what appears to be retrospective altering of the evaluability criteria prior to final analysis of the clinical data.

Specifically, why was this performed and what was the timing of such changes with respect to previous analyses of the clinical trials data base? Why should we not consider this data-dredging to reach a desired outcome?

- (10) An explanation, if any, other than clinical trial outcomes for believing that a cephalosporin with a 2-hour half-life can be dosed q 12 hours with satisfactory clinical and microbiologic outcomes.
- (11) An explanation for the rejection of the cefepime marketing application by the national regulatory authorities in Canada, Norway, and Denmark.

In addition, are you aware of any other rejections of a marketing application for cefepime by a national regulatory authority or have you withdrawn a submitted marketing application for cefepime from any regulatory authority?

- (12) An explanation for the approval of cefepime only for the treatment of severe pneumonia by the national regulatory authority of Sweden.

Specifically, were approval of other indications sought from the Swedish regulatory authority? If so, please provide an explanation for their rejection.

- (13) Approved package labeling from New Zealand.

We understand that this product has been approved for marketing in France, Sweden, Belgium, New Zealand, Finland, and Italy. Approved labeling from France, Belgium, Italy, Finland, and Sweden have been submitted previously.

- (14) An explanation for the apparent discrepancy in the patients-treated denominator used in the safety assessment of the patients treated in the protocols.

Specifically, our calculations are that there were 1781 total patients treated with cefepime and ceftazidime in the pneumonia protocols (pneumonia = 1114 cefepime and 380 ceftazidime; cefepime and 65 ceftazidime). In addition, there were 27 total patients treated with cefotaxime for a total of 1808 patients treated in these protocols for these indications. The adverse drug event denominators given by you are 1596 and 516, respectively, for lower respiratory tract infections.

- (15) The case record forms for the deaths and discontinued patients reported in the final safety updates (amendments #83, #95, and #96 to the NDA).
- (16) An assessment of the comparability of the susceptibility of specific pathogens for which you desire an indication that were isolated from European patients and those isolated from North American patients in order to allow extrapolation of the microbiologic and clinical efficacy demonstrated in European patients to American patients.
- (17) Full-sized mock-ups of your proposed package labels for this product.
- (18) The total number of patients in the cefepime arms versus the control arms of the skin infection protocols who used antimicrobial soaps at any time during the study.
- (19) The required NDA debarment certification.

NDA 50-679

Page 5

As part of our commitment to provide you with a complete assessment of your NDA, at this time, we have concluded that you have not provided substantial evidence that cefepime is effective in the treatment of patients with:

Pages 6-8

Deleted

Please submit, in triplicate, the advertising copy that you intend to use in your proposed introductory promotional and/or advertising campaign. Submit one copy to the Division of Anti-Infective Drug Products and two copies to the Division of Drug Marketing, Advertising and Communications, HFD-240, 5600 Fishers Lane, Rockville, Maryland 20857. Submit all proposed materials in draft or mock-up form, not in final print. Do not use form FDA-2253 for this submission; that form is for routine use, not proposed materials.

Please note that any advertisement or promotional labeling for Maxipime will be considered false and misleading under section 502 of the Act if it utilizes *in vitro* microbiologic data to imply clinical efficacy or to imply clinical superiority over other products if such indications or clinical superiority have not been established in adequate and well-controlled clinical trials. *In vitro* microbiologic data establish *in vitro* microbiologic activity only. Appropriate use of such data in advertising and promotional labeling requires a balanced presentation of how such data should be interpreted in view of the established clinical efficacy of these products.

In addition, any advertisement or promotional labeling for Maxipime will be considered false and misleading under section 502 of the Act if it attempts to minimize, by print size or presentation emphasis, the fact that clinical data from adequate and well-controlled trials are not available establishing the efficacy of these products in treating disease due to the organisms contained in the "not clinically supported" (i.e., the second) grouping of organisms in the *Microbiology* section of the product's labeling.

In addition, any advertisement or promotional labeling for Maxipime will be considered false and misleading under the Act if it does not include the entire description of individual indications as written in the **INDICATIONS AND USAGE** section of the labeling including sites, severities, and organism(s) when referring to the indications for which this product is approved. All components of the entire description of the indication must be presented in advertising or promotional pieces in the same print size and with the same impact.

In addition, any advertisement or promotional labeling for Maxipime will be considered false and misleading under the Act if it does not include the entire **DOSING** section of the labeling when referring to the dosing regimens for which this product is approved. All statements in the **DOSING** section are considered integral parts of the approved dosing regimens and may not be deleted or edited. Also, in advertising or promotional labeling, part of the approved dosing such as specific organisms or disease entities or disease severity may not be spatially separated from

other wording in the DOSING section so as to minimize their impact. Such information must be presented in advertising or promotional pieces in at least the same print size and with at least the same impact as any other information from this section of the labeling.

Finally, any advertisement or promotional labeling for Maxipime will be considered false and misleading under the Act if it states or implies that this product may be used in the treatment of sepsis, septicemia, bacteremia (as a stand alone indication), sepsis syndrome, or any other "sepsis/bacteremia" connotation other than "concurrent bacteremia in association with" the various primary indications specified in the final approved labeling.

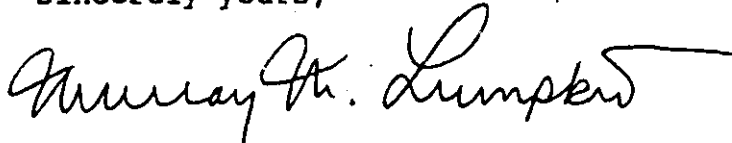
This guidance constitutes notice of activities that may be considered to be violations of the Act. Failure to comply with this guidance may result in regulatory action without further notice.

Within 10 days of the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other alternatives under 21 CFR 314.110. In the absence of such action, the Food and Drug Administration (FDA) may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions regarding this application, please contact Mr. Carmen DeBellas of the Project Management Staff at 301-443-6797.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Murray M. Lumpkin". The signature is written in a cursive style with a long horizontal stroke at the end.

Murray M. Lumpkin, M.D.
Deputy Director for Review Management
Center for Drug Evaluation and Research

EXCLUSIVITY SUMMARY FOR NDA # 50-679 SUPPL # _____

Trade Name Maxipime Generic Name cefepime

Applicant Name Bristol-Myers Squibb HFD # 520

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES / / NO / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Revised 5-90

cc: Orig NDA

Div File

HFD-85

This NDA is regulated under 507 of the Act and therefore is ~~ineligible~~ for ^{waiver} exclusivity. *CMJ 6/2/93*

d) Did the applicant request exclusivity? *see above*

YES / ___ / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES / ___ / NO / ___ /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / ___ / NO / ___ /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/ .

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		:	
IND # _____	YES /___/	:	NO /___/ Explain: _____
		:	_____
Investigation #2		:	
IND # _____	YES /___/	:	NO /___/ Explain: _____
		:	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1		:	
YES /___/ Explain _____		:	NO /___/ Explain _____
_____		:	_____
_____		:	_____
Investigation #2		:	
YES /___/ Explain _____		:	NO /___/ Explain _____
_____		:	_____
_____		:	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Carmen DeBelleo, PhD
Signature
Title: Project Manager

June 1994
Date

[Signature]
Signature of
Division Director

Date

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 50-679 Trade (generic) names Maxipime (cefepime) Injection

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.
 - a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
 - b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
 - a. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing.
 - (2) Protocols have been submitted and approved.
 - (3) Protocols have been submitted and are under review.
 - (4) If no protocol has been submitted, on the next page explain the status of discussions.
 - b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

___ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer
Project Manager

June 1994
Date

cc: Orig NUA
MFO-___/Div File
NUA Action Package

SMO RESPONSE TO DR. LUMPKIN'S MEMORANDUM

July 26, 1994

NOTE: The NDA for cefepime was reviewed by two Medical Officers. Dr. Sherman reviewed the indications of pneumonia and overall safety and wrote the introduction. She has written a document responding to Dr. Lumpkin's questions.

The indications of uncomplicated and complicated urinary tract infections, including pyelonephritis, skin and skin structure infections and were reviewed by Dr. Erhardt. Dr. Erhardt has completed his fellowship program and departed from the Agency in early June, 1994. Therefore, the questions pertinent to his indication will be addressed in this SMO Memorandum.

SKIN AND SKIN STRUCTURE INFECTIONS:

- 1) This information is not provided in the MOR. The question should be posed to the company in the action letter.
- 2) According to Tony ElHage, Dr. Gelfand is on the "assurances given" list and can perform clinical studies at this time.
- 3) The Medical Officer's comment should read: The majority of patients in both treatment groups were enrolled at 6 of the 33 centers participating (013, 027, 028, 029, 054 and 055). Center 013 was inadvertently omitted.
- 4) Yes, we have now told about Mr. DeBellas has gathered the necessary background information and submitted it to Tony ElHage. Dr. Albrecht spoke with Mr. ElHage about this site and his comment was that would inspect but not as a highest priority because the company has already censored this investigator's data and the data were not being used to support approval.
- 5) Typo noted: the numbers should be moved from under the heading "Clinically Evaluable" to under the heading "Fully evaluable".
- 6) The second sentence in the second paragraph should read
"There was a similar disparity in the microbiological eradication rates, the applicant reporting a 73/95 (77%) eradication rate and the medical officer reporting a 13/24 (54%) eradication rate."

- 7) Noted: the phrase "may be less efficacious" will not be reflected in the labeling.
- 8) Phrase on page 100 crossed out and initialed.
- 9) No explanation is provided why the number of patients considered MO clinically evaluable and evaluable in the controlled clinical trials is similar, while the number of MO clinically evaluable and evaluable in the uncontrolled clinical trials is different. (MOR pp 87, 89)

Bacteriology

Eradication rates for approvable pathogens

	<u>cefepime</u>	<u>control</u>
<i>S. aureus</i>	80/88 (91%)	53/58 (91%)
<u><i>S. pyogenes</i></u>	<u>37/39 (95%)</u>	<u>32/33 (97%)</u>
Total	117/127 (92%)	85/91% (93%)
	95% C.I. = (-0.09, +0.07)	

In addition, typographical errors on the following pages have been corrected and initialed:

pages 9, 14, 17, 44, 51, 61, 64, 71, 79, 87c, 88, 100, 103, 104, 126.

URINARY TRACT INFECTIONS

- 1) Urinary tract infections is a "bacteriologically-driven" indication, and as such, an examination of the data based on the culture results and pathogens isolated was undertaken, as well as one evaluation of the clinical outcome in the evaluable patients. Of note, the patients considered evaluable for this indication had to have met both clinical and microbiological evaluable criteria. In most cases, there was only one evaluable pathogen per evaluable patient. A few patients had two evaluable pathogens. This approach has been used in other recently approved NDAs, such as Vantin.
- 2) If cystitis occurred in the presence of a neurogenic bladder, obstruction, or other complicating factor, etc., it was considered a complicated UTI.
- 3) Typically, protocols for the treatment of urinary tract (and other) infections call for an on therapy culture. Being a protocol-defined visit, it is used in evaluating patient progress and response on therapy. Some reviewers have used it strictly and considered a patient with a positive on-therapy culture to represent a drug failure, some have expanded the window to any day on therapy, and some may have omitted this information in patient analysis.

- 4) Agreed: After a 10-day course of therapy and 5-9 day off treatment follow-up, a patient's clinical outcome should be classified as cure or failure. This topic has been discussed with medical officers by this SMO.
- 5) Agreed: A statistical review of this NDA has also been written.
- 6) The definitions for laboratory abnormalities were defined by the MO for this indication, while the company's definitions are presented in the table on p 117. Note that an integrated safety review was compiled by Dr. Sherman, examining and presenting laboratory data based on the company's definitions and outcome and based on an analysis done by FDA statisticians and incorporated in the safety review.
- 7) Although not stated in the review, it is believed that 7 doses was the minimum number necessary for designation of either cure or failure.
- 8) See #3, above
- 9) The last sentence in the COMMENT on p. 11 should read,

"The numbers of patients who had 4 to 6 week post-therapy evaluations was approximately 50% for all protocols submitted in support of this NDA."
- 9a) Please see Comment at the top of the page. The pathogen of concern is *Pseudomonas aeruginosa*, an organism which does not show good *in vitro* susceptibility to cefepime and one which is removed from both the Microbiology subsection and the INDICATIONS AND USAGE section.
- 10) Agreed: The recommendations for the approvability of the urinary tract indications (UTI) was based on the examination of all the data, including uncomplicated UTI, complicated UTI and pyelonephritis.
- 11) As addressed also in the response by Dr. Sherman, sometimes physicians would prescribe an oral antibiotic for a patient coming off parenteral antibiotic, even though the organism was no longer present and the patient was making a clinical recovery. This is a pattern we have noted in other NDA's; as the duration of parenteral therapy and hospitalization was restricted by _____ yet physicians felt the need to administer a certain duration of therapy, oral antibiotics were used. These types of patients were excluded from analysis.

This kind of patient is distinguished from ones that (a) get oral antibiotics for cause, or (b) are in NDA's for oral antimicrobials where one oral course is followed by another

course of oral antibiotics. These patients would be called failures.

- 12) The same dosing was testing in uncomplicated and complicated UTI's.
- 13) Exclusion for "treatment failures" occurred under the heading "incomplete treatment" (see #7 above). E.g., if a patient received 2 doses of drug and a physician made a decision to switch therapy because of the patient's clinical condition, such a patient was considered not evaluable.
- 14) The patient is not considered a failure for the reason described in #11) above.
- 14a) Study 411-111, conducted in Europe, enrolled 91 patients, of whom only 38 were considered evaluable. It is possible many of the misrandomized patients were actually excluded from evaluation of efficacy. This study did not figure prominently in the regulatory decision regarding the UTI indications.
- 14b) Chart headings corrected.
- 14c) Missing chart cannot be located in the Wordperfect file; last paragraph crossed out on page 229.
- 14d) Missing page is present in original yellow copy (xeroxing omission)
- 14e) It is believed that infusion site refers to IV infusions sites.
- 15) The inconsistency is noted, and represents an editing error from previous version.
- 16) Final recommendations concur with Divisional recommendations.

In addition, typographical errors on the following pages have been corrected and initialed:

pages 26, 48, 69, 181, 226, 227, 229, 250.

- 3) The missing text is now included as paragraph one on page 41.
- 4) The action letter does include a statement that patient validation was not undertaken by the FDA reviewer because even the company's analysis did not support approval of this indication.



Renata Albrecht, M.D.

orig NDA
HFD-520
HFD-520/CSO/DeBellas
HFD-520/MO/TBA
HFD-520/SMO/Albrecht

concurrence only
HFD-520/ActDir/Gavrilovich
HFD-2/DepDir/Lumpkin

RESPONSE TO DR LUMPKIN'S MEMORANDUM
Received by L. Sherman 7/18/94

GENERAL:

1. It is unknown to me why the applicant made so little effort to conduct blinded studies. Dr. Albrecht was the medical officer during most of the development program. In speaking with her on 7/19/94, Dr. Albrecht suggested a possible explanation was the disparity in dosing. Cefepime was dosed twice daily in comparison with ceftazidime's thrice daily dosing.
2. The best answer to the question of randomization is how it was described by the applicant in the protocol of one of their large comparative studies [A1411-070].

"Patients will be randomly assigned to one of the two treatment groups. The randomization scheme for this study calls for the allocation of patients to the two treatment groups at a 2:1 ratio. Thus for every two (2) patients who will be assigned to receive cefepime, there will be one (1) patient who will be assigned to receive ceftazidime.

The randomization schedule, a listing of patient numbers and the treatment assigned to that patient number, will be generated by a SAS program. Patient numbers will be blocked appropriately to insure that patients are allocated to the two treatment groups at a 2:1 ratio continually throughout the duration of the study. Patients will be assigned patient numbers sequentially." (p. 16 of the original protocol)

Also according to Dr. McIlhenney: "Patients are screened for clinical trials and if they qualify and sign informed consent they are given a randomization number and enrolled. These are simultaneous events. Patients then proceed to receive therapy by protocol."

3. In answer to the question about non-consecutively numbered centers, Dr. McIlhenney of BMSq stated that centers were often "lined up" and given a consecutive number. If no patients were enrolled or if a decision was made not to conduct the study at a particular center, a record of that center is maintained in the applicant database for bookkeeping purposes. However, that number will not appear in the for a particular study.
4. On some occasions amendments were submitted which allowed a change in evaluability criteria. For example, the minimum number of doses were changed from 8 to 7 in an amendment. However, there were many instances in which the text implied that the changes were made at the time of the final analysis. For example, the following is taken from the final study report of study A1411-070.

"The original Protocol required at least one post-treatment (Day + 1 or after) chest X-ray for any patient with a diagnosis of pneumonia. However, retroactively, it was decided that this post-treatment X-ray could be omitted if an X-ray was taken during therapy (Day 3 to last day of treatment)." (p. 44 of the study report)

5. With regards to a paragraph on the semantic issues, how is the following?

TO THE READER:

Semantics in the world of regulation is important. In the review, there was an effort to employ certain words consistently. The term "support" is used in relationship to data from "two adequate and well controlled trials" to substantiate a claim of efficacy/safety. In contrast, the

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word "corroborate" is a lay term that usually implies that one fact verifies another. Similarly, the word "equivalent" is applied in statistical discussions and the word "similar" has different connotations. With regard to the severity of illness, descriptive words such as "severe," "serious," and "life-threatening" are not interchangeable. Definitions decrease ambiguity. The applicant chose to employ these terms at different times; if a definition was available, it was included in the review.

6. With regard to the IM formulation and the indications that I reviewed, there were very few patients ($N < 10$) treated with the IM formulation. Dr. Erhardt had more experience in the indications that he reviewed, in particular, the UTI studies. I believe he was also comforted by the fact that the drug was renally excreted.

With regard to the bioequivalence/bioavailability, I defer my opinion to the expert, Dr. Ette. Please also inquire of Dr. Ette re: my most recent memorandum that noted a study (submitted after the NDA was filed in an amendment) that remarked that the half-life of cefepime is extended one hour in the elderly. I gave Dr. Ette a copy of the study for his review and asked him to determine if a statement was required in the label.

7. In general, I do not believe that cephalosporins with a half-life of 2 hours should be dosed at q12 intervals. However, there may be two possible explanations of why it might work: either 1) in less serious illnesses, i.e. otitis media, the drug suppresses a bacterial load until the body's defense mechanisms finish the job or 2) the half-life of the drug in tissues is longer than two hours.

CLINICAL INTRODUCTION:

1. According to Hugh McIlhenney, cefepime hydrochloride is the USAN designation for the product. Further he states:

"During the early development of the new drug substance, cefepime HCL, several salt forms were assessed. To differentiate between the salts, elemental analysis revealed that cefepime HCL was a dihydrochloride, monohydrate salt. Thus scientists used this phrase or the slightly, shorter designation cefepime dihydrochloride.

Upon further structure elucidation, cefepime HCL was determined to have one chloride bonded to the inner molecule, and hydrochloride salt with one mole of water.

Many scientific reports were written before the approval of the USAN name, cefepime HCL. Therefore, as stated in the beginning section three of the NDA (p. 03-0001), the several designations stated above were used."

2. The date of the teleconference is October 21, 1994. This has been adjusted.
3. As I understand the issue from Mr. DeBellas, the Committee is more of an Advisory Panel. It gives its recommendation and cites serious concerns. If there was a potentially life-threatening conflict, the committee can intervene. Otherwise, their objections are voiced as outlined in the review; they are communicated to the applicant. In the case of cefepime, the applicant sent a rebuttal of the opinion, Amendment 18 (11/6/92), to address the concerns of the Committee.

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According to Dr. McIlhenney, on February 23, 1993, Mr. DeBellis called the applicant to state that Drs. Gavrilovich and Lumpkin had stated that Maxipime® was an acceptable trade name. For further information, I defer to Mr. DeBellis.

I have inserted the following sentence in the review: "The applicant acknowledged the concerns of the Committee. A rebuttal response was submitted on 11/6/92 (Amendment 18). The issue was finally resolved in a teleconference on 2/23/93."

4. According to Dr. McIlhenney, none of the isomers are being marketed. They are potential impurities that are controlled by chemistry and manufacturing specifications for the final drug substance. These specifications also control the potential presence of the isomers in final marketed product.

The BMSq chemists responded with regard to the purity of the cefepime hydrochloride that was used in clinical trials as follows:

"Based on several analytical techniques (e.g. HPLC and specific rotation), the isomeric integrity of cefepime HCL used in clinical trials is assured. The HPLC analysis separates the seven epimer, the anti-isomer of the C-7 position, the delta-2 isomer of the C-3 position from the desired compound. Beta-lactams naturally occur in a specific stereochemical configuration. The specific rotation assay is added assurance that only one enantiomer of cefepime HCL is present."

5. The issue with arginine was initially raised by Dr. Judy Lui before I came to the Agency and the subject of an entire Advisory Committee meeting. Dr. Roberts or Dr. Albrecht have more of the history on this issue than I do.

However, for your reference, ceftazidime also uses an arginine buffer. The statement with regard to pediatric use is as follows: "Safety of the arginine component of Ceptaz® in children has not been established. This product is for use in patients 12 years or older. If treatment with ceftazidime is indicated for pediatric patients, a sodium carbonate formulation should be used." Note: BMSq has been conducting its pediatric trials with the arginine buffer.

I agree with your concern and believe a statement should be included in the pediatric section of the label. It should be consistent with the ceftazidime label; for example, "Safety of the arginine component of Maxipime® in children has not been established. This product is for use in patients 12 years or older."

6. According to Dr. McIlhenney, in amendment 93 (4/18/94), approved labelling in Finland was submitted. Additional information with regard to the approvals in Belgium and Italy were submitted.

Since that time, an additional approval was granted in New Zealand (5/3/94). Therefore, there has been approval in France, Belgium, Finland, New Zealand and Italy (medically approved, but not yet approved for marketing).

The application has also been filed also in Denmark, Luxembourg, Netherlands, Greece, Spain, the UK, Ireland, Portugal, Austria, Switzerland, Canada (responded with a notice of non-

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compliance, this is in preparation), Australia, Japan, South Africa, Brazil, and Argentina.

Denmark had sent a rejection letter, but the company has responded so that the application is still pending. The Norwegian health authorities rejected cefepime; however, the applicant chose not to respond and thus, it is an automatic withdrawal without a response from BMSq. If you would like further information with regard to the "whys," that information is available.

I chose not to update this information in the NDA because 1) final revision date is 6/6/94 and 2) but more importantly, I do not have confirmation of these filings nor confirmation of the approvals/rejections in official submissions. I also do not have the dates that they took place; therefore, I left p. 8 of the Intro as was on 6/6/94.

7. With regard to the chemistry question about the reconstituted solution being "clear to amber," Suva Roy is away at a conference 7/20 and 7/21. I spoke with both Ernie Pappas and Wilson DeCamp about this issue. The final outcome of the conversation was that sometimes color changes are sometimes an intrinsic condition of reconstitution. Dr. DeCamp stated that Dr. Roy is very thorough and he would have noted in his review if this were an issue of significance. I would again have to defer to Dr. Roy.

I spoke with Dr. Roy re: the color change. He responded to you in an Email. The bottom line is that it is not significant.

8. I share your concern about the different concentrations of the reconstituted solutions. I do not know if this was addressed by Dr. Roy. In support of your current concern, you may remember the consults that Dr. Reed and I had from generic drugs with regard to varied container sizes for tobramycin. We rejected the applications for these multiple container sizes, because we felt the differences in concentrations would create too many medication errors.

9. In consult with Dr. Manigi today (9/20/94), to the best of his knowledge, BMSq has submitted all required pre-clinical studies.

10. According to Dr. McIlhenney, he states that the maximum human dosage for the pre-clinical studies were based on mg/kg. Specifically:

"The table is based on maximum human daily dose of 150 mg/kg using a 40 kg human (this involved the top proposed dose of 2g TID). The comparisons in the table were made on a mg/kg basis across all species."

11. In previous discussions with the Biopharmaceutics group, I learned that there were studies submitted that substantiated the claim that the cefepime formulation buffered with NaCl was equivalent to the formulation buffered with arginine for use by the intravenous route. There were no bioequivalence studies submitted that dealt with the buffering solutions submitted with regard to the intramuscular route.

12. I honestly have no explanation for the variability of the drug in serum/plasma. Perhaps this may have some implications with regard to your other question about BID versus QID dosing for a drug with a half-life of two hours. This question is probably best referred to Dr. Ette.

13. Corrected the typo as indicated on page 24.

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1. The dosages of mezlocillin, gentamicin, metronidazole and clindamycin that were administered intravenously during the studies were as follows:

Mezlocillin	4 grams every 6 hours or 3 grams every 4 hours
Gentamicin	1.5 mg/kg every 8 hours
Metronidazole	0.5 g every 6 hours
Clindamycin	0.9 g every 8 hours

The PDR lists the following recommended dosages for the treatment of serious infections (including as follows:

Mezlocillin	4 grams every 6 hours or 3 grams every 4 hours
Gentamicin	1.0 - 1.7 mg/kg every 8 hours (based on lean body mass)
Metronidazole	7.5 mg/kg every 6 hours (approximately 0.5 g for a 70 kg adult)
Clindamycin	0.6 to 2.7 g per day in 2, 3 or 4 equal doses

Therefore, the regimens do fall within the line of approved regimens. The drug with the most deviation from the label is metronidazole.

2. To answer your question with regard to minimum number of doses required for evaluability, I believe I used what I used in all indications which was 9 doses of cefepime minimum to be evaluable as a cure and 5 doses minimum to be evaluable as a failure. For gent/clinda, it was 13 doses of either to be evaluable as a cure and 8 doses as a failure. However, I wrote this so long ago, that I do not remember why I did not write in the failure caveat. I would prefer NOT to modify the sentence since it is correct as it stands, although it does not address the failure category.

Note on pages 24 and 57, all evaluable cefepime patients with an unsatisfactory outcome had been dosed at least 6 days (11-12 doses).

3. With regard to your question p.21 as to why we apply the .15 rule when the test arm is the better of the two arms, I spoke with Ralph Harkins for clarification. Ralph said that this is a Divisional rule (that we believe you instituted). The statement is correct as written on page 21. The fact is according to Ralph "the width of the C.I. is negatively impacted by the extremely small sample sizes. Even if we computed the confidence intervals without the correction, the numbers would be -.16 and +.27 instead of -.20 and +.31. Even without the correction factor of 4%, it doesn't meet the delta regulation, because the lower bound is negative (-).16."
4. Please see the explanation in (2) above.
5. The word changes have been corrected.
6. The effects of the misrandomization are outlined on p. 6 of the review. The result is enrollment was not 1:1 but rather 114:93 in favor of cefepime/MTZ. The implications thereof I cannot answer nor do I know why this was not addressed by
7. Peritoneal symptoms were not part of the case report form because of poor design. One cannot even attribute the design flaw to a consequence of a multi-indication protocol.

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8. The breakdown of diagnoses on the strictly evaluable patients are as follows:

Study AI411-119

Cefepime/MTZ

17 Perforated Appendices
3 Gangrenous Appendices
20

Clinda/Gent

22 Perforated Appendices
5 Gangrenous Appendices
1 Peritonitis
1 Bowel Perforation
29

Study AI411-120

Cefepime

8 Gangrenous Gallbladder
4 Perforated Gallbladder
2 Ascending Cholangitis with
Obstruction
14

Mezlo/Gent

2 Gangrenous Gallbladder
2

9. With reference to the applicant tables with the discrepancy for applicant evaluable cefepime patients, is it 30 or 31 evaluable patients. My review contains the tables as the applicant had presented them.

I have made the adjustment
to correct the tables to 30 evaluable.

10. My comment was in reference to the fact that the investigator could not justify changes made to the case report form. If this were the case, this might call the whole center's data collection into question. If this were the case and knowing that study AI411-119 is essentially a single center study, then the study has essentially no evaluable patients. I wonder why missed the mis-randomization problem.

11. The patients as outlined above are all strictly evaluable patients with complicated infection. The other prophylaxis patients were excluded & non-evaluable. The premise is that one "can" combine these studies for "interest." While looking over these pages, I found two typos (p.72, 73) on the statements for 95% C.I. I have corrected them.

Strictly Evaluable Population: (Studies AI411-119 and AI411-120 combined)
Clinical and Bacteriologic Response Table
N = 207 + 362

Parameter	CEF/MET	COMPARATOR
NO. OF EVALUABLE PATIENTS	34	31
CLINICAL RESPONSE		
SATIS	30 (88%)	25 (81%)
UNSAT	4 (12%)	6 (19%)

The 95% confidence intervals for the above population are -0.131 and +0.283. The cure rates for the experimental drug and the comparator drugs are 88% and 80%, respectively.

NOTE: The underlined 80% should be 81 as in the chart above.

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Clinically Evaluable Only Population: (Studies 119 and 120 combined)

Clinical Response Table

Parameter	CEF/MET	COMPARATOR
NO. OF EVALUABLE PATIENTS	49	39
CLINICAL RESPONSE		
SATIS	44 (90%)	32 (82%)
UNSAT	5 (10%)	7 (18%)

The 95% confidence intervals for the above population are -0.093 and +0.248. The cure rates for the experimental drug and the comparator drugs are 88% and 80%, respectively.

The underlined numbers should be 90% and 82%, respectively. The C.I. values are correct.

**** I presume that Dr. Albrecht is making the corrections with respect to Dr. Erhardt's write-ups with respect to SKIN AND SKIN STRUCTURE INFECTIONS, URINARY TRACT INFECTIONS, I do not have any of his information.

1. With regard to page 10 MO's comment re: 5 day minimum apply to cure and failures: This refers to the IDSA guideline recommendation on page S85 of the guideline which states "Patients who have received at least 5 days of therapy and at least 80% or more of prescribed medication will have an assessment of clinical response." However, with regard to evaluable failures, I write on p.14 number 5: "received a minimum of 4.5 days of therapy (i.e. 9 doses of cefepime for success....(However, a patient could be classified as a failure after only five cefepime doses.)"
2. With regard to why are the efficacy rates so much lower for the reviewer than the sponsor, I believe at least part of the answer lies on p. 19 of the review (reminiscent of the big "T"): "Because investigators did not anticipate a clinically evaluable population; they often elected to prematurely terminate patients, who did not have a valid pathogen, from the study. Since fewer days of observation are required to detect a failure, there were potentially more patients with negative outcomes that were evaluable." Beyond this thought, I would have to re-analyze the data.
3. In general, there are two ways at looking at post-treatment antibiotics. (1) Any patient who receives antibiotics post treatment is a failure or (2) any patient who receive* post-treatment antibiotics is non-evaluable. Many physicians are uncomfortable discharging a patient from the hospital who was treated with a parenteral antibiotic without a little "extra" oral antibiotic. For this reason, I believe it is unfair to judge these patients as failures. This I believe is unique to patients treated with parenteral drugs. The reviewer cannot adopt a double standard; i.e. that all failures with post-treatment antibiotics are evaluable and all patients who are successes but received post-treatment antibiotics are not evaluable. This creates a data bias.

4. Because _____ is such an "iffy" diagnosis to verify, the applicant must define what it is going after and how to prove or validate it. In the case of a super-infection

I would say this is a very difficult diagnosis to capture. Most infections are viral in nature; the radiograph is negative. A transition must take place such that the sputum has now changed to a purulent specimen (>25 PMNs/lpf) with a predominance of a single bacteriological organism in the absence of a chronic respiratory process.

However, an _____ might be easier to at least diagnose ("verify"). In the setting of a _____ (e.g. such as the IDSA defines: "characterized by excessive secretion of mucus in patients who have coughed up sputum on most days during 3 consecutive months for 2 successive years"), a demonstration of a response to treatment could be defined and monitored (recorded) as a trilogy of decreased dyspnea, sputum volume and sputum purulence and finally, the resolution of all symptoms within a stated time interval. The IDSA further suggests that clinical response and the results of pulmonary function tests and/or arterial blood gases can be used to assess efficacy.

Because of the difficulty in clearcut diagnosis, an objective parameter must be used in conjunction with the qualified gram stain. The clinical response definition may be supported e.g. by sequential measurements of the white blood count, by oxygen saturation, by sputum purulence and/or by pulmonary function testing.

This I believe is a long-winded answer to your question which can be bottom-lined as "yes."

5. The hard copy contained different information than the CANDAs presentation. The patient profiles included the category "improved" in addition cure and fail. The CANDAs identified clinical outcome as "satisfactory, unsatisfactory" or "undetermined." In the summary report, the applicant gave the following definitions:

"The primary efficacy analyses were based on the Clinical and Bacteriological Responses as defined in Section 3.9.3." [The protocol stated Sat: (Cured, Improved), Unsat. etc.]

"For each evaluable infection type in a patient, an Overall response to study therapy was assigned on the basis of the combined Clinical and Bacteriologic Responses. The clinical response of the patient was classified as 'satisfactory' (cured or improved or 'unsatisfactory' (Section 3.9.3.1) The Patient Bacteriologic Response for each infection type was classified as 'eradicated' if all original pathogens in that infection type were 'eradicated' or as 'persisted' if one of the original pathogens remained. The overall response was then assigned as follows:

<u>Overall Response</u>	=	<u>Clinical Response</u>	+	<u>Patient Bacteriologic Response</u>
Effective		Satisfactory		Eradicated
Partially Effective				
Clinically		Satisfactory		Persisted
Bacteriologically		Unsatisfactory		Eradicated
Ineffective		Unsatisfactory		Persisted" p.66, vol. 225

In actual fact, the company did not change the outcomes of protocol definition. The protocol defines a satisfactory outcome (as either "improved or cured") and unsatisfactory as clinical outcomes. The CANDAs merely uses the abbreviated format, if you will.

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6. Dr. Albrecht picked up an error on page 349. It involves the number of *S. pneumoniae* organisms in the reviewers strictly evaluable low dose pneumonia population.

THE OLD VERSION:

	<u>Cefepime</u>	<u>Comparator</u>
<i>S. pneumoniae</i>	17/20 (85%)	9/10 (90%)
All pathogens (Total)	34/46 (74%)	21/24 (88%)

CORRECTED VERSION:

	<u>Cefepime</u>	<u>Comparator</u>
<i>S. pneumoniae</i>	17/20 (85%)	9/11 (82%)
All pathogens (Total)	34/46 (74%)	22/26 (85%)

It is now corrected.

7. The denominators for cefepime and ceftazidime according to the reviewer are as follows:

	<u>Cefepime</u>	<u>Ceftazidime</u>	<u>Total</u>
Pneumonia	1114	380	1494 (16 Patients rec'd cefotaxime)

1336 and 445 are a far cry from the ADR denominator given by the applicant as 1596 and 516, respectively. There were several patients included in the that had or some other infection. However, they totaled less than a hundred in number and would not account for the applicant's numbers. If the applicant did explain it somewhere, I do not know where.

I am not sure it makes a regulatory difference since their number (N) of ADR events is higher. However, since we had to rely on their analyses for safety tables and could not generate it ourselves; it makes me uncomfortable when I do not know which denominators they used to generate THEIR tables.

SAFETY:

1. With regard to the FDA summary for the Coombs' test, the SAS files received from the applicant did not contain the data with regard to the Coombs' test.
2. The request for information with regard to whether cefepime causes a false positive glucose test is certainly indicated.
3. With regard to your question about increased pulmonary emboli, cerebrovascular accidents, gastrointestinal bleeding or vascular thrombi as causes of death with cefepime, I believe that this is largely a reflection of the patient population. Without more information, it would be impossible to determine what the actual cause of death really was. Many times, the investigator chose to list either cardiac arrest or pulmonary embolus as a cause of death. Without more autopsy information, this observation would be difficult to sort out. In addition, the underlying diseases of these patients predispose these patients to embolic phenomena and

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bleeding diatheses. Immobility predispose to emboli; age and atherosclerosis predispose to cerebra-vascular accidents; hypercoagulable states of malignancy predispose to thrombi; and chemotherapy leads to bone marrow suppression and bleeding. This would be very difficult to sort out. However, I did take a "quick and dirty look" at the indications to even see if there is a trend. This follows below (remember some patients are represented twice due to the applicant's multiple listings):

		<u>Cefepime</u>	<u>Control</u>
SSTI	deaths/enrollment =	17/985 (1.7%)	10/384 (2.6%)
	Throm-bleed deaths	0	1/384 (0.2%)
	Thr-ble/deaths	0/17 (0%)	1/10 (10%)
UTI	deaths/enrollment =	60/1035 (6.0%)	32/517 (6.0%)
	Throm-bleed deaths	10/1035 (1.0%)	3/517 (0.6%)
	Thr-ble/deaths	10/60 (16.6%)	3/32 (9.3%)
OTHER	deaths/enrollment =	244/4419 (5.5%)	106/1842 (5.7%)
	Throm-bleed deaths	-	-
	Thr-ble/deaths	3/38 (7.8%)	1/6 (16.6%)

Overall, I do not think there is anything here. If there is, we would be hard pressed to prove it without a more detailed review and/or more information.

4. With regard to the changes in phosphorus, the applicant discusses the following in the ISS (vol. 286, p. 105:

"Decreases in phosphorus occurred at rates similar to abnormal liver function tests (low-dose 2.0%; high dose 3.3%), with increases in phosphorus occurring less commonly (low dose 0.3%; high dose 0.7%). The significance of abnormalities in phosphorus is unclear, since phosphorus levels are subject to both circadian (highest in late morning, lowest in evening) and annual rhythms (highest in May and June, lowest in winter). In addition, phosphorus levels fall rapidly in response to diet or intravenous glucose infusions (increased carbohydrate metabolism), phosphate binding antacids, insulin, and severe diarrhea. Phosphorus levels rise in response to renal failure, growth hormone, and diuretics such as furosemide and hydrochlorothiazide. Hemolysis of blood samples and detergent contamination of glassware used in obtaining and testing samples may also produce falsely elevated phosphorus levels. It is impossible to determine the potential influence of these numerous factors in causing the abnormal phosphorus tests encountered in patients treated with cefepime."

The applicant does not remark about calcium.

mOR

Complicated UTI - Bacteriologic Response by Infecting Pathogen

Table ES.7 summarizes the bacteriologic response by infecting pathogen in patients with complicated UTI. Table ES.7A presents the bacteriologic response for pathogens treated with cefepime 500 mg BID compared with the response for pathogens treated with ceftazidime 500 mg TID.

Table ES.7A
Bacteriologic Response of Pathogens Recovered from Patients with Complicated UTI (Including Pyelonephritis)
|| 5-9 Days Post-Therapy Evaluation
|| According to the Medical Officer

	CEFEPIME 500 mg BID	CEFTAZIDIME 500 mg TID	500 mg or
<u>COMPLICATED UTI PATHOGENS</u>			
A. CALCOACETICUS	1/ 1 (100%)	0	
ACINETOBACTER SP.	0	1/ 1 (100%)	
C. DIVERSUS	0	0/ 1 (0%)	
C. FREUNDII	1/ 1 (100%)	2/ 2 (100%)	
E. AEROGES	2/ 2 (100%)	1/ 1 (100%)	
E. CLOACAE	2/ 3 (67%)	4/ 4 (100%)	
E. COLI	68/ 83 (82%)	27/ 41 (66%)	→
ENTEROBACTER SP.	1/ 1 (100%)	0	
K. OXYTOCA	3/ 3 (100%)	2/ 2 (100%)	
K. PNEUMONIAE	8/ 11 (73%)	5/ 7 (71%)	
P. AERUGINOSA	11/ 17 (65%)	10/ 11 (91%)	→
P. MIRABILIS	10/ 12 (83%)	5/ 5 (100%)	→
P. RETTGERI	1/ 1 (100%)	0	
PROTEUS SP.	1/ 1 (100%)	0	
S. AUREUS	1/ 2 (50%)	1/ 1 (100%)	
S. EPIDERMIDIS	2/ 3 (67%)	0	
S. FAECALIS	0	2/ 2 (100%)	
S. HOMINIS	0/ 1 (0%)	0	
S. MARCESCENS	2/ 3 (67%)	0	
S. WARNERI	0	0/ 1 (0%)	
SHIGELLA SP.	0	1/ 1 (100%)	
STREP. (GROUP B)	1/ 1 (100%)	1/ 1 (100%)	
ALL COMPLICATED PATHOGENS	115/146 (79%)	62/ 81 (77%)	→

E. coli, *K. pneumoniae*, *P. aeruginosa*, and *P. mirabilis* were each recovered from greater than 10 evaluable patients treated with cefepime 500 mg BID. For *E. coli*, the bacteriologic responses to cefepime and ceftazidime treatment were equivalent by the 95% confidence interval approach (-2%, +35%). Because of the small number of isolates, a confidence interval analysis of the differential bacteriologic response is not possible for *K. pneumoniae*, *P. aeruginosa* and *P. mirabilis*. Nevertheless, a similar bacteriologic response to both cefepime and ceftazidime was seen with isolates of *K. pneumoniae*. There was a trend toward an inferior bacteriologic response with cefepime compared to ceftazidime in isolates of *P. aeruginosa* and *P. mirabilis*.

Table ES.7B presents the bacteriologic response for pathogens treated with cefepime 2.0 grams BID compared with the response for pathogens treated with ceftazidime 2.0 grams TID.

Table ES.7B
Bacteriologic Response of Pathogens Recovered from Patients with
Complicated UTI (Including Pyelonephritis)
5-9 Days Post-Therapy Evaluation
According to the Medical Officer

2 gms BID

	CEFEPIME 2.0 grams BID	CEFTAZID 2.0 grams TID

COMPLICATED UTI PATHOGENS		
C. AMALONATICUS	0	1/ 1 (100%)
C. DIVERSUS	1/ 2 (50%)	0
C. FREUNDII	0	1/ 1 (100%)
E. AGGLOMERANS	0/ 1 (0%)	0
E. CLOACAE	1/ 1 (100%)	1/ 1 (100%)
E. COLI	36/ 39 (92%)	41/ 46 (89%) →
ENTEROBACTER SP.	1/ 1 (100%)	1/ 1 (100%)
ENTEROCOCCUS	0/ 1 (0%)	0
H. ALVEI	1/ 1 (100%)	1/ 1 (100%)
K. ORNITHINOLYTICA	0	1/ 1 (100%)
K. OXYTOCA	0/ 2 (0%)	2/ 2 (100%)
K. PNEUMONIAE	8/ 9 (89%)	6/ 8 (75%)
KLEBSIELLA SP.	2/ 2 (100%)	1/ 2 (50%)
P. AERUGINOSA	2/ 7 (29%)	3/ 8 (38%)
P. MIRABILIS	4/ 7 (57%)	4/ 6 (67%)
PSEUDOMONAS SP.	0	1/ 1 (100%)
S. AUREUS	4/ 4 (100%)	0/ 1 (0%)
S. FAECALIS	0/ 1 (0%)	0
S. MARCESCENS	0	1/ 1 (100%)
S. VIRIDANS	1/ 1 (100%)	0
STREP. (GROUP B)	3/ 3 (100%)	0

ALL COMPLICATED PATHOGENS	64/ 82 (78%)	65/ 81 (80%) →

Only E. coli was recovered from greater than 10 evaluable cefepime patients. The bacteriologic responses of cefepime and ceftazidime were equivalent by the 95% confidence interval approach for E. coli isolates (-11, +18).

MEDICAL OFFICER'S REVIEW OF ORIGINAL NDA

DATE OF SUBMISSION: June 30, 1992
 DATE OF FINAL REVISION: June 6, 1994

APPLICANT: Bristol-Myers Squibb
 5 Research Parkway, P.O. Box 5100
 Wallingford, Connecticut 06492
 Contact: Hugh McIlhenney, PhD
 (203) - 284-7879

CONTENTS:

The entire submission consists of 343* volumes. These volumes supply the data for each discipline as follows:

Volume 1	Overall Summary Volume
Volumes 2 - 5	Chemistry, Manufacturing and Controls
Volumes 6 - 41	Pharmacology and Toxicology
Volumes 42 - 54	Non-clinical Pharmacology/Pharmacokinetics
Volumes 55 - 84	Human Pharmacokinetic Studies
Volumes 85 - 95	Microbiology
Volumes 96 - 339	Human Clinical Data

*Volume 4 actually consists of 4 volumes (volumes 4A, 4B, 4C, 4D)

AMENDMENTS:

<u>DATE OF SUBMISSION:</u>	<u>CONTENTS (Discipline to Which Submitted):</u>
1. 06-30-92	- Fox-Pro Efficacy Analysis Program/WP5.1 Clinical Reports CANDA System (Clinical) - Patients Profiles (Clinical)
2. 07-08-92	- CRF Imaging System (Clinical) - Revised Fox-Pro/WP5.1 Programs (Clinical) - Patient Profiles (Clinical) - Checklist Information for FDA 45 day-meeting; BMSq grading system for NDA lab data (Clinical)
3. 07-28-92	- Replacement copy of volume 1.289 (Clinical)
4. 08-20-92	- Copies of 3 IND submissions regarding agreements reached with the Division during IND development (Clinical) - Reference to location of reports in NDA for end-of Phase II and two pre-NDA meetings (Clinical) - CRF Dictionary for Pathogen Source (Clinical) - Copy of revised protocol A1411-160 with sample CRFs (Clinical)
5. 09-11-92	

6.	09-11-92	- UTI clinical (data (subsetting patient profiles, supplemental patient profiles) (Clinical)
7.	09-14-92	- Proprietary name selected for review by Nomenclature and Labelling Committee (MAXIPIME®) (Clinical)
10.	09-23-92	- Skin and Skin Structure Infections clinical data (supplemental patient profiles, selected CRF pages) (Clinical)
11.	09-25-92	- Response to Biopharm request for information (study AI411-129-004) (Biopharmaceutics)
12.	09-30-92	- Electronic NDA System Upgrades (FoxPro/WP5.1; CRF Image) (Clinical) - Home Office Fax Installation (Clinical) - Patient Catalogue (draft summary tables) (Clinical) - Generic Table of Contents for Study Reports, concomitant non-antibiotic medications (Clinical) - 45-day FDA meeting checklist of information, BMSq grading system for lab data, overall listing of patients with multiple infection types, summary listing of clinical protocols/CRFs (file copy) (Clinical)
13.	10-06-92	- Clarification of manufacturing sites for drug substance and drug product (Chemistry)
14.	10-08-92	- Finalized patient catalogue (Clinical)
15.	10-08-92	- Response to Biopharm request for information (Study AI411-163-001) (Biopharmaceutics)
16.	10-16-92	- Resubmission of Stability Data on Drug Product (Chemistry)
17.	10-22-92	- Response to Request for individual AUC from time zero to the last sampling time for subjects studied in Study No. AI411-086-001 (Biopharmaceutics)
18.	11-06-92	- Additional request for MAXIPIME® as proprietary name for cefepime (Clinical)
19.	11-10-92	- Response to request for individual subject pharmacokinetic data for certain studies (Biopharmaceutics)
20.	11-13-92	- Revised Fox-Pro Version 1.03 and summary of changes to Case Report Forms (Clinical)
21.	11-19-92	- Response to requests to Statistical Reviewers - SAS data sets for AI411-119, AI411-120 and code files (Statistics)
22.	11-20-92	- Submission of four animal safety reports - generated for Japanese registrational dossier (Pharmacology)
23.	11-20-92	- CMC Amendment - Re. / facility (Chemistry)
24.	12-21-92	- First Safety Update (4-month) (Clinical)
25.	12-22-92	- CMC Amendment - Alternative BMSq Manufacturing

26. 12-30-92 Facility in (Chemistry)
- CMC Amendment - Sterile validation documentation for manufacturing sites (Chemistry)
27. 01-06-93 - Request for a meeting with Anti-Infective Division to discuss NDA databases in support of an indication for the treatment of bacterial septicemia (Clinical)
28. 01-06-93 - CMC Amendment - Information for the review of the Methods Validation Package (Chemistry)
29. 02-12-93 - Amendment to First Safety Update - Summaries of European Deaths & Discontinued Included (Clinical)
30. 02-12-93 - Investigators Comments Pages from Case Report Forms to Support Documentation - Protocols A1411-119 and A1411-120 - (Clinical)
31. 02-17-93 - Upgraded FoxPro Efficacy Analysis Program (Clinical)
32. 02-23-93 - Investigators Comments pages from Case Report Forms - Patients Volumes 32.1 32.3
33. 02-25-93 - Proposal regarding changing definition for the indication (Clinical)
34. 03-10-93 - Upgraded FoxPro Efficacy Analysis Program for Dr. Sherman and FoxPro Efficacy Analysis Program for UTI for Dr. Albrecht (Clinical)
35. 03-17-93 - Agenda for 3/25/93 meeting with the Division to discuss changing definition for the indication of (Clinical)
36. 03-18-93 - Summary Tabulations - Requested by Dr. Sherman (Volume 36.1)
37. 03-18-93 - Investigator Comments pages from Case Report Forms - UTI Patients - for Dr. Erhardt (Clinical)
38. 03-23-93 - Data Diskettes and Laboratory Appendices for UTI patients and Word Perfect User Manual - for Dr. Erhardt (Volumes 38.1 - 38.13) (Clinical)
39. 03-26-93 - Breakdown requested by Dr. Sherman (Clinical)
40. 04-13-93 - Upgraded FoxPro diskette for UTI patients - for Dr. Erhardt (Clinical)
41. 04-15-93 - Summary Tabulations - Skin and Skin Structure Infections - Requested by Dr. Sherman (Clinical)
42. 04-22-93 - Listing of Death & Discontinuations in Skin Structure Infections - Requested by Dr. Sherman (Clinical)
43. 04-22-93 - SAS data files submitted in support of the statistical review of all remaining indications other than (Clinical)
44. 04-23-93 - Summary response to Dr. Sherman's questions regarding specific patients with (Clinical)
45. 04-23-93 Tabulations - One Positive Blood

- Culture Patients to Dr. Sherman (Clinical)
46. 04-26-93 - Summary minutes of meeting with Agency held on 3/25/93 (Clinical)
 47. 04-28-93 - Summary table of laboratory test values for UTI patients, requested by Dr. Erhardt (Clinical)
 48. 04-30-93 - Corrections to Amendments 36, 39 and 45, pertaining to (Clinical)
 49. 05-04-93 - Resubmission of Case Report Form's (Volumes 1.290 - 1.339) and Overview of Clinical Investigations (8-page document contained in Volume 1.96)
 50. 05-11-93 - SAS dataset files requested in support of the statistician's review of the NDA database. (Clinical)
 51. 05-12-93 - Identification of several new variables in support of SAS datasets for statistical review of database (should have accompanied Amendment No. 50) (Biometrics)
 52. 05-21-93 - Proposed labeling changes to "Precautions" and "Overdosage" sections of the package insert. (Clinical)
 53. 05-26-93 - CMC Amendment - Withdrawal of site as manufacturing site for the non-sterile drug substance (Chemistry)
 54. 05-28-93 - Second Safety Update along with proposed revisions to the "Adverse Experience" section of the labeling (Clinical)
 55. 06-02-93 - Correspondence regarding changing definition for the indication of (Clinical)
 56. 06-04-93 - Proposed labeling changes to "MICROBIOLOGY" section of package insert. (Microbiology)
 57. 06-08-93 - Submission of diskettes containing the NDA safety for the non-comparative databases and for the comparative (cefepime vs. ceftazidime) databases to aid in the statistical review of the NDA. (Biometrics)
 58. 06-15-93 - Upgraded FoxPro and WP files - Efficacy Version 1.08 (Clinical)
 59. 06-25-93 - Urinary Tract Infections - Listing identifying those patients classified with clinically relevant laboratory test values, and post-treatment - Provided for Dr. Erhardt. (Clinical)
 60. 06-28-93 - Investigators Comments pages of case report forms for all patients in clinical trials - Provided for Dr. Sherman (Volumes 60.1-60.9) (Clinical)
 61. 06-30-93 - Summary Tabulations - Requested by Dr. Sherman (Clinical)
 62. 06-30-93 - Draft revision to the proposed package insert is submitted. (Clinical)
 63. 07-09-93 - Summary Tabulations -

- 64. 07-13-93 - Infections - Requested by Dr. Sherman (Clinical)
- Statistical analysis of severity measures in UTI patients - Requested by Dr. Erhardt. (Clinical)
- 65. 07-13-93 - Upgraded FoxPro Efficacy Analysis Program to Accept Additional Pathogen Designations (Version 1.09:7/93) (Clinical)
- 66. 07-21-93 - Upgraded FoxPro Efficacy Analysis Program WP 5.1 files to support Dr. Erhardt's Review (Clinical)
- 67. 08-04-93 - CMC Information - Responses to the deficiency letter dated April 14, 1993. (Chemistry)
- 68. 08-09-93 - Summary responses to questions from Dr. Sherman regarding case report forms for patients (Clinical)
- 69. 08-09-93 - Summary Tabulations - Infections - Requested by Dr. Sherman (Clinical)
- 70. 08-10-93 - Summary Tabulations of Adverse Events and Laboratory Test Values for Skin and Skin Structure Infection Patients - to support Dr. Erhardt's review of this indication (Clinical)
- 71. 08-11-93 - Summary Tabulations of Adverse Events and Laboratory Test Values for Infection Patients - to support Dr. Sherman's Review of this Indication. (Clinical)
- 72. 08-20-93 - Approved Foreign Labelling - Swedish and French - (Regulatory)
- 73. 08-20-93 - Preclinical Toxicity Report (Pharmacology)
- 74. 08-23-93 - Summary tabulations of urinalysis results of laboratory tests within the NDA safety database (Clinical)
- 75. 08-30-93 - Data listings on resistant organisms and patients with ventilation assistance - Infections - in response to a request from Dr. Sherman (Clinical)
- 76. 09-10-93 - Final Urinalysis Report (Clinical)
- 77. 09-14-93 - Incidence of Hematuria Associated with Cefepime When Compared to Ceftazidime (Clinical)
- 78. 09-17-93 - Database SIRS/Mortality Tabulations: (Clinical)
- 79. 09-28-93 - Updated Patent Information (Regulatory)
- 80. 09-28-93 - Animal Safety Report Generated for Registration in Germany (Pharmacology)
- 81. 10-13-93 - Draft revision to Proposed Package Insert, based on Anti-Infective Drugs Advisory Committee Meeting on September 24, 1993 Regarding the Indication of (Clinical)
- 82. 10-28-93 - Laboratory Test Values for Skin and Skin Structure Infection Patients - to support Dr. Erhardt's review of this indication. Corrections to data submitted in Amendment No. 70 (Clinical)

83.	11-24-93	- Final Safety Update, including TID safety data and proposed revisions to package insert (Clinical)
84.	12-15-93	- Correction of Summary Tabulation of laboratory test values of Patients, Correction to data submitted in Amendment No. 71
85.	12-22-93	- Updated Patient Profiles for Fever/Neutropenia Patients (for Dr. Erhardt's Review) (Clinical)
86.	12-23-93	- Summary Tabulations - Infections (Clinical)
87.	01-13-94	- Listing of patients in NDA database who received Cefepime by the Intramuscular Route of Administration (Clinical)
88.	02-15-94	- Cross Reference Toxicology Report #50940 to NDA (Pharmacology)
89.	02-15-94	- CMC Amendment - Responses to FDA deficiency letter of 1/14/94 (Chemistry)
90.	02-18-94	- Draft Revision to Proposed Package Insert (Clinical)
91.	02-24-94	- Correction of NDA Study Report 411-097-ALL (Clinical)
92.	03-21-94	- Final Pharmacokinetic Report for Study AI411-111-003 (adds comparative data) (Biopharmaceutics)
93.	04-18-94	- Approved Labelling (Finland); Labelling from Belgium and Italy (Regulatory)

NAME OF DRUG:Generic:

Cefepime hydrochloride

Cefepime is the free-base (inner salt). Consequently, the dihydrochloride acid salt with one mole of water is designated as cefepime hydrochloride. The hydrogen sulfate salt is designated cefepime sulfate.

Trade:

MAXIPIME® (Proposed)

MEDICAL OFFICER'S COMMENTS:

The applicant was informed in a teleconference (10-21-92) of the following concerns raised by the Agency's nomenclature committee from their preliminary review of the proposed trade name for cefepime hydrochloride. (Re: Consult #168 by R. Johnson.) First, the term "maxi" implies some maximum benefit; as yet, this has not been demonstrated. Second, the name has sound similarities with Amoxapine (an anti-depressant) and Maxiquin® (an anti-infective drug). The applicant acknowledged the concerns of the Committee. A rebuttal response was submitted on 11/6/92 (Amendment 18). The issue was finally resolved in a teleconference on 2/23/93.

Code Designation:

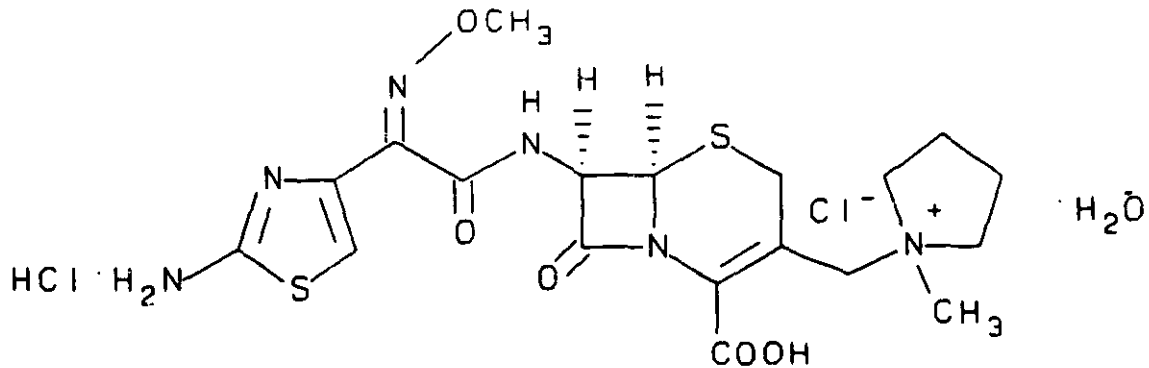
BMY-28142-01

Chemical Name:

Pyrrrolidinium, 1-[[[7-[[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-chloride, monohydrochloride, monohydrate, [6R-(6 α , 7 β (Z))]-

Molecular Formula:C₁₉H₂₆N₆O₈S₂•Cl•HCl•H₂OMolecular weight:

571.5

Structural formula:Isomers:

Three geometric isomers of cefepime are known: the (E)-methoxime (BL-S1384), the Δ^2 isomer (BB-S953) and the 7-epimer (7 α cefepime).

Dosage Strength:

Vials of 500 mg, 1 g, 2 g

Composition:

Cefepime is administered with a vehicle, L-arginine. The final product is a mixture of the sterile, dry powder cefepime hydrochloride and L-arginine.

The ratio of sterile cefepime hydrochloride to sterile L-arginine is approximately the same in all three dosage strengths. To date that ratio has been determined by the applicant to be 0.6:1.0 w/w L-arginine to cefepime hydrochloride.

MEDICAL OFFICER'S COMMENTS:

Initial studies, under IND were completed with the mixture of the cefepime constituted with . The formulation included 250 mg, 500 mg and 1.0 g strengths; the latter were constituted with solutions of 30.4 mg, 60.8 mg and 121.6 mg of respectively. Some pre-clinical and clinical studies were conducted using the vehicle. These studies are indicated in the review.

US Patents:

1. U.S. Patent No. 4,406,899: expires on September 27, 2000.
2. U.S. Patent No. 4,910,301: expires on September 27, 2000.
3. U.S. Patent No. 4,994,451: expires on February 19, 2008.
4. U.S. Patent No. 5,095,011: expires on March 10, 2009.

Related INDs:

IND

IND

BACKGROUND:

Cefepime is a semi-synthetic broad-spectrum cephalosporin antibiotic intended for parenteral administration. Cefepime is administered with the buffer, L-arginine.

The applicant supplies the following rationale for cefepime development:

"Cefepime offers, in a single agent, an excellent safety and efficacy profile with broad-spectrum activity against the principal bacterial pathogens causing the most important types of moderate, severe, and very severe, life-threatening infections in hospitalized patients. Cefepime displays better *in vitro* potency against *S. aureus* than ceftazidime, and better potency against *P. aeruginosa* than cefotaxime. Cefepime's potency against *Enterobacter*, an increasingly important nosocomial pathogen, is unique among currently available cephalosporins. In studies of the emergence of antibiotic-resistant strains, cefepime produces lower mutational frequencies *in vitro* than ceftazidime; in animal models cefepime produces much less frequent selection of resistant strains than do ceftriaxone or ceftazidime. Cefepime also provides pharmacologic and therapeutic advantages over other cephalosporins. Cefepime displays linear kinetics (parameters unchanged by repeated dosing) with a half-life which permits BID dosing for all except very severe, life-threatening infections. When administered by the intramuscular route, cefepime is 100% bioavailable and better tolerated than ceftriaxone."

Cefepime hydrochloride has been developed by the Bristol-Myers Squibb Research Institute. Marketing Authorization Applications have been filed in France (2/92), Japan (3/92), and Belgium (4/92). Cefepime has been approved in Sweden (June, 1993) and in France (June, 1993).

PROPOSED TREATMENT INDICATIONS:**MEDICAL OFFICER'S COMMENTS:**

The applicant's submission considered both pneumonia

as subsets of the previously

designated single indication, discussed the two conditions, and pneumonia, together. After the Division's 45-day meeting, the applicant was notified that pneumonia and would be reviewed independently. Although the applicant did not resubmit separated study reports, the individual patient profiles and supportive electronic information banks were sorted and re-classified.

URINARY TRACT INFECTIONS:

Complicated Urinary Tract Infections - Including Pyelonephritis caused by *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Enterobacter* species.

Uncomplicated Urinary Tract Infections due to *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species and *Enterobacter* species.

MEDICAL OFFICER'S COMMENTS:

Similarly, the applicant grouped uncomplicated and complicated UTI in their study report discussions. In a subsequent amendment, individual patient profiles and supportive electronic data were sorted and re-submitted.

SKIN AND SKIN STRUCTURE INFECTIONS:

Skin and Skin Structure Infections caused by *Staphylococcus aureus* (methicillin-susceptible strains), *Streptococcus pyogenes* (Group A streptococci), *Streptococcus agalactiae* (Group B streptococci), other β -hemolytic *Streptococcus* species, *Pseudomonas aeruginosa*, *Enterobacter* species, *Klebsiella* species, *Proteaceae* (including *Proteus mirabilis* and *Morganella morganii*), *Escherichia coli*, *Serratia marcescens* and *Acinetobacter calcoaceticus*.

MEDICAL OFFICER'S COMMENTS:

Subsequent to the Division's 45-day meeting, the applicant was advised in a teleconference that the indication as it was previously known, would no longer be granted. The data would be reviewed and, if supportive, a statement with regard to would appear in the label.

The proposed treatment regimens are as follows:

Site and Type of Infection	Dose	Frequency
Mild to moderate urinary tract infections (uncomplicated and complicated)	500 mg - 1 g IV or IM	Q12h
Mild to moderate infections including pneumonia skin and skin- structure infections.	1 g IV or IM	Q12h
Severe infections including pneumonia, urinary tract infections, skin and skin-structure infections.	2 g IV	Q12h
Very severe or life-threatening infections including especially in immunocompromised patients.	2 g IV	Q8h

Impaired Hepatic Function - No adjustment is necessary for patients with impaired hepatic function.

Impaired Renal Function - Cefepime is excreted by the kidneys almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function (creatinine clearance <30mL/min), the dose of cefepime should be adjusted.

CHEMISTRY/MANUFACTURING AND CONTROLS:

The reader is referred to the complete chemistry review by Dr. Suva Roy.

Cefepime is a white to pale yellow powder.

The intended solutions of the trade product are to be as follows:

	Amount of Diluent to be added (mL)	Approximate Available Volume (mL)	Approximate Cefepime Concentration (mg/mL)
<u>Intravenous</u>			
500 mg vial	5	5.6	100
1 g vial	10	11.3	100
2 g vial	10	12.5	160
<u>Piggyback (100 mL)</u>			
1 g bottle	50 or 100	50 or 100	20 or 10
2 g bottle	50 or 100	50 or 100	40 or 20
<u>Intramuscular</u>			
500 mg vial	1.3	1.8	280
1 g vial	2.4	3.6	280

The manufacture of the nonsterile cefepime hydrochloride bulk drug substance is performed by Bristol-Myers Squibb at its facilities in Syracuse, New York, and Latina, Italy.

Bristol-Myers Squibb Company
Bio/Chem Division
315 N. Thompson Road
P.O. Box 4755
Syracuse, New York 13221-4755

Bristol-Myers Squibb S.p.A.
Bio/Chem Division
Sermoneta
Latina, Italy

Further processing to the sterile new drug substance and final quality control, packaging and labeling is performed at the Bristol-Myers Squibb facilities in Latina, Italy (address given above) and Barceloneta, Puerto Rico:

Bristol-Myers Barceloneta, Inc.
Bio/Chem Division - Barceloneta Operations
Carr No. 2, Km 45.4
P.O. Box 657
Barceloneta, Puerto Rico 00617

PHARMACOLOGY/TOXICOLOGY:

The following is a synopsis of the applicant's summary presented in Volume 1.1. For a detailed review of pharmacology/toxicology, the reader is referred to the review by Dr. Kumar Mainigi.

MEDICAL OFFICER'S COMMENTS:

The applicant did not provide information with regard to the number of pre-clinical studies performed in the overall summary volume. A table listing the studies conducted, the dosages tested and the major treatment

related findings would have been helpful. Overall summary statements provided by the applicant are given below.

Pre-clinical studies were completed in rats, mice, dogs and monkeys. The applicant states that the overall metabolic and pharmacokinetic profile for cefepime is similar for animals and humans. Like other cephalosporins, cefepime is primarily excreted in the urine as unchanged drug. The major degradation product, N-methylpyrrolidine, is rapidly converted to N-oxide in humans and in all animals tested.

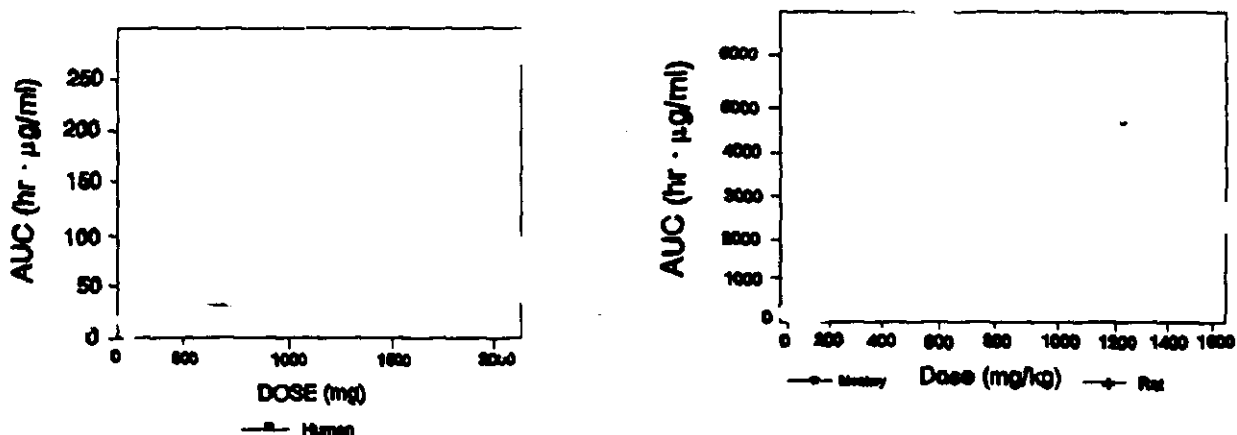
The major toxicities in animals treated with cefepime were as follows:

- 1) in rats, there was cardiovascular failure after intravenous injection of a large bolus.
- 2) in dogs, hematologic toxicity was characterized by thrombocytopenia, leukopenia, and anemia after treatment for more than four weeks.
- 3) in rats, dogs, and monkeys, increased numbers of heterolysosomes were detected in the proximal renal tubular epithelium, after four or more weeks of treatment.
- 4) in rats, increased incidence and severity of nephropathy occurred after a six month treatment with cefepime.

Absorption, bioavailability and pharmacokinetic studies were conducted in animals. The results were presented by the applicant in tabular form as follows:

Note: (The applicant states that pharmacokinetic parameters of cefepime hydrochloride with L-arginine were the same as those of the cefepime [redacted] without L-arginine when tested in humans and rats after an intravenous infusion.)

Relation of AUC(INF) to Cefepime Dose
Cefepime NDA Summary



Absorption Parameters of Cefepime
Cefepime NDA Summary

Species	Strain	n(Sex)	Doses ^a (mg/kg)	Route	C _{MAX} (µg/mL)	T _{MAX} (h)	AUC(INF) (µg·h/mL)	Absorption ^b (% Dose)
Rat	Sprague-Dawley	6(M)	100	SC	33.7 ± 5.2	2.3 ± 1.0	142 ± 17	102 ± 13
		6(M)	800	SC	104.4 ± 17.7	7.3 ± 0.8	1195 ± 141	108 ± 13
		6(M)	2000	SC	282.1 ± 31.0	6.0 ± 1.1	2807 ± 151	101 ± 5
		3(M), 3(F)	500	IP	355 ± 33	0.5 ± 0.1 ^b	684 ± 71	98 ± 10
		3(M), 3(F)	1000	IP	609 ± 61	0.24 ± 0.15	1460 ± 185	105 ± 13
		3(M), 3(F)	1500	IP	629 ± 216	0.50 ± 0.35	1635 ± 460	78 ± 22
		5(N)	891	IV	2136 ± 377	0.25 ^c	1184 ± 194 (1390) ^d	- - -
Dog	Beagle	4(M)	10	IM	24.0 ± 3.6	0.44 ± 0.24	43.4 ± 12.0	102.9 ± 20.5
		4(M)	50	IM	68.2 ± 3.7	0.75 ± 0.20	185.2 ± 17.3	89.0 ± 12.2
		4(M)	100	IV	532.4 ± 75.3	0.10 ^c	421.5 ± 63.9	- - -
Human		6(M)	250	IM	7.8 ± 2.0	1.0 ± 0.3	33 ± 6	99
		6(M)	500	IM	13.9 ± 3.4	1.4 ± 0.9	60 ± 8	90
		6(M)	1000	IM	29.6 ± 4.4	1.6 ± 0.4	137 ± 11	102
		12(M)	2000	IM	57.5 ± 9.5	1.5 ± 0.4	262 ± 23	98
		12(M)	2000	IV	132.2 ± 20.8	0.5 ^c	268 ± 27	- - -

Values are expressed as the Mean ± Standard Deviation.

^a Doses for humans expressed in total milligrams.

^b Based on ratio of AUC(INF) values for cefepime in plasma (non-IV) value/IV-value) normalized to a 1000 mg/kg dose for the rat, a 100 mg/kg dose for the dog and a 2000 mg dose in humans.

^c T_{MAX} IV = end of infusion.

^d Average AUC(INF) value dose normalized to a 1000 mg/kg dose from B7-1507 mg/kg dose data.

Pharmacokinetics Parameters of Cefepime
Cefepime NDA Summary

Species	Strain	n (Sex)	Doses ^a (mg/kg)	C _{MAX} (µg/mL)	Infusion Time (hr)	AUC (MFI) (µg·h/mL)	T-HALF (h)	VD _{SS} (L/kg)	CLT (mL/min/kg)	UR (%Dose)
Rat	Sprague- Dawley	5(M)	28							
		6(M)	89							
		6(M)	200							
		7(M)	386							
		6(M)	87							
		6(M)	371							
		5(M)	891							
		5(M)	1440							
		6(M)	1502							
		3(M)	16							
3(F)	10									
Dog	Beagle	4(M)	100							
Monkey	Cynomol- gus	3(M)	10							
		3(M)	100							
		3(M)	300							
		3(M)	600							
		2(F)	31.6							
Human		4(M)	125							
		4(M)	250							
		4(M)	500							
		4(M)	1000							
		4(M)	2000							

Values expressed as the Mean $\pm$ Standard Deviation, after IV administration.

^a Doses for humans are expressed as total milligrams.

^b Data not collected in this study.

Serum Protein Binding:

Cefepime is not extensively bound to serum proteins. *In vitro* binding of radiolabelled cefepime to rat and dog serum proteins was 7% and 3%, respectively. Human serum protein binding was 17% *in vitro*.

Distribution in Tissue:

In studies of rats and monkeys, intravenously infused radiolabelled cefepime did not localize in any specific tissue, except the kidney.

Cefepime radiolabelled in the N-methylpyrrolidine moiety was infused intravenously into pregnant rats. The results of the tissue distribution are given below:

Distribution of Radiolabelled Cefepime in Pregnant Rats
after IV Administration of 10 mg/kg
Cefepime NDA Summary

Sacrifice(h)	0.25	1	3	24
Tissue:				
Amniotic fluid	0.14 ± 0.02	0.23 ± 0.06	0.27 ± 0.04	0.06 ± 0.01
Brain	0.87 ± 0.27	0.25 ± 0.02	0.08 ± 0.03	ND ^a
Fetus #1 ^b	0.39 ± 0.05	0.31 ± 0.04	0.34 ± 0.02	0.05 ± 0.01
Fetus #2 ^b	0.38 ± 0.01	0.33 ± 0.06	0.32 ± 0.04	0.06 ± 0.01
Fetus #3 ^b	0.39 ± 0.05	0.33 ± 0.06	0.34 ± 0.06	0.06 ± 0.01
Heart	8.16 ± 1.08	1.73 ± 0.33	0.39 ± 0.06	0.08 ± <0.01
Kidney	55.56 ± 11.95	22.14 ± 0.88	9.64 ± 0.61	3.09 ± 0.12
Liver	5.10 ± 0.22	2.68 ± 0.26	2.07 ± 0.42	0.37 ± 0.02
Lung	12.34 ± 0.94	3.72 ± 0.36	1.20 ± 0.10	0.28 ± 0.01
Ovaries	11.11 ± 0.95	3.45 ± 0.38	0.88 ± 0.13	0.17 ± 0.04
Placenta	6.52 ± 0.12	3.00 ± 0.16	1.63 ± 0.32	0.43 ± 0.08
Uterus	15.93 ± 1.12	5.59 ± 0.41	2.24 ± 1.47	0.46 ± 0.05
Plasma	29.53 ± 1.53	7.04 ± 0.73	1.34 ± 0.20	0.18 ± 0.04
Whole-blood	18.62 ± 1.00	4.65 ± 0.51	1.02 ± 0.15	30.19 ± 0.03

Results expressed as µg equivalents of cefepime zwitterion/g of tissue (Mean ± Standard Deviation).

^a: ND = None Detected; ^b: Fetuses from each rat were pooled.

**Recovery of Radiolabelled Cefepime from Stomach of Nursing
Rat Pups after IV Administration to the Mother^a
Cefepime NDA Summary**

Pup No.	1		2		3		Mean ± SD	
	Milk	Carcass	Milk	Carcass	Milk	Carcass	Milk	Carcass
0.5	0.003	<0.043	0.003	<0.044	0.001	<0.049	0.002 ± 0.001	<0.047
1	0.005	0.086	0.003	<0.051	0.011	0.200	0.006 ± 0.004	0.112
2	0.018	0.126	0.015	<0.051	0.008	0.198	0.014 ± 0.005	0.125
6	0.011	0.078	0.008	0.060	0.011	0.357	0.010 ± 0.002	0.165 ± 0.167

Results expressed as total % of dose administered.

^a: 10 mg/kg administered IV daily for 7 days.

Metabolism:

Cefepime was not extensively metabolized in rats, dogs, monkeys, or humans. After IV infusion, cefepime labelled in either the N-methylpyrrolidine (NMP) or the aminothiazole moiety was nearly all (>90%) recovered in the urine. More than 80% of that was unchanged cefepime, the remainder was NMP and its oxide metabolite, and the C-7 epimer of cefepime. The proposed metabolic pathway from cefepime to the C-7 epimer, NMP, and the N-oxide is shown below.

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Effect on Hepatic Enzyme Systems:

In rats, daily infusion of 40 mg/kg over fourteen days did not induce hepatic cytochrome P-450, microsomal 7-ethoxycoumarin-o-deethylase, or aminopyrine-N-demethylase activity. *De novo* synthesis of hepatic microsomal protein did not increase.

Excretion:

Cefepime administered parenterally to rats, dogs, monkeys, and humans was almost exclusively excreted in the urine; < 5% was recovered in feces. Of the cefepime recovered in the urine, > 80% was unchanged cefepime. In rats administered cefepime subcutaneously daily for up to 6 months, the recovery of cefepime in urine was consistent with lack of accumulation and constant elimination.

Comparative Pharmacokinetics:

The mean pharmacokinetic parameters from studies of rats, dogs, and humans are summarized in the following tables.

Pharmacokinetics Parameters in Selected Single Dose Studies (Cefepime NDA Summary)

Species	Rat	Rat	Rat	Rat	Dog	Monkey	Man ^a
Route	IV (15 min)	IV (bolus)	SC	IP	IV (6 min)	IV (5 min)	IV (30 min)
Dose (mg/kg)	87	89	100	500	100	100	57
No. of animals	5	6	6	6	4	3	7
Gender	M	M	M	3M, 3F	M	M	M
C _{MAX} ^b (µg/mL)							
T _{MAX} (h)							
AUC(INF) ^d (µg·h/mL)							
T-HALF (h)							
VDSS (L/kg)							
CLT (mL/min/kg)							
UR (% of dose)							
F (% of dose)							

Results expressed as Mean (±SD).

a = For assessment in man, dose, VDSS, and CLT normalized for 70 kg body weight.

b = C_{max} normalized to 100 mg/kg dose.

c = Value not determined.

d = CLT for dog normalized to 10 kg body weight.

e = UR in 6 rats given 40 mg/kg IV.

f = UR (0-6h) in 3 monkeys given 10 mg/kg.

g = F value calculated by comparison to IV study.

**Pharmacokinetics Parameters After a Single Dose of Cefepime
Cefepime NDA Summary**

Species:	Rat	Rat	Rat	Dog	Monkey	Man
Route:	IV Infusion (5 min)	SC	IP	IV Infusion (6 min)	IV Infusion (5 min)	IV Infusion (30 min)
Dose (mg/kg):	807	800	1000	100	600	29 ^a
n	5	6	5	4	3	12
C _{MAX} (µg/mL)						
AUC(INF) (µg·h/mL)						
T _{-HALF} (h)						
Maximum Dose in mg/kg/day in Toxicity Studies (Study Duration)						

^a 2000 mg dose normalized using an average body weight of 70 kg.

TOXICOLOGY:

Acute Toxicity Studies:

The manifestations of acute toxicity in mice, rats, dogs or monkeys were limited to brief periods post-cefepime injection. The estimated single lethal doses of cefepime are listed below.

**Estimated Lethality of Single Doses
Cefepime NDA Summary**

SPECIES	ROUTE	FORMULATION	DOSES (MG/KG)	ESTIMATED SINGLE MINIMUM OR MEDIAN* LETHAL DOSE (MG/KG)
Mouse	IV	/L-arg	1000-2000	>1500* ♂ & ♀
	IV	NaCl	2500-3500	>3500* ♂, >3000* ♀
Rat	IV	/L-arg	700-1500	1272* ♂, 1067* ♀
	IV	NaCl	400-1800	775-866* ♂ & ♀
	IV	Base	300-900	667-669* ♂ & ♀
	IM	NaCl	3000	>3000 ♂ & ♀
	IP	NaCl	3000	>3000 ♂ & ♀
	SC	NaCl	5000	>5000 ♂ & ♀
Rabbit	IV	NaCl	2000-2500	>2000 ♂ & ♀
Dog	IV	/L-arg	2000	>2000 ♂ & ♀
	IV	NaCl	2500	>2500 ♂ & ♀
Monkey	IV	NaCl	4000	>4000 ♂ & ♀
	IV	Base	4000	>4000 ♂ & ♀

The acute effects were as follows:

- RATS: Death a few minutes after intravenous injection
- DOGS: CNS manifestations including salivation, emesis, retching and tremors
- MONKEYS: CNS manifestations including dilated pupils
- RABBITS: Death post-treatment related to enterotoxemia

MEDICAL OFFICER'S COMMENTS:

For rats, the lethal intravenous bolus dose was significantly lower than for other species; lethal doses administered by slow intravenous infusion were comparable to other species. The dramatic cardiovascular effects seen in bolus administration of cefepime to rats prompted concern by the applicant and the Division during the Phase I period of development. It was because of this finding that the initial human pharmacokinetic study was conducted in a single patient with extensive cardiovascular monitoring. In retrospect, it appears that the cardiovascular effects seen in rats were species specific and rate related phenomena.

Chronic Toxicity Studies: The chronic (4 week, 12 week, and 26 week) toxicity studies are summarized below:

Dosages in 4, 12, and 26 Week Studies
Cefepime NDA Summary

SPECIES AND STUDY DURATION	ROUTE	FORMULATION	DAILY DOSES (MG/Kg)	MULTIPLE OF MAXIMUM RECOMMENDED HUMAN DOSE	
RAT: 4-Week	IV	Base	0, 100, 400, 800	0.7 - 5.3	
	IV	/L-arg	0, 100, 400, 800	0.7 - 5.3	
	IP	NaCl	0, 500, 1000, 1500	3.3 - 10.0	
	12-Week	SC	NaCl	0, 100, 500, 1000	0.7 - 7.0
		SC	/L-arg	0, 100, 500, 1000	0.7 - 7.0
	26-Week	SC	/L-arg	0, 100, 500, 1000	0.7 - 7.0
DOG: 4-Week	IV	/L-arg	0, 100, 300, 600	0.7 - 4.0	
	IV	/L-arg	0, 50, 300, 600	0.3 - 4.0	
	IN	/L-arg	0, 100	0.7	
	26-Week	IV	/L-arg	0, 50, 150, 450	0.3 - 3.0
		IV	/L-arg	0, 50, 150, 450	0.3 - 3.0
MONKEY: 4-Week	IV	Base	0, 100, 300, 600	0.7 - 4.0	
	IV	L-arg	0, 600	4.0	
	12-Week	IV	NaCl	0, 100, 300, 600	0.7 - 4.0

Deaths in Chronic Toxicity Studies:

- Rats:
 - 4 weeks: Death only after bolus injection
 - 12 weeks: Two deaths
 - 26 weeks: Four deaths
- Dogs:
 - 4 weeks: No deaths
 - 12 weeks: No deaths
 - 26 weeks: Two deaths (one due prothrombin deficiency & other not stated)
- Monkeys:
 - 4 weeks: No deaths
 - 12 weeks: One death (cause unknown)

MEDICAL OFFICER'S COMMENTS:

The denominators for the above studies were not given. In addition, information with regard to the mg/kg dosage administered was not given (except for the two dogs in the 26 week study) in the applicant's summary. Therefore, the reader is referred to the toxicology review by Dr. Mainigi for further detail.

The major pathological findings found in the repeated dose studies were related to the kidneys. Hematologic abnormalities were detected in dogs in studies of cefepime administration conducted for 26 weeks.

Pathological Changes (Renal):

TYPE:	ANIMAL:
-Increased Heterolysosomes in the Proximal Tubule	Rats, Dogs, Monkeys (>4 week treatment)
-Increased Kidney Weights	Rats (4 & 26 week studies)
-Increased Age Related Nephropathy	Rats (26 week study)
-Increased Urine Volumes	Dogs (one 4 week study)
-Casts, Increased Protein, & Increased Specific Gravity	Monkey (single study)

Pathological Changes (Hematological):

TYPE:	ANIMAL:
-Severe Anemia	Dogs (26 week study)
-Thrombocytopenia	Dogs (26 week study)
-Leukopenia	Dogs (26 week study)

The thrombocytopenia and leukopenia resolved in two weeks post-treatment; the anemia resolved in seven weeks. If treatment with cefepime resumed, the hematologic deficiencies re-appeared more rapidly than with their initial onset. Consistent findings of hemosiderosis and extramedullary hematopoiesis were demonstrated.

Two rats developed fibrosarcomas after chronic subcutaneous injection of cefepime. The applicant notes that "these are not believed to reflect direct tumorigenicity as similar neoplasms have been observed with long-term injections of glucose, sodium chloride, and other agents."

MEDICAL OFFICER'S COMMENTS:

Based on the findings in the animal toxicity studies, a careful safety assessment of cardiovascular, hematologic and renal parameters is required for all human clinical studies.

SPECIAL STUDIES:**Intramuscular Irritation:**

Minor effects were noted at the injection sites in rabbits.

Degradation and Metabolism:

There was initial concern for the potential toxicity of the major degradation product (N-methylpyrrolidine). However, NMP is rapidly converted to the non-toxic by-product, N-oxide.

Testicular Toxicity:

No testicular toxicity was noted in rats given 100 or 500 mg/kg/d for 6-19 days after birth.

Neonatal Toxicity:

The major findings noted in 4 week rat toxicity studies completed in neonates were 1) irritation at the injection site and 2) renal changes consistent with those seen in the adult rat studies.

Nephrotoxicity:

A comparison study between cephaloridine and cefepime was conducted in rabbits. A single, parenteral dose of cefepime at 1000 mg/kg was not nephrotoxic; a single dose of 100 mg/kg of cephaloridine did show evidence of renal toxicity.

Immunogenicity:

Both free cefepime and cefepime conjugated to heterologous proteins were weakly immunogenic in mice and guinea pigs.

***In vitro* Hemolysis:**

Human red blood cells did not hemolyze when tested *in vitro* with up to 250 mg/mL of cefepime.

Interaction between Cefepime/Venoprin (aspirin combined D,L-lysine):

As a result of an adverse event with Venoprin in Japan, a dog study was conducted to explore the interaction of cefepime and aspirin. No interaction was detected.

Pharmacodynamics:

The potential for cardiovascular and CNS effects were observed in anesthetized rats and dogs. No effects were noted in rats administered doses of up to 400 mg/kg or in dogs administered doses of up to 450 mg/kg. However, an intravenous bolus dose of 450 mg/kg of cefepime produced a transient decrease in blood pressure, heart rate and peripheral vascular resistance in dogs.

L-arginine toxicity:

Many pre-clinical studies included control animals treated with the L-arginine vehicle alone. In rats, the single lethal intravenous dose of L-arginine is estimated at > 1000 mg/kg. In rats, a single IV injection of 1100 mg/kg of L-arginine caused brief ataxia, decreased activity, and flushing of the extremities. In dogs, rapid IV administration of 430 mg/kg of L-arginine was associated with minimal toxicity (salivation, retching, emesis, and flushing of the extremities) of brief duration. No significant toxicity was seen in rats given > 700 mg/kg/day of L-arginine SC for 26 weeks. Dogs given L-arginine IV at > 300 mg/kg/day for 26-weeks had brief periods of flushing, salivation, and occasionally emesis or retching. Fertility studies in rats given 724 mg/kg of L-arginine and teratology studies in rabbits given 72 mg/kg of L-arginine demonstrated no adverse effects.

REPRODUCTION STUDIES:**Segment I Fertility Studies:**

At dosages as high as 1000 mg/kg SC, no adverse effects on fertility or reproductive performance were observed. Some reduced testicular weight was observed at the 100 mg/kg dosage in F1 males in one study, but this did not appear to affect reproductive performance. In a special study

to assess effects on testis, neonatal male rats treated with up to 1000 mg/kg/day of cefepime with arginine did not show any adverse effects on testes.

Segment II - Teratology:

Cefepime was administered to pregnant mice, rats, and rabbits during the major periods of organogenesis. No evidence of teratogenicity was detected in rats with either cefepime/NaCl or cefepime/L-arginine at doses up to 1000 mg/kg, with cefepime/NaCl in rabbits given up to 100 mg/kg, or in mice given up to 1200 mg/kg.

Segment III - Perinatal and Postnatal Assessment:

Cefepime was administered to dams at doses as high as 1000 mg/kg from day 16 of gestation through lactation; development or reproductive capacity was not affected. However, F1 pups weighed less at the 1000 mg/kg dosage regimen.

Genotoxicity Studies:

In vitro genotoxicity assays were conducted. All of the following were negative:

1. The Ames/Salmonella mutation assay
2. *E. coli* WP2uvrA reverse mutation assay
3. Chinese hamster ovary (CHO)/HGPRT mammalian cell gene mutation assay
4. DNA damage and repair study with cultured hepatocytes
5. Clastogenesis study with CHO fibroblasts (A clastogenesis study was positive in a primary human lymphocyte culture after a 20 hour exposure, but not after a 4 hour exposure.)
6. Sister chromatid exchange and chromosome aberration tests in non dividing lymphocytes

In vivo, mice treated with single doses of > 1000 mg/kg of cefepime exhibited no evidence of bone marrow genotoxicity.

MICROBIOLOGY:

The following is a synopsis of the applicant's data presented in Volume 1.1. For a detailed review of the microbiology, the reader is referred to the review by Dr. Pandu Soprey.

Mode of action:

Cefepime, like other cephalosporins, inhibits bacterial wall synthesis by binding to penicillin binding proteins (PBPs). Similar to the other broad spectrum cephalosporins, cefepime has the greatest affinity for PBP3. Its affinity for PBP2 appears to be greater than that of other drugs of this class.

The following tables with modal MIC values were taken from the applicant's summary volume.

MEDICAL OFFICER'S COMMENTS:

The tables provided by the applicant catalog the modal 50% MICs, the modal 90% MICs and the number of investigators who provided the information. However, it should be noted that the tables do not include the number of isolates that were examined to provide the respective MIC values.

Cefepime MICs for Gram-Negative Bacteria
Cefepime NDA Summary

Organism	# Invest- igators	Mode MIC (µg/mL)		Organism	# Invest- igators	Mode MIC (µg/mL)	
		50%	90%			50%	90%
<i>E. coli</i>	38	0.03	0.06	<i>P. putida</i>	5	1	8
<i>K. pneumoniae</i>	24	0.03	0.25	<i>P. testosteroni</i>	1	0.5	1
<i>K. oxytoca</i>	12	[0.03]	0.25	<i>P. pseudomallei</i>	1	4	8
<i>K. ozaenae</i>	1	0.13	0.25	<i>P. acidivorans</i>	4	32	64
<i>E. cloacae</i>	25	0.06	0.5	<i>P. stutzeri</i>	4	0.12	0.12
<i>E. aerogenes</i>	19	0.06	0.25	<i>P. paucimobilis</i>	1	8	-
<i>E. agglomerans</i>	8	0.03	0.25	<i>P. pickettii</i>	1	16	-
<i>E. sakazakii</i>	1	0.25	1	<i>X. maltophilia</i>	15	32	32
<i>S. marcescens</i>	26	0.13	1	<i>Alcaligenes spp.</i>	1	4	-
<i>S. liquefaciens</i>	4	0.06	[0.25]	<i>A. calcoaceticus</i>			
<i>C. freundii</i>	19	0.06	0.8	<i>var. anitratus</i>	12	4	15
<i>C. diversus</i>	8	0.03	0.03	<i>var. lwoffii</i>	5	0.8	8
<i>C. koseri</i>	1	0.03	0.06	<i>Achromobacter spp</i>	1	4	-
<i>C. amalonaticus</i>	1	≤0.13	0.5	<i>H. influenzae</i> ^c			
<i>P. mirabilis</i>	19	0.06	0.06	<i>combined P⁻, P⁺</i>	10	0.06	0.06
<i>P. vulgaris</i>	18	0.06	0.25	<i>P⁻</i>	5	≤0.008	0.06
<i>M. morgani</i>	20	0.015	0.13	<i>P⁺</i>	7	0.03	0.06
<i>P. penneri</i>	2	>0.06, 0.25	0.06, 0.06	<i>M. catarrhalis</i>			
<i>H. alvei</i>	4	0.03	[0.12]	<i>combined P⁻, P⁺</i>	5	0.13	0.5
<i>Kluyvera spp</i>	1	≤0.13	-	<i>P⁻</i>	1	0.13	0.5
<i>F. rettgeri</i>	10	[0.03]	0.5	<i>P⁺</i>	2	0.25	4
<i>P. stuartii</i>	11	0.06	0.25	<i>N. gonorrhoeae:</i>			
<i>P. alcalifaciens</i>	3	[0.03]	0.25	<i>combined P⁻, P⁺</i>	7	[0.008]	0.06
<i>Salmonella spp</i>	12	0.03	0.06	<i>P⁻</i>	4	≤0.008	≤0.008
<i>Shigella spp</i>	10	0.015	0.06	<i>P⁺</i>	5	≤0.008	0.015
<i>Aeromonas spp</i>	6	0.03	[0.13]	<i>N. meningitidis</i>	7	≤0.008	0.008

**Cefepime MICs for Gram-Negative Bacteria
Cefepime NDA Summary**

Organism	# Investigators	Mode MIC (µg/mL)		Organism	# Investigators	Mode MIC (µg/mL)	
		50%	90%			50%	90%
Vibrio spp	1	0.25	1	Capnocytophaga spp	2	≤0.03	0.06
Y. enterocolitica	6	[0.03]	[0.03]	G. vaginalis	1	0.06	0.25
Campylobacter spp	3	1	1	H. ducreyi	1	0.016	0.06
P. aeruginosa	47	2	8				
P. fluorescens	7	4	8				
P. cepacia	12	[8.0]	[64.0]				
P. acidovorans	4	[16.0]	[32]				

Median values are bracketed. P- = penicillinase negative; P+ = penicillinase positive; combined P-,P+ = not specified.
Investigators = Number of investigators from whom data were obtained for a given species.

**Cefepime MICs for Gram-Positive Bacteria
Cefepime NDA Summary**

Organism	# Investigators	Mode MIC (µg/mL)	
		50%	90%
<i>S. aureus</i> ^a			
P ⁻	6	2	2
P ⁺	6	2	2
NS	8	[2] ^b	[4] ^c
MR	15	8	128
unspecified	13	4	[8]
<i>S. epidermidis</i>	17	2	4
<i>S. haemolyticus</i>	2	>32	>32
<i>S. hominis</i>	2	3	6
<i>S. warneri</i>	1	2	-
<i>S. saprophyticus</i>	2	4	2, 32
<i>S. pyogenes</i>	12	≤0.015	0.03
<i>S. agalactiae</i>	10	0.06	0.06

	#	Mode MIC ($\mu\text{g/mL}$)	
Streptococcus, Groups C, F, G	6	0.03	0.12
Viridans streptococci	6	0.12	1
<i>S. pneumoniae</i>	15	0.03	(0.06] ^b
<i>S. bovis</i>	3	0.03	(0.12] ^b
<i>E. faecalis</i>	12	32	64
<i>E. faecium</i>	4	>120	>128
<i>E. avium</i>	1	8	-
<i>L. monocytogenes</i>	2	16	16,51
<i>M. tuberculosis</i>	1	2.8	39
<i>M. avium</i> complex	3	17	31
<i>Nocardia</i> spp.	1	64	≥ 64
^a P⁻ (penicillinase-negative), P⁺ (penicillinase-positive), MS (methicillin-sensitive), MR (methicillin-resistant), unspecified (methicillin and penicillinase status not specified). ^b Median MIC₅₀ values in brackets ^c Median MIC₉₀ values in brackets			

Cefepime MIC for Anaerobic Bacteria
Cefepime NDA Summary

Organism	# Investi- gators	Mode MIC (µg/mL)	
		50%	90%
B. fragilis	7	32	>128
B. bivius	1	32	128
B. melaninogenicus	1	8	16
B. thetaiotaomicron	1	256	>256
Bacteroides (oral spp) ^c	1	0.6	11.8
F. nucleatum	1	2	-
F. necrophorum	1	0.25	-
C. perfringens	2	0.1	0.5
C. difficile	2	128	128
Peptostreptococcus spp.	3	[1] ^a	[10] ^b
Veillonella spp.	1	2	-
Mobiluncus spp.	1	0.25	1

a Median MIC₅₀ value in brackets.
b Median MIC₉₀ value in brackets.
c Includes 1 B. bovis, 1 B. buccae, 1 B. gingivalis, 1 B. oris, 1 B. veroralis, 1 B. distans, 3 B. capillus, and 1 B. zooglyphiformans.

MEDICAL OFFICER'S COMMENTS:

Additional isolates providing relative MICs of comparative drugs was provided in the applicant's summary. However, the MICs for each individual drug were not provided. A relative value is generally not helpful. To state that ceftazidime has an MIC four times higher than cefepime may have little meaning if the two MIC values were .04 µg/mL and .01 µg/mL, respectively.

By examination of the *in vitro* data, cefepime appears to be a broad spectrum anti-infective drug. *In vitro*, it has moderate gram positive, good gram negative and minimal anaerobic activity.

In the proposed label, the applicant has suggested the following breakpoints based on (a) a standardized single 30 mcg cefepime disk and (b) standardized dilution methods:

<u>Zone Size (mm)</u>	<u>Interpretation</u>	<u>MIC (mcg/mL)</u>	<u>Interpretation</u>
≥ 18	(s) Susceptible	≤ 8	(s) Susceptible
15-17	(i) Intermediate	16	(i) Intermediate
≤ 14	(r) Resistant	≥ 32	(r) Resistant

Animal Infection Models:

The applicant conducted several *in vivo* studies with immunocompetent and immunocompromised mice. In models of infections with meningitis, endocarditis, respiratory tract, urinary tract, thigh muscle, endophthalmitis, bacteremia, the applicant concludes that cefepime performed as well as, if not better than other broad spectrum cephalosporins.

MEDICAL OFFICER'S COMMENTS:

The details of the studies (the number of animals tested, the dosages administered, the comparative drugs, etc.) were not provided in the summary volume. For a more detailed analysis, the reader is referred to Dr. Mainigi's review.

Bactericidal Activity:

Bactericidal activity was measured by time-kill analysis and minimum bactericidal concentrations. The bacteria tested included *S. aureus*, *S. epidermidis*, *P. aeruginosa*, *E. coli*, *E. cloacae*, *C. freundii*, *K. pneumoniae*, *S. marcescens*, and *Acinetobacter* species. By either method, bactericidal activity was either at concentrations less than or twice that of the MIC.

Interaction with Other Antibiotics:

Fractional inhibition coefficient methods and time-kill analyses were applied to assess synergy between cefepime and other antibiotics. Cefepime and aminoglycosides may be synergic against some Gram-negative bacteria; however, this has not been rigorously tested. Antagonism was seen between cefepime and imipenem/polymyxin B.

Post-Antibiotic Effect (PAE):

The PAE were dose-dependent for *E. coli*, *K. pneumoniae*, *S. marcescens*, *E. cloacae*, *S. aureus*, and *S. epidermidis*, but not for *P. aeruginosa*. The PAE intervals of cefepime were 50% to 100% longer than those for ceftazidime when tested for *E. coli*, *E. cloacae*, and *S. aureus*. At the peak concentrations ($\approx 65 \mu\text{g/mL}$), PAE intervals ranged between 0.5 and 5 hours for the gram negative organisms tested. The PAE intervals ranged between 1.4 and 4.4 hours for the staphylococci.

Activity Against Multi-Resistant Bacteria:

Cefepime was active against bacteria that were resistant to other broad spectrum cephalosporins (See table below). A majority of the strains that were resistant had high levels of chromosomal β -lactamase.

Susceptibility of Bacteria Resistant to Other Cephalosporins
Cefepime NDA Summary

Organism	# Strains Tested	Number of strains resistant to: ^a					
		FEP	CAZ	CTX	CRO	CPZ	HR
<i>Enterobacter spp</i>	19	0	10	10			0
<i>E. cloacae</i>	4	0	4				
	30	0	30	30	27	28	
<i>E. aerogenes</i>	2	0	2				
	17	0	16	13	2	17	
<i>C. freundii</i>	4	0	4				
	9	0	9	7	6	8	
<i>M. morgani</i>	2	0	0				
	7	0	1	0			0
<i>S. marcescens</i>	29	0	1	2			1
<i>Klebsiella spp</i>	3	0	1	1			0
<i>E. coli</i>	2	0	1	1			0
<i>Enterobacteriaceae</i>	33	0 ^b		33 ^b		33 ^b	
<i>P. aeruginosa</i>	4	1	2				
	32	6	17	30		28	
	24	15	4	24			21
	173	45	39	147			
	41	9 ^b		41 ^b		41 ^b	
<i>Pseudomonas spp</i>	8	4	8				8
	3	1	1	3			2
	34	5		34			10
<i>Acinetobacter spp</i>	3	1	0	1			2
	14	3 ^b	14			14 ^b	
<i>Staphylococcus aureus</i>	17	2 ^b		17 ^b		17 ^b	
<i>Coagulase-Negative Staphylococcus</i>	19	0 ^b		19 ^b		19 ^b	

^a MIC breakpoint for resistance: cefepime (FEP) ≥ 32 µg/mL; ceftazidime (CAZ) 32 µg/mL; cefotaxime (CTX) 64 µg/mL; ceftriaxone (CRO) 64 µg/mL; cefoperazone (CPZ) 64 µg/mL; ceftiprone (HR) 32 µg/mL.

^b Study used MIC breakpoint for resistance: FEP ≥ 16 µg/mL; CTX ≥ 32 µg/mL; CPZ ≥ 32 µg/mL.

Development of Resistance:

The potential for cefepime selecting spontaneous, single step, stable drug resistant mutant bacteria was low when tested against *P. aeruginosa*; the selection rate was from 10^{-2} to 10^{-6} lower relative to other cephalosporins.

Mutants of *P. aeruginosa* with resistance to cefepime were obtained by serial passage; however, more passages were required than with cefotaxime, ceftazidime, or ceftiprome.

The development of drug resistance in mice treated for peritonitis caused by *E. cloacae*, *S. marcescens*, and *P. aeruginosa* was consistent with that found *in vitro*.

BIOPHARMACEUTICS:

The following is a synopsis of the applicant's summary presented in Volume 1.1. For a detailed review of clinical biopharmaceutics, the reader is referred to the review by Dr. Eric Ette.

The pharmacokinetics, excretion, and metabolism of cefepime after intravenous (IV) administration have been studied in single- and multiple-dose studies of healthy volunteers. Studies in patients with renal or hepatic insufficiency, in elderly subjects, in patients with cystic fibrosis and in healthy women were conducted. An *in vivo* assessment of the secretion of cefepime in milk and of the interaction of cefepime and amikacin were completed.

The pharmacokinetics of cefepime administered by intramuscular (IM) administration were also studied.

The penetration of cefepime into various tissues/fluids including blister fluid, appendix, gallbladder, prostate, bronchial mucosa, bile, peritoneal fluid, and sputum were investigated.

The following table is a list of the pharmacokinetic studies conducted with cefepime.

List of Cefepime Clinical Pharmacokinetic Protocols
Cefepime NDA Summary

Study Number	Title	Cefepime PK Subjects	Total PK Subjects
411-050-001	A Phase I Single-Dose Study of the Safety, Tolerance, Plasma Profile and Excretion Characteristics of BMY-28142	1	1
411-056-001	A Phase I Single-Dose Comparative Study of the Safety, Tolerance, Plasma Profile and Excretion Characteristics of BMY-28142 and Ceftazidime	39	40
411-058-001	A Multi-Dose Human Safety and Pharmacokinetic Study of BMY-28142	35	47
411-063-001	A Multi-Dose Human Safety and Pharmacokinetic Study of BMY-28142 (1 g Q8h)	15	22
411-064-001	A Multi-Dose Human Safety and Tolerance Study of BMY-28142	6	9

411-073-001 (07A1A-001-001)	Pharmacokinetics of Cefepime (BMY-28142) in Subjects with Renal Insufficiency ¹	27	27
411-077-001	Disposition of ¹⁴ C-Cefepime (BMY-28142) in Normal and Renally Impaired Subjects	8	8
411-079-001	A Comparison of the Tolerance of Healthy Male Volunteers to IM Cefepime (BMY-28142) Formulations and to IM Ceftriaxone	20	20
411-082-001	An Evaluation of the Pharmacokinetics and Tissue Penetration of a Single Dose of Cefepime (BMY-28142) in Healthy Male Volunteers	6	6
411-083 Clinical Trial	A Comparative Study of Cefepime (500 mg BID) Versus Ceftazidime (500 mg BID) in the Treatment of Patients with Urinary Tract Infections	1	1
411-085-001	An Evaluation of the Level of Penetration of Cefepime (2 g IV) into the Bronchial Mucosa of Volunteers	20	20
411-086-001	A Randomized, Single-Dose, Cross-Over, Drug Safety and Pharmacokinetic Study of Two Formulations of Cefepime (BMY-28142)	12	12
411-090-001	A Multi-Dose Human Safety and Pharmacokinetic Study of Cefepime (BMY-28142) Dihydrochloride/Arginine (2 grams Q8h)	7	10
411-093-002	Pharmacokinetics of Cefepime (BMY-28142) in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis	10	10
411-096-001	Safety, Tolerance, and Pharmacokinetic Evaluation of Cefepime Following Single and Multiple Intramuscular Doses to Normal Male Volunteers	31	34
411-097 Clinical Trial	A Multi-investigator Comparative Study of Cefepime and Ceftazidime in the Treatment of Serious Bacterial Infections	3	3
411-1J4-001	Pharmacokinetics and Fecal Flora Study: 1 g of Cefepime BID in Volunteers -- A Double-Blinded, Placebo-Controlled Study	8	12
411-109-001	The Pharmacokinetics of a Single IV Dose of Cefepime (BMY-28142) in Young and Elderly, Male and Female Normal Volunteers	48	48
411-111 Clinical Trial	A Multi-investigator Comparative Study of Cefepime and Ceftazidime in the Treatment of Serious Bacterial Infections (European)	10	10
411-112-001	Pharmacokinetics of Cefepime in Normal and Hepatically Impaired Male Subjects	23	23
411-113 Clinical Trial	A Study Comparing Intramuscular Cefepime Dihydrochloride Arginine and Ceftazidime in the Treatment of Patients with	40	60
411-117-001	Pharmacokinetics of a One-Gram Intravenous Infusion of Cefepime Dihydrochloride Arginine in Subjects with Varying Renal Status	23	23
411-119 Clinical Trial	A Comparative Study of Cefepime/Metronidazole and Gentamicin/Clindamycin in the Management of		

¹ Twenty-seven subjects in this study received 36 courses of cefepime.

	39	45
411-120-016 Clinical Trial	A Randomized Study Comparing the Efficacy and Safety of Cefepime Versus the Combination of Gentamicin and Mezlocillin for Treatment of Patients with Suspected Biliary Tract Infections Undergoing Surgery ²	
	16	16
411-127-001	A Comparison of the Serum and Blister Fluid Pharmacokinetics and Bactericidal Activity of a Single IV Dose of Cefepime, Ceftazidime, and Cefoperazone in Healthy Male Volunteers	
	6	7
411-128-001	A Single-Dose, Safety, Tolerance and Pharmacokinetic Study of Cefepime in Pediatric Patients	
	9	9
411-129 Clinical Trial	A Non-comparative Study of the Safety, Efficacy and Pharmacokinetics of Cefepime in Pediatric Patients with Serious Bacterial Infections	
	13	15
411-130-001	A Multi-Dose Human Safety and Pharmacokinetic Study of Cefepime (BMY-28142) Dihydrochloride/Arginine (4 grams Q8h)	
	9	12
411-135 Clinical Trial	A Non-comparative Study of Cefepime in the Management of Bacterial Endocarditis Including Patients Who Are Intravenous Drug Abusers	
	3	3
411-140 Clinical Trial	A Study of Cefepime in the Treatment of Serious Bacterial Infections Particularly Those Caused by Staphylococci, <u>Pseudomonas</u> , and Other Less Common Gram-Negative Bacilli	
	2	2
411-151-001	Penetration of Cefepime (BMY-28142) into Human Breast Milk; A Pharmacokinetic Study	
	10	10
411-153-001	An Evaluation of the Level of Penetration of 2 Grams Cefepime into Prostate Tissue of Patients Undergoing Elective Prostatectomy	
	44	44
411-154-001	Pharmacokinetic Interaction Between Cefepime (BMY-28142) and Amikacin (Amikin [®]) in Normal, Healthy, Male Volunteers	
	16	16
411-155-001	A Safety and Dose Proportionality Study of Cefepime in Normal, Healthy, Male Volunteers	
	13	13
411-163-001	Pharmacokinetics of Cefepime After Administration of a Single Intravenous Dose to Normal and Cystic Fibrosis Volunteers	
	24	24

NOTE: A total of 597 individuals received at least one dose of cefepime in these studies. Of the 597 subjects, one subject received two additional single doses and seven received one additional single dose each. Each additional dose was written up on a new case report form and was counted as though it was for a new subject; therefore, data are reported for 606 subjects. The subjects who received extra doses were in Study 07A1A-001 (Study 411-073), in which the pharmacokinetics of cefepime was studied in subjects with renal insufficiency.

MEDICAL OFFICER'S COMMENTS:

The following statements are derived from the synopsis provided by the applicant in the summary volume (1.1).

² A non-random selection of patients in these two clinical studies had fluid and tissue samples obtained for pharmacokinetic analyses.

Intravenous administration of cefepime was accomplished by 30 minute, constant rate infusions. Single and repeated IV administration of 250 to 2000 mg doses of cefepime to normal, healthy volunteers demonstrated linear, dose-proportional pharmacokinetics. Accumulation after the administration of multiple doses (Q8h or Q12h) for up to 10 days was less than 13%. Cefepime had a T-HALF of about 2 h. Steady-state volume of distribution (VDSS) ranged from approximately 15 to 20 L and was stable with respect to dosage level. (See tables that follow this discussion).

Absorption of cefepime was rapid and essentially complete after IM administration. Over a dosage range from 250 mg to 2000 mg IM, peak plasma levels (C_{MAX}) were about half those observed when the same dose was administered by 30-minute constant rate IV infusion. C_{MAX} values and area under the plasma-concentration vs time curve, extrapolated to infinity, increased in a dose-proportional manner. The plasma elimination half-life (T-HALF) was about 2-2.5 h and independent of dose. The absolute bioavailability of cefepime after IM administration was 100%, based on estimates from both plasma level and urinary excretion data. Accumulation of less than three percent resulted from multiple IM dosing (Q12h) for 10 days in normal volunteers.

In early clinical studies, the cefepime was administered intravenously. The bioequivalency of this formulation and the formulation intended for marketing (the mixture of cefepime dihydrochloride and L-arginine) was evaluated. A 2000 mg dose of cefepime in each formulation was administered by 30 minute, constant rate IV infusion. The formulations are considered bioequivalent, based upon statistical analyses of the plasma pharmacokinetic parameters and urinary excretion data. The data suggest that the systemic exposure to both formulations (cefepime and cefepime dihydrochloride/L-arginine) of cefepime was virtually identical.

MEDICAL OFFICER'S COMMENTS:

The above studies demonstrate the pharmacokinetic equivalence of the two formulations administered intravenously. However, a similar equivalence was not demonstrated for the two formulations when administered intramuscularly.

The major route of elimination of the parent drug was by renal excretion. Clearance was on the order of magnitude of 130 mL/min. In healthy subjects, the renal clearance was between 75-92% (slightly less than creatinine clearance). Most of administered cefepime was recovered in the urine as unchanged drug. The mechanism of elimination appears to be glomerular filtration, with negligible tubular secretion.

Cefepime is not extensively metabolized in humans. In a study of cefepime labelled with ^{14}C , 96% of the administered radiolabel was recovered in the urine of subjects with normal renal function. The proportions of the recovery were as follows: 87.9% as cefepime, < 1% as N-methylpyrrolidine (NMP), 6.8% as the N-oxide of N-methylpyrrolidine (NMP-N-oxide) and 2.5% as the 7-epimer of cefepime.

The mean T-HALF of cefepime was somewhat longer (3 hours vs 2 hours) in the elderly after a single 1000 mg IV dose. The magnitude of difference between the elderly and younger volunteers is of the order of magnitude that dosage adjustment in the elderly is not warranted.

Renal insufficiency directly affected clearance of cefepime. T-HALF was inversely proportional to creatinine clearance. Patients with a renal clearance of less than 10 mL/min had a T-HALF of 13 hours. Steady state volume of distribution (VDSS) was not affected by renal impairment. Cefepime clearance was directly correlated with creatinine clearance and therefore forms the basis of the dosage

adjustment nomogram. Hemodialysis results in a T-HALF of 2.3 hours, similar to the T-HALF of normal healthy subjects. Clearance in patients undergoing continuous ambulatory peritoneal dialysis is about 10% of individuals with normal renal function. Q48 hour dosing is recommended in all CAPD patients.

Pharmacokinetic parameters in patients with hepatic insufficiency were similar to those observed in normal volunteers. Dosage adjustment is not required in these patients.

The clearance of a single 2000 mg dose of cefepime was significantly greater in patients with cystic fibrosis than in normal volunteers. There was no significant change in the volume of distribution. Cystic fibrosis patients administered 50 mg/kg IV of cefepime q8H had steady state pharmacokinetic parameters comparable to those administered after a single dose. The serum concentration exceeded the MIC₉₀ for most of the critical pathogens. The applicant concluded that it was "not necessary to alter the dose or frequency of cefepime administration in patients with cystic fibrosis."

MEDICAL OFFICER'S COMMENTS:

The usual dosing regimen for cefepime is q12 hours. The dosing interval for the cystic fibrosis study was every eight hours. Also, the clearance of cefepime is increased in cystic fibrosis patients. It is, therefore, unclear how the applicant concludes that dosage adjustment is not required in patients with cystic fibrosis.

Pharmacokinetic parameters in normal volunteers and the special populations are illustrated in the following tables.

**Summary of Cefepime Pharmacokinetic Parameters in Healthy Volunteers
Cefepime NDA Summary**

Study No.	IV Dose ^a (mg)	Number & Sex of Subjects	Parameter Means (S.D.)							
			C _{MAX} (µg/mL)	MRT(IV) ¹ (h)	T-HALF (h)	AUC ^b (h·µg/mL)	CLT ^b (mL/min)	CLR ^b (mL/min)	VOSS (L)	UR ^j (%)
A1411-058-001	82.5 Single dose	4 M								
	125 " "	4 M								
	250 " "	4 M								
	500 " "	4 M								
	1000 " "	4 M								
	2000 " "	4 M								
	2000 - 3 min IV infusion	4 M								
	2000 - 5 min " "	4 M								
	2000 - 10 min " "	4 M								
	2000 - 15 min " "	3 M								
A1411-058-001	250 (Day 1)	8 M								
	250 TID (Day 1) ^c	8 M								
	500 (Day 1)	17 M								
	500 TID (Day 1) ^c	9 M								
	1000 (Day 1)	7 M								
	1000 BID (Day 1) ^d	7 M								
A1411-063-001	1000 (Day 1)	7 M								
	1000 TID (Day 1) ^c	7 M								
	2000 (Day 1)	7 M								
	2000 TID (Day 1) ^c	6 M								

Summary of Cefepime Pharmacokinetic Parameters in Healthy Volunteers
Cefepime NDA Summary

Parameter Means (S.D.)

Study No	IV Dose ^a (mg)	Number & Sex of Subjects	C _{MAX} (µg/mL)	MRT(IV) ^f (h)	T-1/2 ^g (h)	AUC ^b (h·µg/mL)	CLT ^h (mL/min)	CL ^h (mL/min)	VDSS (L)	UR ⁱ (%)
A1411-185-001	250 Single dose	9 M								
	500 "	9 M								
	1000 "	9 M								
	2000 "	9 M								
A1411-090-001	2000 IV (Day 1)	7 M								
	2000 IV, TID (Day 11)	7 M								
	4000 IV (Day 1)	7 M								
A1411-090-001	250 IM Single dose	6 M								
	500 IM "	6 M								
	1000 IM "	6 M								
	1000 IM, BID (Day 12)	6 M								
A1411-151-001	2000 IM Single dose	12 M								
	2000 IV "	12 M								
A1411-151-001	1000 Single dose	9 F								

^f MRT = Mean Residence Time
^g CLT = Total Body Clearance
^h CLR = Renal Clearance
ⁱ UR = Urinary Recovery.

^a 30 min constant rate infusion.
^b Represents AUC(0-∞) for single dose and first dose of multiple dose studies, and AUC(0-T) for last dose of multiple dose studies.
^c Parameters are for last day of TID dosing; AUC is for 0-6h period; UR is for 0-6h period.
^d Parameters are for last day of BID dosing; AUC is for 0-12h period; UR is for 0-12h period.
^e MRT(IV)

Summary of Cefepime Pharmacokinetics Parameters in Special Populations
Cefepime NDA Summary

Study No	IV Dose (mg)	Number & Sex of Subjects	Parameter Means (S.D.)							
			C _{MAX} (µg/mL)	MRT(INF) (h)	T _{1/2} (h)	AUC(INF) (h·µg/mL)	CLT (mL/min)	CLR (mL/min)	VDSS (L)	UR (%)
A1411-109-001 Age and Gender	1000 Single dose	12 M ^a								
	1000 " "	12 M ^b								
	1000 " "	12 F ^c								
	1000 " "	12 F ^d								
07A1A-001-001 Renal Impairment	1000 Single dose	5 M ^e								
	1000 " "	5 M ^f								
	1000 " "	5 M ^g								
	1000 " "	5 M ^h								
	1000 " "	5 M ⁱ								
A1411-077-001 C-14 ADME in Normal & Renal Impairment	1000 Single dose	4 M ^o								
	1000 " "	4 M ^j								
A1411-093-002 CAPD	1000 Single dose	5 M ^k								
	2000 " "	5 M ^k								
A1411-112-001 Hepatic Impairment	1000 Single dose	11 M ^m								
	1000 " "	11 M ⁿ								

^a Age range 20-40 yrs (av. 30)

^b Age range 65+ (av. 67)

^c Age range 20-40 yrs (av. 33)

^d Age range 65+ (av. 69)

^e Creatinine Clearance = > 90 mL/min

^f Creatinine Clearance = 61-90 mL/min

^g Creatinine Clearance = 31-60 mL/min

^h Creatinine Clearance = 11-30 mL/min

ⁱ Creatinine Clearance = < 10 mL/min

^j Creatinine Clearance = 7-47 mL/min

^k Creatinine Clearance in 3 CAPD patients was negligible

^l The mean (S.D.) clearance of cefepime by CAPD was 3.9(0.6) and 4.4(0.7) mL/min for the 1000 mg and 2000 mg doses, respectively

^m Normal control subjects

ⁿ Subjects with hepatic impairment (verified by biopsy)

Other *in vivo* Studies:

Pharmacokinetic parameters are not altered in patients who were administered cefepime and amikacin simultaneously.

The results of tissue and body fluid sampling confirm that cefepime is primarily distributed in the extracellular fluid space. The tissue/body fluid elimination T-HALF approximated the plasma T-HALF of approximately two hours.

Cefepime excretion into breast milk was negligible.

The effect of cefepime on the intestinal microflora was examined in a placebo-controlled study in normal volunteers who received 1000 mg cefepime IV twice a day for 8 days. A slight decrease in the number of *Bifidobacteria* and *E. coli* in feces was noted in the cefepime group whereas the number of bacteroides and Clostridia increased. Cefepime treatment did not alter the number of yeast, gram-positive cocci or other enterobacteria in the feces.

The following table illustrates the concentration data for various tissues and body fluids.

Mean (SD) Concentrations of Cefepime in Various Body Fluids and Tissues
Cefepime NDJ. Summary

Tissue or Fluid	Dose/Route	Number of Patients	Mean (SD) Hours Post-Dose of Sample Collection	Conc. in Tissue (µg/g) or Fluid (µg/mL)	Conc. in Plasma (µg/mL)
Urine	500 mg IV	8	0-4 (0)	297 (101)	4.9 (1.0)*
	1 g IV	12	0-4 (0)	926 (559)	10.5 (2.0)*
	2 g IV	12	0-4 (0)	3120 (2014)	20.1 (3.6)*
Bile	2 g IV	20	9.4 (4.7)	17.8 (15.9)	14.7 (23.1)
Peritoneal Fluid	2 g IV	19	4.4 (3.4)	18.3 (25.0)	24.8 (24.4)
Blister Fluid	2 g IV	6	1.5 (0)	81.4 (24.5)	72.5 (20.0)
Bronchial Mucosa	2 g IV	20	4.8 (4.4)	24.1 (17.8)	40.4 (28.1)**
Appendix	2 g IV	31	5.7 (3.7)	5.2 (6.2)	17.8 (22.8)
Gallbladder	2 g IV	38	8.9 (4.6)	11.9 (22.6)	16.7 (28.6)
Prostate	2 g IV	5	1 (0)	31.5 (6.8)	61.2 (8.7)**
		4	12 (0)	6.8 (9.2)	5.4 (2.4)
Sputum	50 mg/kg IV	5	4 (0)	7.4 (5.7)	32.4 (14.2)

* Mean plasma concentration at 4 h post dose.

** Serum

Serum Protein Binding:

In studies employing ¹⁴C-cefepime labeled in the aminothiazole moiety, binding ranged from 0% to 7%.

In a study using an agar diffusion microbiologic assay, cefepime bound to approximately 19% of human serum proteins, at a serum concentration of 25 $\mu\text{g}/\text{mL}$. In another study, using an HPLC/UV assay, binding of drug to protein in human serum was estimated to be 14% to 19% within a concentration range of $\mu\text{g}/\text{mL}$. The negligible binding of cefepime should preclude drug-drug interactions due to displacement of drugs bound to serum protein. The *in vitro* binding of NMP and NMP-N-oxide to human serum proteins was negligible (<5%).

Summary:

The studies demonstrate that cefepime exhibits linear pharmacokinetics over a dosage range of 250 mg to 2000 mg. The major route of elimination of the parent drug is glomerular filtration. Total and renal clearance of cefepime is directly proportional to creatinine clearance; dosage adjustments are required for individuals with renal impairment. No adjustments are required for the elderly, the hepatically impaired or the cystic fibrosis patient.

CLINICAL STUDIES:

The following table lists all clinical studies conducted with cefepime. The number of enrolled and applicant evaluable patients are also noted.

SUMMARY OF ENROLLMENT IN CLINICAL EFFICACY TRIALS
Cefepime NDA Summary

Location/Protocol No. (Type)	Indication Treatment	Number (%) of Patients		Location of Report in Clinical Sect.
		Enrolled	Evaluable	
NA 411-061 (Non-comparative)	UTI, SSTI, (Cefepime)	594	265 (45)	V. 1.154-1.168 starting on page 08-21145
EU 411-067 (Non-comparative, Low Dose)	UTI, SSTI (Cefepime)	239	111 (46)	V. 1.170-1.176 starting on page 08-26932
EU 411-067 (Non-comparative, High Dose)	UTI, SSTI, (Cefepime)	156	33 (21)	V. 1.177-1.181 starting on page 08-29689
NA 411-070 (Comparative, Blinded)	Cefepime Ceftazidime	65 34	35 (54) 17 (50)	V. 1.143-1.146 starting on page 08-17671
NA 411-070 (Comparative, Non-blinded)	Cefepime Ceftazidime	225 111	103 (46) 49 (44)	V. 1.129-1.137 starting on page 08-12060
EU 411-070 (Comparative, Non-blinded)	Cefepime Ceftazidime	97 49	20 (21) 19 (39)	V. 1.138-1.142 starting on page 08-15707
NA 411-071 (Comparative, Non-blinded)	UTI Cefepime Ceftazidime	32 16	19 (59) 10 (63)	V. 1.111-1.113 starting on page 08-5376
NA 411-075 (Comparative, Non-blinded)	SSTI Cefepime Ceftazidime	104 50	38 (37) 20 (40)	V. 1.98-1.010 starting on page 08-397
NA 411-081 (Comparative, Non-blinded)	SSTI Cefepime Ceftazidime	199 100	94 (47) 37 (37)	V. 1.102-1.108 starting on page 08-1863
EU 411-081 (Comparative, Non-blinded)	SSTI Cefepime Ceftazidime	32 15	5 (16) 6 (40)	V. 1.109-1.110 starting on page 08-4529
NA 411-083 (Comparative, Non-blinded)	UTI Cefepime Ceftazidime	246 125	118 (48) 62 (50)	V. 1.114-1.121 starting on page 08-6272
EU 411-083 (Comparative, Non-blinded)	UTI Cefepime Ceftazidime	59 36	23 (39) 16 (44)	V. 1.122-1.125 starting on page 08-9364
NA 411-097 (Comparative, Blinded)	UTI, SSTI, Cefepime Ceftazidime	104 103	39 (33) 37 (36)	V. 1.210-1.215 starting on page 08-42009

SUMMARY OF ENROLLMENT IN CLINICAL EFFICACY TRIALS
Cefepime NDA Summary

Location/Protocol No. (Type)	Indication Treatment	Number (%) of Patients		Location of Report in Clinical Sect.
		Enrolled	Evaluable	
NA 411-097 (Comparative, Non-blinded)	, UTI, SSTI, Cefepime Ceftazidime	439	182 (41)	V. 1.182-1.206 starting on page 08-31497
		443	184 (42)	
NA 411-097-027 (Comparative, Non-blinded) **	UTI, SSTI, Cefepime Ceftazidime	84	**	V. 1.207-1.209 starting on page 08-41119
		76		
EU 411-106 (Comparative, Non-blinded, Low Dose)	Cefepime Cefotaxime	12	6 (50)	V. 1.149-1.150 starting on page 08-19759
		6	2 (33)	
EU 411-106 (Comparative, Non-blinded, High Dose)	Cefepime Cefotaxime	41	16 (39)	V. 1.151-1.153 starting on page 08-20206
		21	7 (33)	
NA 411-108 (Comparative, Blinded)	UTI Cefepime Ceftazidime	39	29 (74)	V. 1.126-1.128 starting on page 08-10939
		41	18 (44)	
EU 411-110 (Non-comparative) **	UTI Cefepime	15	**	V. 1.169 starting on page 08-26600
EU 411-111 (Comparative, Non-blinded)	UTI, SSTI, Cefepime Ceftazidime	173	44 (25)	V. 1.216-1.224 starting on page 08-44388
		175	51 (29)	
EU 411-113 (Comparative, ** Non-blinded)	Cefepime Ceftazidime	112	**	V. 1.147-1.148 starting on page 08-19063
EU 411-115 (Non-comparative)	Cefepime	37	12 (32)	V. 1.237 starting on page 08-52801
NAI 411-118 (Comparative, Non-blinded)	F/N Cefepime/ Piperacillin/ Gentamicin	50	*	V. 1.256-1.259 starting on page 08-60292
		46	*	
NA 411-119 (Comparative, Non-blinded)	Cefepime/ Metronidazole Gentamicin/ Clindamycin	114	34 (30)	V. 1.239-1.243 starting on page 08-53745
		93	43 (46)	
NA 411-120 (Comparative, Non-blinded)	Cefepime Gentamicin/ Mezlocillin	241	31 (13)	V. 1.244-1.250 starting on page 08-55557
		121	13 (11)	

SUMMARY OF ENROLLMENT IN CLINICAL EFFICACY TRIALS
Cefepime MDA Summary

Location/Protocol No. (Type)	Indication Treatment	Number (%) of Patients		Location of Report in Clinical Sect.
		Enrolled	Evaluate	
NA 411-121 (Comparative, Non-blinded) **	Cefepime Cefotaxime	159 72	** 96 (60) 36 (50)	V. 1.251-1.255 starting on page 08-58212
NA1 411-123 (Comparative, Non-blinded) **	Cefepime Cefuroxime	19 8	**	V. 1.270 starting on page 08-64970
NA1 411-126 (Comparative, Non-blinded) **	Cefepime Cefotaxime	2 2	**	V. 1.270 starting on page 08-65047
NA1 411-129 (Non-comparative, Non-blinded) **	Cefepime	65	**	V. 1.270 starting on page 08-65194
NA1 411-131 (Comparative, Non-blinded)	F/N Cefepime Ceftazidime	22 25	* *	V. 1.260-1.263 starting on page 08-61775
NA1 411-132 (Comparative, Non-blinded) **	Cefepime Ceftriaxone Ceftazidime	23 7 3	**	V. 1.271 starting on page 08-65377
NA1 411-134 (Non-comparative) **	Cefepime	85	**	V. 1.271 starting on page 08-65490
NA 411-135 (Non-comparative) **	Cefepime	17	**	V. 1.238 starting on page 08-53296
NA1 411-137 (Comparative, Non-blinded) **	F/N Cefepime Mez(ocillin/ Gentamicin	13 15	**	V. 1.264 starting on page 08-63221
NA 411-140 (Non-comparative)	UTI, SSTI, Cefepime	321	116 (36)	V. 1.225-1.235 starting on page 08-48172
NA 411-140-D21 (Non-** comparative)	UTI, SSTI Cefepime	50	**	V. 1.236 starting on page 08-52365
EU 411-143 (Non-comparative)	F/N Cefepime	84	*	V. 1.265-1.269 starting on page 08-63332
EU1 411-146 (Non-comparative) **	Cefepime/ Amikacin	38	**	V. 1.272 starting on page 08-65626

SUMMARY OF ENROLLMENT IN CLINICAL EFFICACY TRIALS
Cefepime NDA Summary

Location/Protocol No. (Type)	Indication Treatment	Number (%) of Patients		Location of Report in Clinical Sect.
		Enrolled	Evaluable	
NA1 411-157 (Comparative, Non-blinded) **	(Pediatric Pts.) Cefepime Cefotaxime	1 2	**	V. 1.271 starting on page 08-65302
EU 411-158 (Non-comparative) **	F/N Cefepime	11	**	V. 1.273 starting on page 08-66078
NA1 411-999 (Non-comparative) ** (Compassionate Use)	Serious or Life-threatening Inf. Cefepime	4	**	V. 1.273 starting on page 08-66301
Summary of Enrollment				
NA Cefepime	-	3317	1271 (38)	-
NA Comparatives	-	1493	597 (40)	-
EU Cefepime	-	1126	354 (32)	-
EU Comparatives	-	359	101 (28)	-
Total Cefepime	-	4423	1625 (37)	-
Total Comparatives	-	1852	598 (32)	-

* An Intent-To-Treat Analysis was performed for all febrile episodes.
 ** No efficacy claims are based on this study at this time; safety data are presented for this study.
 † At cut-off date for this submission this was an ongoing study; all other studies were complete.

Medical Officer's Review of New Drug Application

Applicant: Bristol-Myers Squibb Company
Wallingford, CT 06492

Submitted: June 30, 1992
Received by Agency: July 1, 1992
Received by Medical Officer: July 29, 1993
First Draft Submitted: October 29, 1993
Review Completed: February 17, 1994

Material Reviewed:

This review contains the safety and efficacy data generated in seven studies of patients with infections of the skin and soft tissues (SSTI). The studies reviewed were 411-061, -067, -075, -081, -097, -111, -140. The remaining indications were reviewed by Dr. Linda Sherman of the Division of Anti-Infective Drug Products and are included under a separate cover.

COMMENT: Studies submitted in support of this new drug application were designed in a manner such that patients with multiple infections (e.g. pneumonia, and UTI) could be evaluable for each indication. Therefore, patients appearing in this review may also appear in Dr. Sherman's review of other indications.

Section I - GENERAL INFORMATION

Generic Drug Name: Cefepime

Trade Name Requested: MAXIPIME®

Manufacturer's Identifier: BMY-28142

Chemical Name: Pyrrolidinium, 1-[[7-[[[(2-amino-4-thiazolyl(methoxyimino)acetyl]-amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methy-chloride, monohydrochloride, monohydrate, [6R-[6 α , 7 β (Z)]]

Structural Formula:

Molecular Formula: C₁₈H₂₂N₄O₅S₂•Cl•HCl•H₂O.

Molecular Weight: 571.5

Route of Administration: Parenteral

Dosage Form: 500 mg, 1g, and 2g Vials

COMMENT: Maxipime® is supplied as a sterile dry mixture of cefepime hydrochloride and L-arginine. The L-arginine, at an approximate concentration of 725 mg/g of cefepime, is added to control the pH of the reconstituted solution.

Pharmacologic Category:

Cefepime is a parenterally administered semisynthetic cephalosporin. According to the applicant, cefepime has the following unique characteristics: The in-vitro activity of cefepime against methicillin-sensitive staphylococci was four-fold greater than the activity of ceftazidime, yet, the in-vitro potency of cefepime against *Pseudomonas aeruginosa* was comparable to ceftazidime. In addition, cefepime has increased potency against *Enterobacter* when compared with other cephalosporins. The sponsor claims that when *P. aeruginosa* and *Enterobacter* were exposed to cefepime, ceftazidime and ceftriaxone in-vitro, cefepime-resistance was selected at a lower rate than was ceftriaxone-resistance or ceftazidime resistance.

Section I.2 - APPROVAL STATUS

At the time the NDA was submitted, cefepime had not been approved for sale in any country. Applications have been filed in France, Japan and Belgium.

Section I.3 - PROPOSED LABELLING

The applicant proposes the following text concerning infections of the skin and soft tissues for inclusion in the approved product labelling for cefepime hydrochloride.

INDICATIONS AND USAGE

Skin and Skin Structure Infections caused by *Staphylococcus aureus* (methicillin-susceptible strains), *Streptococcus pyogenes* (Group A streptococci), *Streptococcus agalactiae* (Group B streptococci), other β -hemolytic *Streptococcus* species, *Pseudomonas aeruginosa*, *Enterobacter* species, *Klebsiella* species, *Proteaeae* (including *Proteus mirabilis* and *Morganella morganii*), *Escherichia coli*, *Serratia marcescens* and *Acinetobacter calcoaceticus*.

DOSAGE AND ADMINISTRATION

The usual adult dosage and route of administration is 1 g administered intravenously or intramuscularly every 12 hours. However, the dosage and route vary according to the susceptibility of the causative organisms, the severity of the infection and the condition and renal function of the patients. Guidelines for dosage of MAXIPIME® are provided in the following table. The usual duration of therapy is 7-10 days; however, more severe infections may require longer treatment.

Table SSTI.1
Recommended Dosage Schedule for MAXIPIME®

Site and Type of Infection	Dose	Frequency
Mild to moderate urinary tract infections (uncomplicated and complicated)	500 mg 1 g IV/IM	q 12h
Mild to moderate infections including pneumonia and skin and skin-structure infections.	1 g IV or IM	q 12h
Severe infections including pneumonia, urinary tract infections, skin and skin-structure infections.	2 g IV	q 12h
Very severe or life-threatening infections including especially in immunocompromised patients.	2 g IV	q 8h

Section II - MANUFACTURING AND CONTROLS

The reader is referred to the microbiologist's manufacturing and controls review.

The drug substance is manufactured by Bristol-Myers Squibb at its facilities in Syracuse, New York and Latina, Italy:

Bristol Myers Squibb Co.
Bio/Chem Division
315 N. Thompson Road
P.O. Box 4755
Syracuse, New York 13221-4755

Bristol-Myers Squibb S.p.A.
Bio/Chem Division
Sermoneta
Latina, Italy

Further processing, packaging and labeling is performed at the Bristol-Myers Squibb facilities in Latina, Italy and Barceloneta Puerto Rico:

Bristol-Myers Barceloneta, Inc.
Bio/Chem Division
Carr No. 2 Km 45.4
P.O. Box 657
Barceloneta, Puerto Rico 00617

Section III - PHARMACOLOGY

The reader is referred to the pharmacologist's review and to the NDA review of non-SSTI indications conducted by Dr. L. Sherman.

Section III.1 - PHARMACOKINETICS

The reader is referred to the pharmacokineticist's review and to the NDA review of non-SSTI indications conducted by Dr. L. Sherman.

The following table summarizes the result of tissue penetration studies after intravenous administration of cefepime. Serum and blister fluid concentrations of cefepime observed after an intravenous dose of 2 g is presented.

Table - SSTI.2
Mean Concentration of Cefepime in Blister Fluid and Plasma

Tissue	Dose	Number of Patients	Sample Collection Time (hrs)	Blister Fluid Concentration ($\mu\text{g/mL}$)	Plasma Concn. ($\mu\text{g/mL}$)
Blister Fluid	2 g	6	1.5	24.5	72.5

Section IV - MICROBIOLOGY

The reader is referred to the microbiologist's review and to the NDA review of Non-SSTI indications conducted by Dr. L. Sherman.

The applicant has proposed the following guidelines to be used in interpretation of the zones of inhibition produced by a 30 mcg cefepime disk.

Table - SSTI.3
Interpretation of Zones of Inhibition

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible
15 - 17	Intermediate
≤ 14	Resistant

Table SSTI.4, on the following page, summarizes the applicant's data of modal MIC values for Gram-negative and Gram-positive pathogens commonly encountered in infections of the skin and skin structures.

COMMENT: After a 2 gram intravenous dose, the modal MIC_{90} is exceeded in both plasma and blister fluid for most of the commonly encountered pathogens. The modal MIC_{90} is not exceeded for *Enterococcus* species or for methicillin resistant *S. aureus*.

Table - SSTI.4
Cefepime MIC for Gram-Positive and Gram-Negative Bacteria
(BMS Table)

Organism	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)
Gram Negative		
<i>E. coli</i>	0.03	0.06
<i>K. pneumoniae</i>	0.03	0.25
<i>K. oxytoca</i>	0.03	0.25
<i>K. ozaenae</i>	0.13	0.25
<i>E. cloacae</i>	0.06	0.5
<i>E. aerogenes</i>	0.06	0.25
<i>E. agglomerans</i>	0.03	0.25
<i>E. sakazakii</i>	0.25	1.00
<i>S. marcescens</i>	0.13	1.00
<i>S. liquefaciens</i>	0.06	0.25
<i>C. freundii</i>	0.06	0.8
<i>C. diversus</i>	0.03	0.03
<i>C. koseri</i>	0.03	0.06
<i>C. amalonaticus</i>	<0.13	0.5
<i>P. mirabilis</i>	0.06	0.06
<i>P. vulgaris</i>	0.06	0.25
<i>M. morgani</i>	0.015	0.13
<i>P. penneri</i>	0.25	0.05
<i>H. alvei</i>	0.03	0.12
<i>Kluyvera spp.</i>	<0.13	-
<i>P. rettgeri</i>	0.03	0.50
<i>P. stuartii</i>	0.06	0.25
<i>Salmonella spp.</i>	0.03	0.06
<i>Shigella spp.</i>	0.015	0.06
<i>Aeromonas spp.</i>	0.03	0.13
<i>Vibrio spp.</i>	0.25	1.00
<i>Y. enterocolitica</i>	0.03	0.03
<i>P. aeruginosa</i>	2	8
<i>P. fluorescens</i>	2	8
<i>P. cepacia</i>	8	64
<i>P. acidovorans</i>	16	32
<i>P. putida</i>	1.00	1.00
<i>P. testosteronei</i>	0.5	1.00
<i>P. pseudomallei</i>	4	8
<i>P. acidivorans</i>	32	64
<i>P. stutzeri</i>	0.12	0.12
<i>P. paucimobilis</i>	8	-
<i>P. pickettii</i>	16	-
<i>X. maltophilia</i>	32	32
Gram-Positive		
<i>S. aureus</i>		
MS	2	4
MR	8	128
<i>S. epidermidis</i>	2	4
<i>S. haemolyticus</i>	>32	>32
<i>S. hominis</i>	2	2
<i>S. warneri</i>	2	-
<i>S. saprophyticus</i>	4	32
<i>S. pyogenes</i>	<0.015	0.03
<i>S. agalactiae</i>	0.06	0.06
Streptococcus, Group C,F,G	0.03	0.12
Viridans Streptococci	0.12	1
<i>S. pneumoniae</i>	0.03	0.06
<i>S. bovis</i>	0.03	0.12
<i>E. faecalis</i>	32	64
<i>E. faecium</i>	>128	>128
<i>E. avium</i>	8	-
<i>L. monocytogenes</i>	16	16, 51

Section V - CLINICAL STUDIES

The applicant is seeking approval for the treatment of skin and skin structure infections caused by a variety of pathogens (see proposed labelling on page-4). The applicant proposes that a dose of 1 gram every 12 hours be used for mild to moderate infection. The applicant proposes that a dose of 2 grams every 12 hours be used for severe infections.

In support of their application, 1331 patients with SSTI were enrolled in the clinical trials of cefepime. Of the 1331 patients, 1185 (cefepime=851, ceftazidime=334) were submitted to substantiate the applicant's claims of safety and efficacy for cefepime. Because technical difficulties, the remaining 146 patients were submitted only in support of the claim for safety of cefepime. An additional 40 patients with SSTI were studied in clinical trials designed to evaluate other indications, these patients are included in the safety analysis only.

Section V.1 - Experimental Protocols

Clinical trials designed to demonstrate the safety and efficacy of cefepime were conducted in both the United States and Europe. The various clinical trials essentially shared a common protocol. The major differences between the clinical trials involved the severity of disease studied and the dose of test and control drug employed.

The following section will describe those elements common to all SSTI protocols submitted in support of this new drug application. Variations from the common protocol will be noted in the specific review of individual studies.

Section V.1.1 - Investigational Plan

Design Overview: In general most SSTI studies were open, randomized, comparative clinical trials.

Inclusion Criteria: Males or females 18 years of age or older could be enrolled. Prospective female patients were required to have a negative pregnancy test or to practice effective contraception. Prospective patients were required to have symptoms consistent with skin or soft tissue infection (e.g., cellulitis, pyoderma, furuncle, abscess, or post-operative wound infection likely to be caused by a pathogen susceptible to both cefepime and ceftazidime. Prospective patients were required to give written informed consent.

Medical Officer's Comments: Cellulitis, pyoderma, furuncle, abscess or post-operative wound infection were not defined in the protocol. The diagnosis of each patient was left to the discretion of the individual investigator.

Exclusion Criteria: Prospective patients were excluded if they reported history of a serious hypersensitivity reaction to penicillins or cephalosporins. Patients with impairment in hepatic or renal function; previous enrollment in a cefepime study; infection that was likely to require long-term antimicrobial therapy; granulocytopenia; pregnancy; or a medically significant disorder that could influence the results of the study were also excluded.

Specific to the indication, patients with SSTI associated with atopic/allergic dermatitis; severe burns; or decubitus ulcers were excluded.

Procedures and Observations:

Pre-Therapy Procedures: (To be performed 48 hours before the start of treatment)

1. Medical History and Physical Exam.
2. Evaluation of signs and symptoms of SSTI. Investigators were asked to assess the following signs and symptoms of SSTI: fever, chills, inflammation, tenderness in affected area, warmth in affected area, erythema, induration, edema, fluid accumulation, abscess, skin ulceration, drainage, exudate, foul smelling, pustule, lymphangitis, lymphadenopathy, lesion, and pruritus. Signs and symptoms were recorded as present or absent.

Medical Officer's Comments: There was no attempt made to make a quantitative or qualitative assessment of clinical signs and symptoms.

3. Bacteriologic confirmation of SSTI. A sterile swab was to be obtained from open skin areas. Abscesses, vesicles, cellulitis or closed wounds were to be aspirated with a sterile needle.
4. Recovered pathogens were to be tested for susceptibility to both cefepime and ceftazidime.
5. A panel of laboratory safety tests were to be performed.

Treatment Group Assignment:

Patients in comparative studies were assigned to cefepime or ceftazidime in accordance with a randomization schedule provided by BMS. Dose regimen and duration of therapy varied between studies and is discussed in detail in the individual study reports. Except were noted both investigator and patient were aware of the treatment group assignment. *where 2/2/89*

During Treatment Procedures (The following procedures were to be conducted on days 2-6).

1. Physical exam with assessment of clinical signs and symptoms of SSTI was to be performed at least once and whenever clinically indicated.
2. If available, an appropriate specimen was to be obtained for culture. If, because of improvement, appropriate material was not available for culture the investigator could report "NO SOURCE TO CULTURE".
3. The panel of standard clinical laboratory tests were to be repeated.

Medical Officer's Comment: Non-drug therapy that was indicated for the patient's condition (e.g., incision and drainage, debridement, etc.) were permitted at the discretion of the investigator. The performance of all such procedures were to be recorded on the case report form.

Post-Treatment Procedures:

The procedures outlined below were to be carried out on day 1-14 for patients enrolled before June 1, 1988. Patients who enrolled after June 1, 1988, were to have post-treatment assessments on days 5 to 14.

Medical Officer's Comments: The change in follow-up period from 1 to 14 days to 5 to 14 days resulted from discussions between the applicant and the FDA. The follow-up period of 5 to 14 days for patients with SSTI was agreed upon by both parties and submitted to the IND as submission #046, General Correspondence, on April 13, 1989.

1. A physical exam and a clinical assessment of signs and symptoms of SSTI was

- to be performed.
2. A culture was to be taken if the specimen source remained. If, because of improvement, there was no material available for culture the investigator could report "NO SOURCE TO CULTURE".
 1. The panel of standard laboratory tests were to be repeated.

Table SSTI.5 summarizes the procedures and observations that were performed during the study.

Table SSTI.5
Procedures and Observations
(BMS Table)

Procedure	Within 48 hrs Pre- treatment	Days 2-6 During treatment	Days 1-14 Post- treatment
Eligibility Criteria	X	-	-
Informed Consent	X	-	-
Medical History	X	-	-
Physical Examination	X	X ^a	X
Clinical Evaluation	X	X	X ^b
Bacteriologic Tests ^c	X	X	X
Laboratory Tests	X	X	X

a Abbreviated examination to assess clinical signs and symptoms.

b After Amendment 2, the post-treatment clinical assessment was to be performed on days 5-14 for those patients who had not previously been considered failures.

c Bacteriologic tests include culture, subculture, and susceptibility tests.

Section V.1.2 - Criteria for Evaluability

According to the Applicant, the following criteria were used to determine if a patient was evaluable for the determination of efficacy.

1. An SSTI was diagnosed clinically and confirmed by a pre-treatment culture within 48 hours of the start of study medication.
2. The causative pathogen was tested for susceptibility and found to be susceptible to both cefepime and ceftazidime.
3. A culture was performed on post-treatment days 1-14 (or no source to culture was documented on the case report form (CRF)).
4. A clinical assessment was performed within 1-14 days post-treatment for those patients enrolled prior to June 1, 1988 or within 5-14 days post-treatment for those patients enrolled after June 1, 1988.
5. Patients who used the following topical antimicrobials were considered evaluable: betadine soap, phisohex soap, betadine scrub, soaps containing iodine or oxidizing agents for normal wound cleaning, and betadine or chlorpactin in a whirlpool. Patients who used xeroform or iodoform dressing one time or one day in the during or post-treatment period were also considered evaluable.
6. Patients who used xeroform or iodoform dressing more than one time or patients who used betadine soak, betadine packing, silvadine cream, or chlorpactin dressing at any time prior to the post-treatment evaluation were considered not evaluable.
7. A minimum of 7 doses of cefepime or 11 doses of ceftazidime were administered.
8. Patients who were considered clinical or microbiologic failures and who had

at least one reason for exclusion from the efficacy analysis if the failure preceded the reason for exclusion.

Medical Officer's Comments: The medical officer used different criteria from the applicant to determine evaluability.

Appropriate microbiologic documentation of an SSTI is notoriously difficult to obtain. Cultures from infected skin sites are often contaminated with normal skin flora. In addition, chronic skin conditions (such as vascular insufficiency ulcers and chronic dermatitis) may be colonized by potentially pathogenic microbiota. In consideration of the known difficulties in obtaining adequate microbiologic specimens for SSTI, the Division of Anti-Infective Drug Products (DAIDP), in the "Points to Consider" document allows for the existence of a clinically evaluable population as well as a clinically and microbiologically evaluable sub-population in trials designed to demonstrate the safety and effectiveness of drugs for SSTI.

In the review of this indication, the medical officer, therefore, has adopted an approach which allows independent assessments of a patient's clinical and microbiologic evaluability. This approach allowed the medical officer to capture important clinical data from patients who were excluded by the applicant for problems with the microbiologic diagnosis (such as the failure to perform appropriate cultures at appropriate times). In addition, this approach allowed the medical officer to be selective in the microbiologic data which was included without sacrificing clinical information.

Thus, the medical officer created two evaluable populations. One population was clinically evaluable only. One population was both clinically and microbiologically evaluable, which was referred to as the "fully evaluable" population by the medical officer.

The following criteria were used by the medical officer to define a clinically evaluable patient:

1. An SSTI was diagnosed clinically by the presence of at least three signs and/or symptoms specifically associated with SSTI. The medical officer defined "signs and/or symptoms specifically associated with SSTI" from among those signs and/or symptoms which the applicant asked the investigators to observe and record on the case report form (CRF). Those signs/symptoms included: inflammation, tenderness, warmth, erythema, induration, edema, drainage, foul smell, lymphangitis and lymphadenopathy. Diagnoses such as "ulcer, pustule, and abscess" were not considered signs/symptoms of disease. In addition, because patients enrolled in protocols for this NDA were allowed to have multiple simultaneous infections, the medical officer did not consider systemic indicators of inflammation, such as fever, leukocytosis, etc. to be evidence of evaluability for SSTI.
2. A clinical assessment was performed within 5 to 14 days post-treatment. Although the applicant considered patients in whom the post-therapy assessment was performed on days 1-4 evaluable the medical officer considered these patients to be not evaluable. The medical officer feels that some time must elapse between the cessation of antimicrobial therapy and the assessment of efficacy. A period of time must be allotted for drug to be eliminated from the patients' system (cefepime serum half-life = 2 hours, 5 elimination half-lives = 10 hours), and, time must be allowed for the re-development of signs and symptoms of

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infection in patients whose bacterial population was suppressed but not eradicated by the study therapy. The time required for the re-development of symptoms will vary depending on the infecting organism and the type of infection. Also, potential post-antibiotic effect must be considered. Therefore, the medical officer considered patients whose post-treatment assessment were performed prior to 5 days after the completion of therapy, regardless of the date of enrollment, to be not evaluable.

3. A minimum of 4 days of drug therapy was required before a patient could be judged to have a satisfactory clinical outcome, however, patients could be considered to be clinical failures if they had received at least 2 full days of study drug therapy.
4. The medical officer concurred with the applicant's guidelines for evaluability regarding topical antimicrobial use.

The following criteria were used by the medical officer to define a fully evaluable patient:

1. A fully evaluable patient must meet all the above mentioned criteria for clinical evaluability.
2. Because the recovery of pathogens from polymicrobial infections can be influenced by pre-treatment with antimicrobials even though clinical signs/symptoms of disease are still present, no antimicrobial agent could be administered within 24 hours of the pre-treatment culture.
3. A pre-treatment culture was performed by appropriate technique within 48 hours of enrollment. A needle aspirate, performed in a sterile fashion, was always considered an acceptable technique. Swab cultures of exudate from acutely infected areas were also considered acceptable. Swab cultures of exudate from chronic lesions (such as ulcers, dermatitis, etc) were never considered acceptable.
4. A pathogenic bacteria was recovered. In the majority of cases, the recovery of coagulase negative staphylococci, *Corynebacterium* species and diptheroids represent the normal flora of the skin. Therefore the medical officer considered patients in whom only these organisms were recovered to be not-evaluable.
5. Susceptibility testing must be performed and the pathogen must be susceptible to both the test and study drugs.
6. A post-treatment culture was performed from 5 to 14 days after the completion of therapy, or, "no source to culture" was documented on the CRF.

Section V.1.3 - Efficacy Outcome Definitions

Clinical Response: According to the applicant, each patient was assessed by the investigator and assigned a clinical response category at the post-treatment assessment. Clinical response categories were as follows:

Satisfactory: All signs and symptoms of the infection that were present prior to therapy were improved or resolved, and no new signs or symptoms of the infection were present at the post-treatment follow-up.

Unsatisfactory: One or more signs or symptoms of the infection persisted or worsened, or one or more new signs or symptoms of the infection were evident at the post-treatment follow-up; or after 72 hours of therapy, the patient was designated a clinical failure.

Undetermined: All cases where a response could not be determined (e.g., no follow-up evaluation).

Medical Officer's Comments: The medical officer also assigned a clinical response at the 5-14 day post-treatment evaluation. Response categories used by the M.O. were as follows:

Cure: The complete resolution of all major signs and symptoms used to initially document the infection. No new signs or symptoms of infection could have developed either during or after treatment.

Failure: The persistence of any major signs or symptoms of SSTI or the development of any new signs or symptoms of SSTI.

n.b.: A response of failure could be assigned after 48 hours on therapy if the patient was removed from the study for the persistence or worsening of symptoms.

A response category of indeterminate is not necessary, since by the medical officer's definitions any patients who can not be assigned a clinical response would not be considered evaluable.

Microbiologic Response: According to the applicant, cultures obtained both during- and post-treatment were to be used to assess the Bacteriologic Response. Each pathogen was to be assigned a response as follows:

Eradicated: The pathogen was not present in the post-treatment culture; or, there was no suitable specimen source.

Persisted: The continued presence of the pathogen in the post-treatment culture; or the continued presence of the pathogen in the during-treatment culture and the patient was removed from therapy.

Undetermined: The response could not be evaluated; for example, because the follow-up SSTI or blood culture was not obtained.

Medical Officer's Comments: According to the medical officer, Evaluable patients could be assigned a microbiologic outcome indicating failure at any time after receiving 48 hours of the study drugs. The microbiologic outcome of eradication could only be assigned at the post-therapy evaluation. The medical officer used the following response categories to describe the microbiologic outcome:

Eradication: At the post-treatment assessment, the causative organism was not recovered from a culture of the involved area; or sufficient clinical resolution had occurred such that there was no material/site available for culture.

Documented Failure/Persistence: The causative organism was recovered from a post-treatment culture or the causative organism was recovered from a during treatment culture and the patient was placed on alternative antimicrobial therapy.

Documented Failure/New Infection: A new organism, known to cause the clinical syndrome present in the patient, was recovered from the post-treatment culture and signs and/or symptoms of SSTI continued to be present in the patient; or a new organism was recovered from a during-therapy culture and the patient was started on an alternative antimicrobial therapy.

Presumptive Failure: The patient had continued signs and/or symptoms of

SSTI at the post-therapy evaluation, however, no organisms could be recovered from culture; or the patient was placed on alternative anti-microbial therapy at any time after the first 48 hours of study drug therapy for the persistence or worsening of signs and/or symptoms and no organism was recovered from culture or a culture is not performed.

Indeterminate: The microbiologic response could not be assessed for any reason

n.b.: In reporting the outcome of their SSTI trials, the sponsor differentiated between patients with "documented eradication" (i.e. that a culture was performed post-therapy and was sterile) and "presumptive eradication" (i.e. that there was no site available to culture) Given that the clinical outcome in SSTI is of paramount important, the medical officer does not see the relevance of this distinction and combined all those patients with eradication into one category.

Section V.1.4 - Safety Assessment

During administration of the drug, investigators were to observe their patients closely for any evidence of systemic or local adverse response. Investigators were asked to grade the adverse event as mild, moderate or severe and to assess the relationship of the adverse event to the study therapy. Investigators were asked to monitor for any evidence of intolerance at the infusion or injection site.

Laboratory tests for which results were abnormal were to be repeated at appropriate intervals until the values returned to normal.

Section V.1.5 - Concomitant Therapy

With the exception of antimicrobial agents, there was no restriction on the use of concomitant medication. Concomitant antimicrobial therapy was permitted provided the agent used had no known activity against the genus of organism involved in the original infection.

Section V.1.6 - Early Discontinuation

Early discontinuation of the study drug was allowed for the following conditions:

1. No pathogen isolated from pretreatment culture.
2. The pathogen isolated was not susceptible to cefepime or ceftazidime.
3. A poor clinical response was evident after 72 hours of therapy.
4. A serious or alarming adverse event occurred.
5. The patient developed an intercurrent illness.
6. The patient requested withdrawal from the study.
7. The investigator decided it was in the best interest of the patient to withdraw from the study.
8. Administrative reasons.

Section V.1.7 - Statistical Analysis

Group Comparability: Appropriate two-sample procedures were used to compare the treatment groups with respect to demography, presenting condition, concomitant medications and relevant medical history.

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Efficacy: The primary efficacy analysis consisted of the ~~the~~ comparison of the clinical and microbiologic response seen in the two treatment groups as defined

previously.

Safety: The incidence of adverse clinical events (ACE) and evidence of local intolerance at the infusion type was compared between the two treatment groups.

Laboratory data were evaluated by comparing during- and post-treatment values with laboratory normal ranges and with pretreatment values. If a patient's pretreatment test value was normal, then that patient's during- and post-treatment results were examined to detect any changes to levels outside the normal range in the direction of toxicity. A patient's most severe during- or post-treatment value was taken for this analysis. Additionally, test results of patients who had abnormal pretreatment values were compared with during- and post-treatment values to detect any further worsening of the result that might be due to study therapy.

Section V.2 - Efficacy Results**Section V.2.1 - The Comparative Trials**

The safety and efficacy of cefepime was studied in four comparative trials. In study #075, cefepime was studied at a dose of 0.5 grams every 12 hours. In study #081, cefepime was studied at a dose of 1 gram every 12 hours. In studies #097 and 111 cefepime was studied at a dose of 2 grams every 12 hours. Drug was administered by the intravenous route in most cases, however, a small minority of patients received drug by the intramuscular route.

Medical Officer's Comments: In the following sections, the individual studies submitted to support this indication are reviewed. Most studies used the criteria, definitions and procedures described above. Differences between individual protocols and the common protocol will be described in highlighted text.

Section V.2.1.1 - 0.5 grams every 12 hours.**North American Protocol #075:**

Protocol Description: Study #075 was an open, randomized (2:1 cefepime:ceftazidime), comparative, North American study. The protocol used the common inclusion and exclusion criteria described previously. The study used the common pre-, during-, and post-treatment procedures described previously. Cefepime was administered at a dose of 500 mg every 12 hours. Cefazidime was administered at a dose of 500 mg every 8 hours. Evaluability criteria and efficacy outcome definitions described previously for the common protocol were employed.

Enrollment: Patients were enrolled in study #075 between April 8, 1988 and January 14, 1990 at 5 centers within the United States. Table 075.1 lists the principal investigator, the location of the study center and the enrollment at each of the five study centers.

Table 075.1
Enrollment by Study Center
(Table Provided by the Applicant)

Center	Principal Investigator*	Location	Number of Patients	
			Cefepime	Ceftazidime
001	R. Geckler	Baltimore, MD	77	37
002	G. Plotkin	Wilkes-Barre, PA	5	3
003	W. Mogabgab	New Orleans, LA	12	5
008	C. Hanna	Spartanburg, SC	9	5
013	D. Gremillion	Raleigh, NC	1	0
Total			104	50

Evaluability

Evaluability was determined by the applicant and the medical officer according to predetermined criteria previously described. Table 075.2 summarizes the evaluability at each study center according to both the applicant and the medical officer.

Table 075.2
Evaluability

Center	Enrollment		BMS Evaluable ¹		M.O. Clinically Evaluable ¹		M.O. Fully Eval. ¹	
	Cefep.	Ceftaz.	Cefep.	Ceftaz.	Cefep.	Ceftaz.	Cefep.	Ceftaz.
001	77	37	21 (58)	13 (65)	22 (63)	10 (67)	14 (52)	10 (67)
002	5	3	5 (13)	3 (15)	5 (14)	3 (20)	5 (19)	3 (20)
003	12	5	5 (13)	3 (15)	4 (11)	1 (7)	4 (15)	1 (7)
008	9	5	5 (13)	1 (5)	4 (11)	1 (7)	4 (15)	1 (7)
013	1	0	1 (3)	0	0	0	0	0
Total	104²	50²	37	20	35	15	27	15

1- Number in parenthesis are percent of total patients evaluable.

2- In reality, 105 patient numbers were assigned in the cefepime treatment group and 51 patients numbers were assigned in the ceftazidime treatment group. Two patients were enrolled twice, with different patient numbers assigned for each enrollment. Only the first enrollment of each patient was evaluated by the applicant and the medical officer.

Medical Officer's Comments: All principal investigators have M.D. degrees. None of the principal investigators are listed in the Division of Scientific Investigations (DSI) list of restricted investigators.

Medical Officer's Comments: The majority of patients in both the sponsor's and the medical officer's evaluable populations were enrolled at center #001. This high relative enrollment at one study center casts doubt on the multi-center nature of this trial.

Exclusions from the Efficacy Analysis: The most common reason for which the applicant considered patients not-evaluable, in both treatment groups, was the exposure to non-study antimicrobial drugs.

Table 075.3 presents the reasons for which patients were considered not-evaluable for the efficacy analysis by the medical officer. Unlike the applicant, the most common reason for which the medical officer excluded patients from the efficacy analysis was the premature termination of therapy (Please see table 075.4 for reasons for premature termination of therapy). There were no significant differences between the two treatment groups in the rate of exclusion for any reason.

Table 075.3
Reasons for Exclusion from the Analysis of Efficacy
(M.O. Table)

Reason for Exclusion	# Excluded (Percent)	
	Cefepime	Ceftazidime
Exclusions from The Clinically Evaluable Population		
Incomplete treatment	32 (46)	15 (41)
Other antimicrobial administered	21 (31)	10 (29)
Fatal Protocol Violation ¹	2 (3)	2 (6)
Insufficient Follow-Up	10 (15)	6 (18)
Mild Infection	4 (6)	2 (6)
Total Excluded	69	35
Exclusions from The Fully Evaluable Population		
No Pathogen Isolated	1 (12)	0
Inadequate Culture ²	1 (12)	0
Resistant Organism	0	0
No Susceptibility Testing	1 (12)	0
Inappropriate Pathogen Isolated	2 (25)	0
Antimicrob. < 24 hours Pre-Enroll	3 (39)	0
Total Excluded	8	0

1-Incorrect diagnosis for protocol

2-Swab of infected ulcer

Differences in Evaluability Between the Applicant and the M.O.: Nine patients in the cefepime treatment group who were considered not evaluable by the applicant were considered evaluable by the medical officer. The reasons the medical officer considered these patients evaluable were as follows: exposure to non-study antimicrobials for the persistence or worsening of symptoms(5), susceptibility testing not required for clinical efficacy(2), isolation of a susceptible organism not required for clinical efficacy(1), and a pre-treatment culture is not required for clinical efficacy(1).

Eleven patients in the cefepime group who were considered evaluable by the applicant were considered not evaluable by the medical officer. The reasons the medical officer considered these patients not evaluable were: inadequate follow-up(1), less than 8 doses of cefepime given(5), mild infection(3), topical antimicrobial given(1), and premature discontinuation(1).

Five patients in the ceftazidime treatment group who were considered evaluable by the applicant were considered not evaluable by the medical officer. The reasons for which the medical officer considered these patients not evaluable were as follows: oral antimicrobial given pre-post therapy visit(1), less than

12 doses of ceftazidime given(1), mild infection(2) and diagnosis not appropriate for protocol (patient had concurrent osteomyelitis(1)).

Medical Officer's Comments: The evaluability of 20/104 patients (19%) in the cefepime treatment group was changed by the medical officer, in contrast, the evaluability of 5/50 patients (10%) in the ceftazidime treatment group was changed by the medical officer. The reason for this disparity is unclear.

Patient Disposition:

Table 075.4 describes the eventual disposition of each enrolled patient. Most patients in both treatment groups completed therapy. For patients removed from therapy prematurely, the reason given by the investigators for the early discontinuation are listed. The reader will note that 8/104 patients in the cefepime treatment group were removed from therapy because the therapy was thought to be ineffective while no patients in the ceftazidime group were removed from therapy for ineffective treatment.

Table 075.4
Termination of Therapy
(Table Generated from M.O. Analysis)

Outcome Reason	# of Enrolled Patients (Percent)	
	Cefepime	Ceftazidime
Patients Enrolled	104	50
Therapy Completed	64 (61)	35 (70)
Therapy Discontinued Early	40 (39)	15 (30)
No Pathogen/Resistant Pathogen	14 (14)	7 (10)
Treatment Ineffective	8 (8)	0
Adverse Reaction	1 (1)	1 (2)
Physician's Decision ¹	10 (10)	2 (10)
Patient's Decision ²	4 (4)	3 (6)
Error ³	3 (3)	2 (4)

- 1- Includes: "I.V. treatment no longer necessary"; "affected area amputated"; and "lack of IV access".
- 2- Includes: left against medical advice.
- 3- Includes: no susceptibility testing performed; and incorrect diagnosis for protocol.

Medical Officer's Comments: The premature discontinuation of therapy did not, a-priori, result in a patient who was not-evaluable. Patients who were removed from therapy early because of ineffective treatment were considered evaluable failures if they received greater than or equal to 2 full days of therapy prior to their removal.

Population Demographics: The majority of patient in both treatment groups were Black males. The mean age and weight in both treatment groups was comparable. Table 075.5 summarizes the demographic data of the enrolled population.

Table 075.5
Demographic Characteristics of the Enrolled Population
(Table Generated by BMS)

Characteristic	Cefepime	Ceftazidime	p-value
N	104	50	
Sex: N (%)			0.556
Female	45 (43)	19 (38)	
Male	59 (57)	31 (62)	
Race: N (%)			0.357
Black	65 (63)	27 (54)	
White	39 (38)	23 (46)	
Age Distribution: N (%)			
18-24 years	15 (14)	4 (8)	
25-44 years	42 (40)	20 (40)	
45-64 years	27 (26)	16 (32)	
65-84 years	20 (19)	9 (18)	
85 years	0	1 (2)	
Age: (years)			0.568
Mean	45.1	46.7	
Median	42	45	
S.D.	18.5	17.4	
Minimum	19	22	
Maximum	83	85	
Weight: (kg) ^a			0.661
Mean	78.33	78.86	
Median	77.1	74.8	
S.D.	19.78	22.57	
Minimum	33.6	47.6	
Maximum	138.8	178.3	
Height: (cm) ^b			0.383
Mean	171.63	170.00	
Median	170.2	167.6	
S.D.	9.89	9.02	
Minimum	149.9	152.9	
Maximum	200.7	188.0	

a Weight not recorded for 23 cefepime and 15 ceftazidime patients.

b Height not recorded for 17 cefepime and 11 ceftazidime patients.

Table 075.6 presents the same demographic variable seen in table 075.5 for the evaluable populations (BMS, M.O. clinically evaluable and M.O. fully evaluable).

Table 075.6
Demographic Characteristics of the Evaluable Populations
(Table Generated by M.O.)

Parameter	Cefepime			Ceftazidime		
	BMS	Clinic Eval.	Fully Eval.	BMS	Clinic Eval.	Fully Eval
N	37	35	27	20	15	15
Female	15 (41)	14 (40)	10 (37)	5 (25)	5 (33)	5 (33)
Male	22 (59)	21 (60)	17 (63)	15 (75)	10 (67)	10 (67)
White	20 (54)	20 (57)	17 (63)	9 (45)	7 (47)	7 (47)
Black	17 (46)	15 (43)	10 (37)	11 (55)	8 (53)	8 (53)
Mean Age	52.6	53.3	54.4	49.3	51.9	52
Median Age	52	52	54	47	52	52
Age Range						
18-24	5 (14)	2 (6)	2 (7)	0	0	0
25-44	8 (22)	9 (26)	6 (22)	9 (45)	5 (33)	5 (33)
45-64	11 (30)	12 (34)	9 (33)	6 (30)	5 (33)	5 (33)
65-84	13 (35)	12 (34)	10 (37)	5 (25)	5 (33)	5 (33)
Mean Weight	83.37	82.8	85.4	73.57	74.2	74.2
Median Weight	85	78	78	71	72	72
Range						

Medical Officer's Comments: All evaluable populations have similar demographic profiles to the enrolled population indicating that no selection bias was introduced during the assessment of evaluability.

With regard to intergroup differences, patients in the ceftazidime treatment group tended to have younger ages and lower weights compared with patients in the cefepime treatment group. The difference between the treatment groups in mean weight was statistically significant for all evaluability groups ($p < 0.05$).

Clinical Diagnosis: Table 075.7 summarizes the clinical diagnosis at study entry for the medical officer's fully evaluable and clinically evaluable populations. There was a trend toward more patients with the diagnosis of cellulitis in the ceftazidime treatment group, however, this trend did not reach significance (by χ^2 test).

Medical Officer's Comments: The medical officer accepted the diagnosis of the investigator as recorded in the patient summary or on the "investigator comment page" of the case report form. When the diagnosis in the patient profile differed from that in the investigator's narrative comments, the diagnosis from the case report form was preferred.

Table 075.7
Clinical Diagnosis at Study Entry
(M.O. Table)

Diagnosis	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
Cellulitis	15 (43)	9 (60)	7 (26)	9 (60)
Abscess	9 (26)	5 (33)	12 (44)	5 (33)
Wound Infection	8 (23)	1 (7)	2 (7)	1 (7)
Infected Ulcer	3 (9)	0	6 (22)	0
Total	35	15	27	15

Severity: Table 075.8 summarizes the severity of infections in the medical officer's evaluable populations.

Medical Officer's Comments: Severity was determined by the individual investigator and graded as mild, moderate or severe. There was no definition of "mild, moderate or severe" in the protocol.

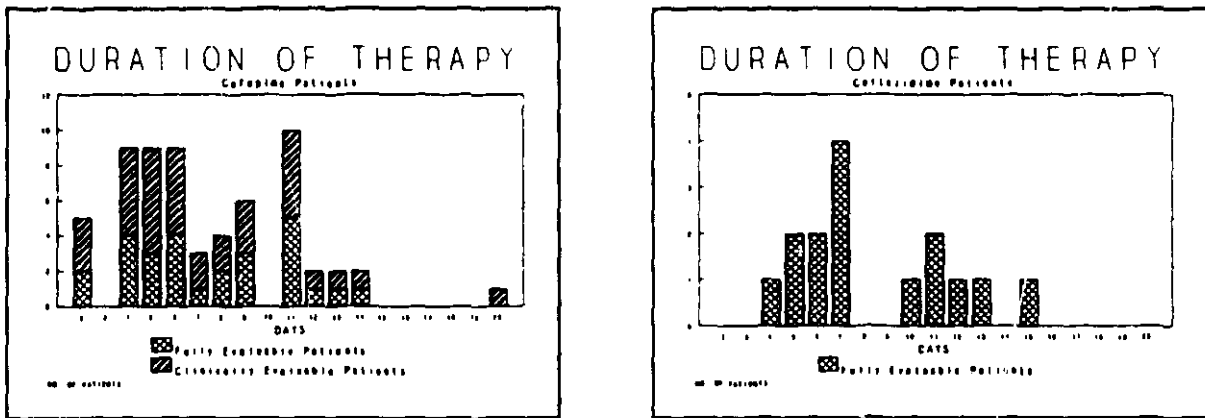
Table 075.8
Severity of Infection
(M.O. Table)

Severity	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
N=	35	15	27	15
Mild	0	0	0	0
Moderate	30 (86)	12 (80)	23 (85)	12 (80)
Severe	5 (14)	3 (20)	4 (15)	3 (20)

Medical Officer's Comments: There is a trend toward increased severity of infection in the ceftazidime treatment group in both the clinically and fully evaluable populations.

Duration of Therapy: The mean duration of therapy in the cefepime treatment group was 6.9 days in the clinically evaluable population and 6.5 days in the fully evaluable population. The mean duration of therapy in the ceftazidime treatment group was 8.2 days in the clinically evaluable population and 8.6 days in the fully evaluable population. Figure 075.9 displays the distribution of treatment durations for both treatment groups.

Figure 075.9
Distribution of Treatment Duration



Medical Officer's Comments: The mean duration of therapy is slightly longer in the ceftazidime treatment group, however, the mean duration of therapy is not significantly different between the two treatment groups.

Clinical Efficacy: Table 075.10 presents the applicant's and the medical officer's assessment of the clinical efficacy. The applicant's data is presented in the shaded boxes, all other data is derived from the medical officer's evaluable populations.

Table 075.10
Clinical Efficacy Table
(M.O. Table)

Clinical Response	Fully Evaluable		Clinically Evaluable	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
BMS	37	20	NA	NA
Satisfactory	33 (89%)	19 (95%)		
Unsatisfactory	4 (11%)	1 (5%)		
Overall	27	15	35	15
Cure	22 (81%)	15 (100%)	26 (74%)	15 (100%)
Failure	5 (19%)	0	9 (26%)	0
Cellulitis	12	9	15	9
Cure	8 (67%)	9 (100%)	9 (60%)	9 (100%)
Failure	4 (33%)	0	6 (40%)	0
Abscess	7	5	9	5
Cure	7 (100%)	5 (100%)	8 (89%)	5 (100%)
Failure	0	0	1 (11%)	0
Wound Infection	6	1	8	1
Cure	6 (100%)	1 (100%)	8 (100%)	1 (100%)
Failure	0	0	0	0
Infected Ulcers	2	0	3	0
Cure	1 (50%)	0	1 (33%)	0
Failure	1 (50%)	0	2 (67%)	0

Medical Officer's Comments: The 95% confidence intervals around the true difference in the overall clinical cure rates are as follows:

	Corrected	Uncorrected
BMS:	[-24, +12]	[-20, +8]
M.O. Fully Evaluable:	[-45, +6]	[-40, -11]
M.O. Clinically Evaluable:	[-38, +1]	[-33, +4]

Therefore, according to the medical officer's analysis, cefepime does not fulfill the regulatory definition of equivalence. The reader will recall, however, that a significant difference was noted in the weight distribution between the two treatment groups: patients in the cefepime treatment group had a higher average weight than patients in the ceftazidime treatment group. To explore the effect of weight on the observed clinical outcome, the medical officer created 2 sub-groups, based on weight, from the clinically evaluable data set. The results of the sub-group analysis are tabulated below:

Table 075.10A
Effect of Weight on Clinical Outcome
(M.O. Table)

Weight Cut off:	Mean Weights		Number Cured/Number Evaluable(%)	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
<73.5 KG	63.4	63.1	7/10 (70%)	7/7 (100%)
<84.4 KG	70.1	65.9	13/19 (68%)	9/9 (100%)
ALL	82.9	74.2	26/35 (74%)	15/15 (100%)

As indicated in the above table, even when a weight cut-off is used such that the mean weight in the two treatment groups become equal, the difference in clinical outcome persists, therefore, it is the conclusion of the medical officer that the observed difference in clinical outcome between the two treatment group is not due to the difference in mean weights observed between the groups. Admittedly the above analysis is somewhat crude, the issue will likely be addressed with greater skill during the statistical review.

In addition, another issue must be addressed. As observed earlier center #001 enrolled the majority of patients in the trial. It is of interest to determine if the eradication rates at the other four centers differ significantly from the rate seen at center 001. The clinical outcome rates, by study center, are summarized in Table 075.10B

Table 075.10B
Effect of Study Center on Clinical Outcome
(M.O. Table)

Study Center	Number Enrolled		Number Cured/Number Evaluable(%)	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
001	77	37	16/22 (73%)	10/10 (100%)
Other Centers	27	13	10/13 (77%)	5/5 (100%)
Overall	105	50	26/35 (74%)	15/15 (100%)

Since the clinical cure rates are similar at center 001 and at all other centers combined, it is unlikely that the preponderance of data from this center skewed the overall results of the clinical efficacy. Again, one must await the statistical review for confirmation of this conclusion.

Susceptibility of Pathogens: According to the applicant, 8/169 pathogens recovered (4%) were resistant to cefepime; these include (Enterococcus spp. (2), Methicillin resistant *S. aureus*(1), Peptostreptococcus spp. (1), Bacteroides spp. (2); and *P. aeruginosa*(2). Similarly, 10/162 pathogens recovered (5%) were resistant to ceftazidime.

Microbiologic Efficacy: Table 075.11 summarizes the microbiologic response at the patient level for the applicant's and the medical officer's evaluable populations.

Medical Officer's Comments: In patients infected with multiple organisms, the microbiologic response at the patient level was determined by the organism with the worst outcome.

Table 075.11
Microbiologic Outcome for Evaluable Patients
(M.O. Table)

Clinical Response	Fully Evaluable	
	Cefepime	Ceftazidime
BMS	37	20
Documented Eradication	4	2
Presumed Eradication	28 (86%) ¹	18 (100%) ¹
Documented Persistence	4	0
Presumed Persistence	1 (14%) ²	0
Medical Officer	27	15
Eradication ³	23 (85%)	15 (100%)
Documented Persistence	2 (7%)	0
Presumed Persistence	2 (7%)	0
Documented New Infection	0	0

¹Numbers in parenthesis are proportion of patient with outcome of eradication (both presumed and documented).

²Numbers in parenthesis are proportion of patients with outcome of persistence (both presumed and documented)

³Includes both presumed and documented eradication.

Medical Officer's Comments: As was seen in the clinical outcome, in both the applicant's evaluable population and the medical officer's evaluable population, the success rates seem to be higher in the ceftazidime treatment group than in the cefepime treatment group, no formal statistical analysis was performed by the M.O. on this data.

Microbiologic Efficacy by Infecting Pathogen: Table 075.11A lists the eradication rates by organism recovered for each infection type for the medical officer's fully evaluable population.

Table 075.11A
Microbiologic Response for Evaluable Pathogens
M.O. Fully Evaluable Population

Parameter	CEFEPIME 500 mg BID	CEFTAZID 500 mg TID

SSTI/ABSCESS		
PEPTOSTREPTOCOCCUS SP.	0	1/ 1 (100%)
S. AUREUS	6/ 6 (100%)	4/ 4 (100%)
S. INTERMEDIUS	1/ 1 (100%)	0
STREP. (GROUP A)	0	1/ 1 (100%)
STREP. (GROUP B)	2/ 2 (100%)	0
STREP. (GROUP F)	1/ 1 (100%)	0
TOTAL ABSCESS	10/ 10 (100%)	6/ 6 (100%)

SSTI/CELLULITIS		
A. ANITRATUS	1/ 1 (100%)	0
E. AEROGENES	0	1/ 1 (100%)
E. TARDA	1/ 1 (100%)	0
K. PNEUMONIAE	0/ 1 (0%)	0
M. MORGANII	1/ 1 (100%)	0
P. AERUGINOSA	0	1/ 1 (100%)
P. MIRABILIS	1/ 1 (100%)	1/ 1 (100%)
S. AUREUS	5/ 7 (71%)	6/ 6 (100%)
S. MARCESCENS	1/ 1 (100%)	0
STREP. (GROUP A)	0/ 1 (0%)	1/ 1 (100%)
STREP. (GROUP B)	0	2/ 2 (100%)
TOTAL CELLULITIS	10/ 14 (71%)	12/ 12 (100%)

SSTI/INFECTED ULCER		
STAPH. COAGULASE (-)	1/ 1 (100%)	0
STREP. (GROUP B)	1/ 1 (100%)	0
TOTAL INFECTED ULCER	2/ 2 (100%)	0

SSTI/WOUND INFECTION		
E. CLOACAE	1/ 1 (100%)	0
K. OXYTOCA	1/ 1 (100%)	0
P. AERUGINOSA	1/ 1 (100%)	0
S. AUREUS	3/ 3 (100%)	0
STREP. (ALPHA HEMOLYTIC)	1/ 1 (100%)	0
STREP. (GROUP A)	1/ 1 (100%)	1/ 1 (100%)
STREP. (GROUP G)	1/ 1 (100%)	0
TOTAL WOUND INFECTION	9/ 9 (100%)	1/ 1 (100%)

TOTALS	31/ 35 (86%)	19/ 19 (100%)

Organisms Persisting: According to the medical officer, *S. aureus*(2), *K. pneumoniae*(1) and Group-A beta-hemolytic *Streptococci*(1) persisted after treatment with cefepime. No organisms persisted after treatment with ceftazidime.

New Infections: There were no documented new infections in either the cefepime or ceftazidime treatment groups.

Medical Officer's Comments: A patient must have signs/symptoms of infection to be classified as having a new infection by the medical officer. The recovery of a pathogen was not sufficient evidence of new infection.

Efficacy Conclusions - 0.5 grams every 12 hours: Study #075 was the only study submitted to the NDA to study the safety and effectiveness of cefepime for the treatment of SSTI at a dose of 0.5 grams every 12 hours. The applicant does not propose to include this dosage regimen for SSTI in the approved package insert for cefepime. The applicant states that "...therapy in this range of doses is not appropriate for severe, rapidly-progressing infections, or infections associated with septicemia. In addition, higher dose therapy is advised for the treatment of difficult to treat pathogens such as *Pseudomonas aeruginosa*."

The primary determinant of efficacy for SSTI is the clinical response. For all potential evaluable populations (BMS, M.O./Fully Evaluable, M.O./Clinically Evaluable) the lower bound of the 95% confidence interval around the true difference in clinical outcomes exceeded -10%, the lower limit of equivalence for an expected cure rate >90% (Please see page 25 of review for 95% confidence intervals). Therefore, neither the applicant, nor the medical officer, was able to demonstrate statistical equivalence between the two treatment groups. The difference in clinical outcome remained even after the medical officer attempted to correct for the discrepancy in weight between the two treatment groups. The trend toward superiority of ceftazidime was observed in all diagnostic groups (i.e.: cellulitis, superficial abscess, and wound infections).

With respect to the microbiologic response, both drugs performed well in eradicating the major pathogens of SSTI (*S. aureus* and Beta-Hemolytic Streptococci), however, the eradication rates with ceftazidime tended toward superiority. (The difference was not statistically significant).

In conclusion, the available data does not support the efficacy for cefepime in the treatment of SSTI at a dose of 0.5 grams every 12 hours.

Section V.2.1.2 - 1 grams Every Twelve Hours

United States Protocol #081:

Protocol Description: Study #081 was an open, randomized (2:1, cefepime:ceftazidime), comparative clinical study conducted at multiple centers in the United States and Puerto Rico. The protocol used the common inclusion and exclusion criteria described previously. In addition, protocol #081 tried to enroll patients with a greater severity of disease than were enrolled in protocol #075. Thus patients with cellulitis, pyoderma, ecthyma, furuncle, carbuncle, abscess, or post-operative wound infection were eligible for enrollment.

Medical Officer's Comments: In contrast to study #075, in study #081 the applicant is attempting to define a population with SSTI of greater severity that would justify the use of the higher dose of antimicrobials employed in this study. In addition, by including the diagnosis ecthyma in the inclusion criteria, the sponsor is attempting to capture patients with SSTI due to *Pseudomonas aeruginosa*.

Cefepime was administered at a dose of 1 gram every 12 hours either via the intravenous or intramuscular route. Ceftazidime was administered at a dose of 1 gram every 8 hours either via the intravenous or intramuscular route. Evaluability criteria and efficacy outcome definitions described previously for the common protocol were employed.

Enrollment: Patients were enrolled in study #081 between June 23, 1988 and May 8, 1990 at 19 North American study Centers. Table 081.1 summarizes the principal investigator, the location and the enrollment at each of the study centers.

Table 081.1
Enrollment by Study Center
(Table Provided by the Applicant)

Center	Principal Investigator	Location	Number of Patients Enrolled (Evaluable)	
			Cefepime	Ceftazidime
I-001	R. Schwartz	Fort Myers, FL	69	33
I-003	B. Yangco	Tampa, FL	4	4
I-004	S. Farkas	Barberton, OH	5	2
I-005	L. Parish	Philadelphia, PA	19	11
I-008	P. Jurgensen	Savannah, GA	2	1
I-009	C. Ramirez-Ronda	San Juan, PR	24	14
I-010	T. Madhaven	Madison Hts., MI	2	0
I-011	T. Sorg	Dayton, OH	0	1
I-012	G. Plotkin	Wilkes-Barre, PA	2	1
I-013	E. Frank	Neptune, NJ	25	14
I-015	M. Gelfand	Memphis, TN	18	10
I-019	S. Forlenza	East Meadow, NY	1	0
I-022	B. Sieger	Orlando, FL	5	2
I-025	J. Daly	Brighton, MA	2	0
I-028	S. Handwerger	New York, NY	1	0
I-032	C. Lerner	San Antonio, TX	7	4
I-033	R. Prince ^a	Iowa City, IA	4	1
I-036	R. Gainer	Morgantown, WV	7	2
I-037	R. Bolivar-Bricero	Houston, TX	<u>1</u>	<u>0</u>
		Totals	198	100

a This investigator has a Pharm. D.; all others have an M.D.

Medical Officer's Comments: Dr. M. Gelfand is listed in the Division of Scientific Investigations' (DSI) list of "Assurances Accepted for the Performance of Future Studies". Dr. Gelfand was placed on the "Assurances Accepted..." list in 1981. None of the other principal investigator appear on any DSI restricted investigator list.

Evaluability: Table 081.2 presents both the applicant's and the medical officer's assessment of the evaluability at each study center.

Table 081.2
Evaluability by Study Center and Treatment Group
BMS Data in Shaded Columns

Center	Enrollment		BMS Evaluability		M.O. Clinically Eval.		M.O. Fully Eval.	
	Cefep.	Ceftaz.	Cefep.	Ceftaz.	Cefep	Ceftaz.	Cefep.	Ceftaz.
001	69	33	48 (51) ¹	21 (57)	42 (42)	18 (50)	35 (53)	17 (75)
003	4	4	0	1 (3)	1 (1)	1 (3)	0	0
004	5	2	1 (1)	1 (3)	0	0	0	0
005	19	11	12 (13)	5 (14)	13 (13)	6 (17)	2 (3)	0
008	2	1	1 (1)	0	1 (1)	0	0	0
009	24	14	10 (11)	3 (8)	13 (13)	6 (17)	8 (12)	2 (10)
010	2	0	0	0	1 (1)	0	1 (2)	0
011	0	1	0	0	0	0	0	0
012	2	1	2 (2)	1 (3)	2 (2)	1 (3)	1 (2)	1 (5)
013	25	14	7 (7)	2 (5)	10 (10)	3 (8)	6 (9)	1 (5)
015	18	10	5 (5)	2 (5)	8 (8)	1 (3)	4 (6)	1 (5)
019	1	0	1 (1)	0	1 (1)	0	1 (2)	0
022	5	2	3 (3)	0	4 (4)	0	4 (6)	0
025	2	0	0	0	0	0	0	0
028	1	0	0	0	0	0	0	0
032	7	4	1 (1)	1 (3)	2 (2)	0	1 (2)	0
033	4	1	0	0	0	0	0	0
036	7	2	2 (2)	0	2 (2)	0	2 (3)	0
037	1	0	0	0	0	0	0	0
Total	198	100	93	37	100	36	65	22

1- Number in parenthesis are the percent of evaluable patients who were enrolled at each study center (i.e., #eval. from center "x"/Total # evaluable).

Medical Officer's Comments: Again, as in study #075, the majority of patients in both the applicant's and the medical officer's evaluable populations were enrolled at center #001.

Patients Excluded from the Efficacy Analysis: The most common reason for which

the applicant considered patients not-evaluable, in both treatment groups, was the failure to isolate a pathogen pre-treatment. Table 081.3 summarizes the reasons for which the medical officer considered patients to be not evaluable.

Table 081.3
Reasons for Exclusion from the Analysis of Efficacy
(M.O. Table)

Reason	Cefepime	Ceftazidime
Exclusions from The Clinically Evaluable Population		
Diagnosis not established ¹	4 (4)	6 (10)
Mild Infection	1 (1)	2 (3)
Incomplete treatment	50 (51)	26 (40)
Other antimicrobial administered	14 (14)	10 (16)
Fatal Protocol Violation ²	1 (1)	2 (3)
Insufficient follow-up	28 (28)	18 (28)
Total Excluded	98	64
Exclusions from The Fully Evaluable Population		
No Pathogen Isolated	8 (23)	4 (29)
Inadequate Culture ³	12 (34)	6 (43)
Resistant Organism	2 (6)	0
No Susceptibility Testing	0	1 (7)
Inappropriate Pathogen Isolated	8 (23)	1 (7)
Antimicrob. < 24 hours Pre-Enroll	5 (14)	2 (14)
Total Excluded	35	14

¹Includes those patients who did not have a pre-treatment evaluation, or who at the pre-treatment evaluation had less than 3 signs and/or symptoms specific for SSTI.

²Includes those patients who received an improper dosage of study medication, and patients whose diagnosis was not appropriate for study under the given protocol (e.g. osteomyelitis)

³Includes those patients whose culture was not obtained by an acceptable technique (please see preamble to this review for appropriate techniques).

Medical Officer's Comments: In contrast to the applicant's evaluable population, in the medical officer's evaluable population, the most common reason for exclusion from the efficacy analysis was the failure to complete the prescribed course of therapy. Please refer to table 081.4 for the reasons for which patients were prematurely removed from study drug therapy.

Differences in Evaluability Between the Applicant and the Medical Officer

Medical Officer's Comments: Please note that the applicant did not form a "clinically evaluable" group, therefore, patients were required to be both clinically and microbiologically evaluable by the applicant. The M.O. considered patients clinically evaluable if they had appropriate clinical documentation of an SSTI, completed a course of therapy (or were removed from therapy for clinical failure) and were present for all required follow-up evaluations.

There were 18 patients in the cefepime treatment group who were considered not evaluable by the applicant but who were considered clinically evaluable by the medical officer. The reasons for the change in evaluability are as follows: non-study antimicrobial use for clinical failure(3); isolation of a pathogen not required for clinical efficacy assessment(9); susceptibility testing not required for clinical efficacy assessment(4); susceptible pathogen not required for clinical efficacy assessment(2).

Of the 18 patients cited above 1 patient was also considered fully evaluable by the medical officer.

There were 11 patients in the cefepime treatment group who were considered evaluable by the applicant but who were considered not-evaluable by the medical officer for the following reasons: diagnosis not established(1); received < 8 doses of cefepime (10).

There were 5 patients in the ceftazidime treatment group who were considered not evaluable by the applicant but who were considered clinically evaluable by the medical officer. The reasons for the change in evaluability are as follows: isolation of a pathogen not required for clinical evaluability(3); susceptibility testing not required for clinical evaluability(1); non-study antimicrobial use for clinical failure(1).

None of the 5 patients cited above were also considered fully evaluable by the medical officer.

There were 6 patients in the ceftazidime treatment group who were considered evaluable by the applicant but who were considered not-evaluable by the medical officer for the following reasons: diagnosis not established(4); received < 12 doses of ceftazidime (2).

Completion Status: Table 081.4 describes the reasons for which study medication was terminated in each patient.

Table 081.4
Reasons for Discontinuation of Therapy
(M.O. Table)

Reason	Cefepime ¹	Ceftazidime ¹
N =	199	100
Treatment Completed	142 (71)	73 (73)
No Pathogen/Resistant Pathogen	24 (12)	11 (11)
Treatment Ineffective	7 (4)	1 (1)
Adverse Reaction	1 (<1)	1 (1)
Physician's Decision ²	2 (1)	0
Patient's Decision ³	6 (3)	3 (3)
Intercurrent Non-Protocol Illness	4 (2)	1 (1)
Protocol Error ⁴	13 (7)	10 (10)

¹Numbers in parenthesis are percent of total number of patients enrolled.

²Includes: "I.V. treatment no longer necessary"; "affected area amputated; and "lack of IV access".

³Includes left against medical advice

⁴Includes: no susceptibility testing; and incorrect diagnosis for protocol.

Medical Officer's Comments: As was noted in the review of study #075, a greater proportion of patients in the cefepime treatment group were removed from therapy for ineffective treatment. Again, the difference in not significant ($p=0.275$, Fisher's Exact Test)

Population Demographics: Table 081.5 summarizes the demographic data of the enrolled population. The demographic profile of the applicant's and the medical officer's evaluable populations are presented in table 081.6.

Table 081.5
Demographic Characteristics of the Enrolled Population
(BMS Table)

Characteristic	Cefepime	Ceftazidime	p-value
N	198	100	
Sex: N (%)			0.529
Female	64 (32)	30 (30)	
Male	134 (68)	70 (70)	
Race: N (%)			0.718
Black	48 (25)	29 (29)	
White	135 (68)	64 (64)	
Hispanic	15 (8)	5 (5)	
Oriental	0	1 (1)	
Other	0	1 (1)	
Age Distribution: N (%)			
18-24 yr	17 (9)	13 (13)	
25-44 yr	65 (33)	31 (31)	
45-64 yr	56 (28)	28 (28)	
65-84 yr	46 (23)	20 (20)	
85-100 yr	14 (7)	8 (8)	
Age: (yr)			0.342
Mean	51.9	50.9	
Median	52	53	
S.D.	20.9	21.3	
Minimum	18	18	
Maximum	100	98	
Weight: (kg)*			0.563
Mean	80.34	76.71	
Median	77.1	74.4	
S.D.	28.08	19.01	
Minimum	28.1	40.8	
Maximum	215.2	133.8	

a weight was not recorded for 15 cefepime patients and 7 ceftazidime patients.

Medical Officer's Comments: There were no significant differences noted between the two treatment groups in any demographic parameter.

Table 081.6
Demographic Characteristics of the Evaluable Populations
(BMS Data in Shaded Columns)

Parameter	Cefepime			Ceftazidime		
	BMS	Clinic. Eval.	Fully Eval.	BMS	Clinic. Eval.	Fully Eval.
N	93	100	65	37	36	22
Female	27 (29)	27 (27)	11 (17)	13 (35)	12 (32)	6 (27)
Male	66 (71)	73 (73)	54 (83)	24 (65)	24 (67)	16 (73)
White	58 (62)	66 (66)	46 (71)	25 (68)	22 (61)	15 (68)
Black	26 (28)	26 (26)	14 (22)	11 (30)	13 (36)	7 (32)
Hispanic	9 (10)	8 (8)	5 (8)	1 (3)	1 (3)	0
Mean Age	48.1	45.2	44.5	46	49	38
Median Age	44	46	41	42	46	36
Age Range						
18-24	10 (11)	9 (9)	9 (14)	7 (19)	5 (14)	4 (18)
25-44	37 (40)	38 (38)	28 (43)	13 (35)	12 (32)	11 (48)
45-64	24 (26)	28 (28)	18 (28)	10 (27)	11 (31)	7 (30)
65-84	19 (20)	21 (21)	9 (14)	4 (11)	4 (11)	0
85 +	3 (3)	4 (4)	1 (2)	3 (8)	4 (11)	0
Mean Weight	81	81	86	78	78	83
Median Weight	79	79	83	75	81	81
Range						

Medical Officer's Comments: The majority of patients in all treatment and evaluability groups were white males. There were no significant differences in any demographic characteristics between the two treatment groups.

Clinical Diagnosis: Table 081.7 summarizes the clinical diagnosis at study entry for the medical officer's fully evaluable and clinically evaluable populations.

Medical Officer's Comments: The medical officer accepted the diagnosis of the investigator, as recorded in the patient summary or the "investigator comment page" of the case report form. When the diagnosis in the patient summary differed from that in the investigator's narrative comments, the diagnosis from the case report form was preferred.

Table 081.7
Clinical Diagnosis at Study Entry
(M.O. Table)

Diagnosis	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
Cellulitis	63 (63)	21 (58)	42 (65)	16 (73)
Abscess	15 (15)	6 (17)	13 (20)	4 (18)
Furuncle	2 (2)	0	2 (3)	0
Wound Infection	7 (7)	0	6 (9)	0
Infected Ulcer	13 (13)	9 (25)	2 (3)	2 (9)
Total	100	36	65	22

Medical Officer's Comments: A larger percentage of patients in the ceftazidime group were treated for superinfection of a chronic ulcer, an SSTI that is considered difficult to treat, this trend, however, was not significant.

Severity: Table 081.8 summarizes the severity of infections in the medical officer's evaluable populations.

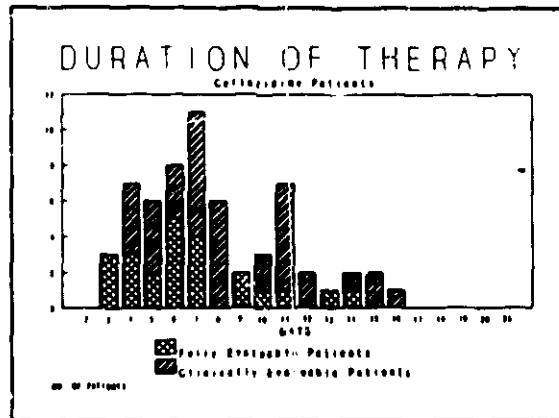
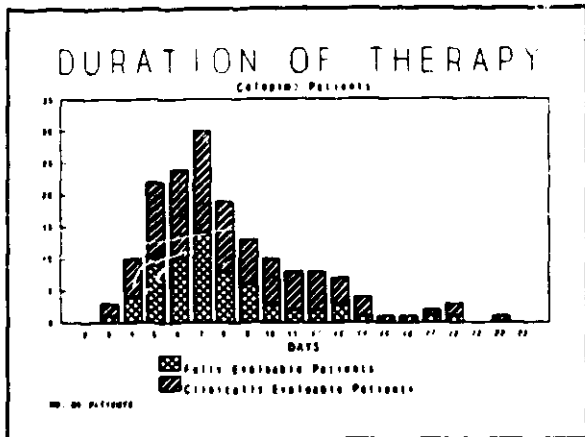
Table 081.8
Severity of Infections
(M.O. Table)

Severity	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftaz.	Cefepime	Ceftaz.
N=	100	36	65	22
Mild	0	0	0	0
Moderate	70 (69)	26 (68)	46 (70)	14 (65)
Severe	30 (30)	10 (26)	19 (30)	8 (35)

Medical Officer's Comments: There were no significant differences in severity of infection noted between the two treatment groups.

Duration of Therapy: According to the medical officer, the mean duration of therapy for the clinically evaluable patients in the cefepime treatment group was 8.4 days, the mean duration of treatment for the fully evaluable patients in the cefepime treatment group was 7.8 days. The mean duration of therapy for clinically evaluable patients in the ceftazidime treatment group was 8.4 days, the mean duration of therapy for fully evaluable patients was 7.3 days. Figure 081.9 displays the distribution of treatment durations in the medical officer's evaluable populations.

Figure 081.9
Duration of Therapy
Medical Officer's Evaluable Populations



Clinical Efficacy: Table 081.10 summarizes the results of the assessment of clinical efficacy for the applicant's (BMS) and the medical officer's evaluable populations. Please note, results from the applicant's data pool are presented in the shaded boxes.

Table 081.10
Clinical Efficacy Table

Clinical Response	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
BMS	NA	NA	93	37
Satisfactory			82 (88%)	33 (89%)
Unsatisfactory			11 (12%)	4 (11%)
Overall	100	36	65	22
Cure	76 (76%)	31 (86%)	53 (82%)	21 (95%)
Failure	24 (24%)	5 (13%)	12 (18%)	1 (4%)
Cellulitis	63	21	42	16
Cure	49 (78%)	19 (90%)	35 (83%)	16 (100%)
Failure	14 (22%)	2 (9%)	7 (17%)	0
Abscess	15	6	13	4
Cure	11 (73%)	5 (83%)	10 (77%)	3 (75%)
Failure	4 (27%)	1 (17%)	3 (23%)	1 (25%)
Furuncle/Carbuncle	2	0	2	0
Cure	2 (100%)	0	2 (100%)	0
Failure	0	0	0	0
Wound Infection	7	0	6	0
Cure	6 (86%)	0	5 (83%)	0
Failure	1 (14%)	0	1 (17%)	0
Infected Ulcers	13	9	2	2
Cure	8 (62%)	7 (78%)	1 (50%)	2 (100%)
Failure	5 (38%)	2 (22%)	1 (50%)	0

Medical Officer's Comments: The 95% confidence intervals around the true difference in the overall clinical cure rates for the evaluable populations are as follows:

	Corrected	Uncorrected
BMS:	[-15, +13]	[-13, +11]
M.O. Clinically Evaluable	[-26, +6]	[-24, +4]
M.O. Fully Evaluable	[-30, +2]	[-27, -1]

Therefore, according to the medical officer's analysis, cefepime does not fulfill the regulatory definition of equivalence. The result from study #081 confirms the finding of study #075 where equivalence was also not demonstrated.

Several issues may have confounded the determination of equivalence and bear investigation. The reader will recall that a great proportion of the evaluable patients in all evaluable populations (both BMS and M.O.) were enrolled at center 001. Table 081.11.A presents the clinical cure rates at center 001 and at all other centers in the study.

Table 081.10.A
Effect of Study Center on Clinical Outcome
M.O. Clinically Evaluable Population

Study Center	Number Enrolled		Number Cured/Number Evaluable	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
001	69	33	38/42 (90%)	17/18 (94%)
Other Centers	130	67	38/58 (66%)	14/18 (78%)
Overall	199	100	76/100 (76%)	31/36 (86%)

From the above data, it can be seen that the large percentage of evaluable patients derived from center 001 may have elevated the overall clinical cure rates, however, the data from center 001 and the data from all other centers lead to the same conclusion (i.e. cefepime and ceftazidime are not equivalent). This finding will need to be addressed during the statistical review of this application.

Another possible confounding variable arises from the experience at center 005. Although the original protocol specifically called for the exclusion of patients with infected decubitus ulcers, center #005 was given a special dispensation to enroll these patients. Since this protocol was not designed to study this population, and since this population is notoriously difficult to treat, the inclusion of these patients may have adversely affected the clinical cure rates. The medical officer, therefore, performed a second analysis where the patients from center 005 were excluded. The results of this analysis are summarized in table 081.10.B.

Table 081.10.B
Effect of Including Patients with Infected Decubitus Ulcer on
Clinical Efficacy
M.O. Clinically Evaluable Population

Study Center	Number Enrolled		Number Cured/Number Evaluable	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
005	19	11	8/13 (62%)	4/6 (67%)
Other Centers	180	89	68/87 (78%)	27/30 (90%)
Overall	199	100	76/100 (76%)	31/36 (86%)

The 95% confidence interval around the true difference in clinical cure rates for study 081 excluding center #005 is [-28, +3] (Corrected) which still does not fulfill the regulatory definition of equivalence.

Susceptibility of Pathogens: According to the applicant, three hundred seventy-six pathogens were isolated in pre-study cultures from the 299 patients. Of the 339 pathogens, 316 (93%) were susceptible to cefepime, 10 (3%) showed intermediate susceptibility and 13 (4%) were resistant (Enterococcus spp. (4), S. aureus(6), Bacteroides spp. (2), P. aeruginosa(1)).

Of the 333 pathogens tested for susceptibility to ceftazidime, 291 (87%) were susceptible, 28 (8%) were of intermediate susceptibility, and 14 (4%) were resistant (Enterococcus spp. (5), S. agalactiae(1), S. aureus(5), B. distasonis(1), and E. cloacae(1))

Medical Officer's Comments: The medical officer urges caution in making conclusions based on the in-vitro susceptibility data here presented. Many of these organisms were obtained by sub-optimal culture techniques (swabs of decubitus ulcer, swabs of exudate on intact skin, etc) and therefore may not be representative of the truly pathogenic organisms.

Microbiologic Efficacy: Table 081.11 summarizes the microbiologic response at the patient level for both the applicant (BMS) and the medical officer's evaluable population.

Table 081.11
Microbiologic Response of Evaluable Patients to Therapy
(M.O. Table)

Clinical Response	Fully Evaluable	
	Cefepime	Ceftazidime
BMS	93	37
Documented Eradication	7	1
Presumed Eradication	77 (90%) ¹	34 (95%) ¹
Documented Persistence	9	2
Presumed Persistence	0 (10%) ²	0 (5%) ²
Medical Officer	65	22
Eradication ³	60 (92%)	21 (95%)
Documented Persistence	5 (8%)	1 (4%)
Presumed Persistence	0	0
Documented New Infection	0	0

¹Numbers in parenthesis are proportion of patients with the outcome of eradication (both presumed and documented).

²Numbers in parenthesis are proportion of patients with outcome of persistence (both presumed and documented)

³Includes both presumed and documented.

Medical Officer's Comments: As was seen with the clinical cure rates, a trend to lower eradication rates in the cefepime treatment group was observed in both the applicant's and the medical officer's evaluable populations.

Microbiologic Response by Infecting Pathogen: Table 081.12A lists the eradication rates by organism recovered

Table 091.12.A
Microbiologic Response of Evaluable Pathogens to Therapy
M.O. Fully Evaluable Population

Parameter	CEFEPIME	CEFTAZID
SSTI/ABSCESS		
E. CLOACAE	1/ 1 (100%)	0
P. ANAEROBIUS	1/ 1 (100%)	0
P. MIRABILIS	1/ 1 (100%)	0
S. AUREUS	7/ 7 (100%)	1/ 2 (50%)
STREP. (ALPHA HEMOLYTIC)	0/ 1 (0%)	0
STREP. (GROUP A)	3/ 3 (100%)	2/ 2 (100%)
STREP. (GROUP B)	1/ 1 (100%)	0
TOTAL ABSCESS	14/ 15 (93%)	3/ 4 (75%)
SSTI/CELLULITIS		
A. ANITRATUS	2/ 2 (100%)	1/ 1 (100%)
C. DIVERSUS	0	1/ 1 (100%)
E. CLOACAE	0/ 1 (0%)	0
K. OXYTOCA	1/ 1 (100%)	0
K. PNEUMONIAE	1/ 1 (100%)	0
P. AERUGINOSA	2/ 2 (100%)	1/ 1 (100%)
P. FLUORESCENS	1/ 1 (100%)	0
P. MALTOPHILIA	1/ 1 (100%)	0
P. MIRABILIS	1/ 1 (100%)	1/ 1 (100%)
P. MULTOCIDA	1/ 1 (100%)	0
S. AGALACTIAE	2/ 2 (100%)	0
S. AUREUS	27/ 30 (90%)	10/ 10 (100%)
S. MARCESCENS	0	2/ 2 (100%)
S. VIRIDANS	0/ 1 (0%)	0
STREP. (BETA HEMOLYTIC)	1/ 1 (100%)	0
STREP. (GROUP A)	15/ 15 (100%)	8/ 8 (100%)
STREP. (GROUP B)	1/ 1 (100%)	1/ 1 (100%)
TOTAL CELLULITIS	56/ 61 (92%)	25/ 25 (100%)
SSTI/FURUNCLE		
S. AGALACTIAE	1/ 1 (100%)	0
S. AUREUS	1/ 1 (100%)	0
TOTAL FURUNCLE	2/ 2 (100%)	0
SSTI/INFECTED ULCER		
P. AERUGINOSA	0	1/ 1 (100%)
P. MIRABILIS	0/ 1 (0%)	0
S. AGALACTIAE	1/ 1 (100%)	0
S. ANGINOSUS	0	1/ 1 (100%)
S. AUREUS	0	1/ 1 (100%)
S. MILLERI	0	1/ 1 (100%)
TOTAL INFECTED ULCER	1/ 2 (50%)	4/ 4 (100%)

Table 091.12.A - continued
 Microbiologic Response of Evaluable Pathogens to Therapy
 M O. Fully Evaluable Population

Parameter	CEFEPIME	CEFTAZID
SSTI/WOUND		
E. CLOACAE	1/ 1 (100%)	0
E. COLI	2/ 2 (100%)	0
M. MORGANII	1/ 1 (100%)	0
P. AERUGINOSA	1/ 1 (100%)	0
P. MIRABILIS	1/ 1 (100%)	0
S. AUREUS	3/ 3 (100%)	0
TOTAL WOUND	9/ 9 (100%)	0
TOTALS	82/ 89 (92%)	32/ 33 (97%)

Organisms Persisting: According to the medical officer, seven organisms persisted after treatment with cefepime (*S.aureus*(3), *P. mirabilis*(1), *viridans Streptococci*(1), alpha-hemolytic *Streptococci*(1), and *E. cloacae*(1)).

Only *S. aureus* persisted after treatment with ceftazidime.

New Infections: According to the medical officer, no patients in either treatment group developed a symptomatic new infection during therapy.

Efficacy Conclusions: Study #081 was a multi-center, randomized, open study designed to assess the safety and efficacy of cefepime, compared with ceftazidime, for the treatment of moderate to severe skin and soft tissue infections. 199 patients were enrolled in the cefepime treatment group and 100 patients were enrolled in the ceftazidime treatment group.

The major determinant of efficacy in skin and soft tissue infection is the clinical response. In the medical officer's clinically evaluable population, the clinical cure rate achieved in the cefepime treatment group was 76%, the cure rate in the ceftazidime treatment group was 86%. The (corrected) 95% confidence interval around the true difference in clinical cure rates was [-26, +6]. Thus, the study does not demonstrate statistical equivalence by the 95% confidence interval approach.

The two treatment groups appeared similar in terms of the microbiologic efficacy. Overall, in the medical officer's fully evaluable population a documented or presumptive eradication was achieved in 92% of patients in the cefepime treatment group and in 95% of patients in the ceftazidime treatment group. The 95% confidence interval around the true difference in eradication rates was [-17, +11] (Corrected).

In conclusion, study #081 does not support the applicant's claim of efficacy for cefepime at a dose of 1.0 gram twice daily for the treatment of patients with moderate to severe SSTI.

European Protocol #081:

Protocol Description: Study #081 was an open, randomized (2:1, cefepime:ceftazidime), comparative, European study. The protocol was identical to the protocol used for study #081 at the North American centers. The reader is referred to the review of North American protocol #081 for a complete discussion.

Enrollment: Forty-seven patients were enrolled in study #081 at the European centers, 32 patients were randomized to the cefepime treatment group, and 15 were randomized to the ceftazidime treatment group.

Table 081E.1 lists the location, principal investigator and enrollment at each of the European study centers.

Table 081E.1
Location, Principal Investigator and Enrollment
by Study Center
(BMS Table)

Site	Principal Investigator	Location	Number of Patients Enrolled (Evaluable)	
			Cefepime	Ceftazidime
I-021	N. Brion	Aubervilliers, France	12	7
I-023	F. Lucht	Saint-Etienne, France	5	2
I-024	J.M. Estavoyer	Besançon, France	2	2
I-029	P. Combemale	Lyon, France	13	4
TOTAL			32	15

Table 081E.2 summarizes the applicant's and the medical officer's assessment of the number of patients evaluable for the purposes of the efficacy assessment.

Table 081E.2
Evaluability by Study Center

Center	Enrollment		BMS Evaluability ¹		M.O. Clinically Eval. ¹		M.O. Fully Eval. ¹	
	Cefep.	Ceftaz.	Cefep.	Ceftaz.	Cefep	Ceftaz.	Cefep.	Ceftaz.
021	12	7	4 (80)	3 (50)	1 (14)	1 (17)	0	0
023	5	2	1 (20)	0	2 (28)	0	0	0
024	2	2	0	1 (17)	1 (14)	2 (34)	0	1 (50)
029	13	4	0	2 (34)	3 (42)	3 (49)	0	1 (50)
Total	32	15	5	6	7	6	0	2

1- Numbers in parenthesis are percent of total evaluable patients assessed at the indicated study center.

Patients Excluded from the Efficacy Analysis: In the cefepime treatment group, the most common reason for which the medical officer considered a patient to be not evaluable was the failure to perform a post-treatment assessment within the window of 5 to 14 days post-therapy.

In the ceftazidime treatment group, the most common reason for which the medical officer considered a patient to be not evaluable was the failure to adequately document the clinical signs and symptoms of infection (i.e. less than three signs and/or symptoms directly referable to the skin were reported).

Differences in Evaluability Between the Applicant and the M.O.: The evaluability of eight patients in the cefepime treatment group was changed by the medical officer. The evaluability of three patients was changed from evaluable to not-evaluable because of the failure to adequately document the the clinical signs and symptoms of the infection. The evaluability of five patients was changed from not-evaluable to evaluable. In all five cases the patients were considered not evaluable because of the failure to isolate a pathogen at the pre-treatment visit. Since the medical officer assessed patients' clinical and microbiological evaluability separately, the failure to isolate a pathogen did not preclude a patient from being clinically evaluable.

The evaluability of four patient^s in the ceftazidime treatment group was changed by the medical officer. The evaluability of two patients was changed from evaluable to not-evaluable for the failure to adequately document the signs and symptoms of the infection. The evaluability of two patients was changed from not-evaluable to evaluable. Both patients were considered not-evaluable by the applicant because of failure to document the involved pathogen. Both patients, however, were considered clinically evaluable by the medical officer.

Completion Status: Table 081E.3 summarizes the reasons for which therapy was discontinued.

Table 081E.3
Reasons for Discontinuation of Therapy
(According to the Applicant)

Reason	Number (%) of Patients	
	Cefepime N=32	Ceftazidime N=15
Treatment Completed	24 (75)	10 (67)
Treatment Ineffective	3 (9)	2 (13)
Subject's Decision	2 (6)	2 (13)
Pathogen Resistant	1 (3)	1 (7)
Intercurrent Illness	1 (3)	0
No Pathogen Isolated	1 (3)	0

Note : The major reason is the only one indicated.

Medical Officer's Comments: The majority of patients in both treatment groups completed therapy. There were no significant differences noted between the two treatment groups with regard to reasons for premature termination of therapy.

Demographic Characteristics: Table 081E.4 summarizes the demographic characteristics of the enrolled population. Table 081E.5 summarizes the demographic characteristics of the evaluable populations.

Table 081E.4
Demographic Characteristics of the Enrolled Population
(BMS Table)

Parameter	CEFEPIME	CEFTAZID
SEX		
FEMALE	10 (31%)	5 (33%)
MALE	22 (69%)	10 (67%)
RACE		
WHITE	30 (94%)	12 (80%)
BLACK	1 (3%)	1 (7%)
ORIENTAL	0 (0%)	1 (7%)
OTHER	1 (3%)	1 (7%)
AGE (YR)		
N	32	15
MEAN	36.3	37.5
MEDIAN	32	35
RANGE		
AGE DISTRIBUTION		
18 - 24	10 (31%)	4 (27%)
25 - 44	14 (44%)	8 (53%)
45 - 64	6 (19%)	1 (7%)
65 - 84	2 (6%)	2 (13%)
WEIGHT (KGS)		
N	32	14
MEAN	72.61	69.21
MEDIAN	72.5	65.5
RANGE		

Medical Officer's Comments: There are no significant differences between the two treatment groups in the enrolled population with regard to any of the demographic parameters assessed.

Table 081E.5
Demographic Characteristics of the Evaluable Populations

Parameter	Cefepime			Ceftazidime		
	BMS	Clinic. Eval.	Fully Eval.	BMS	Clinic. Eval.	Fully Eval.
Female	5 (100)	3 (43)	0	3 (50)	1 (17)	1 (50)
Male	0	4 (57)	0	3 (50)	5 (83)	1 (50)
White	4 (80)	6 (86)	0	5 (83)	5 (83)	1 (50)
Oriental	0	0	0	1 (17)	1 (17)	1 (50)
Other	1 (20)	1 (14)	0	0	0	0
Mean Age	44.6	41.4	-	45.5	45.5	43.0
Median Age	45	31	-	41	47	43
Age Range						
18-24	1 (20)	2 (29)	-	1 (17)	2 (33)	1 (50)
25-44	1 (20)	2 (29)	-	3 (50)	1 (17)	-
45-64	2 (40)	2 (29)	-	-	1 (17)	-
65-84	1 (20)	1 (14)	-	2 (33)	2 (33)	1 (50)
Mean Weight	63.2	75.1	-	66.0	76.4	66.5
Median Weight	59	76	-	63	78	67
Range						

Medical Officer's Comments: There are no significant differences between the two treatment groups, in any evaluable population (applicant, MO/Clinically evaluable, MO/fully evaluable), with respect to any demographic variable assessed.

Clinical Diagnosis: Table 081E.6 summarizes the clinical diagnosis at study entry for the medical officer's clinically evaluable and fully evaluable populations.

Table 081E.6
Clinical Diagnosis at Study Entry
(M.O. Table)

Diagnosis	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftazid.	Cefepime	Ceftazid.
N=	7	6	0	2
Abscess	0	1	-	-
Cellulitis	4	3	-	2
Infected Burn	1	0	-	-
Fascitis	0	1	-	-
Infected Wound	2	1	-	-

Severity: All infection in both treatment groups were either moderate or severe. There were no significant differences between the two treatment groups with regard to severity of infection.

Duration of Therapy: In the medical officer's clinically evaluable population, cefepime was administered from 5 to 14 days. The mean duration of therapy was 8.7 days, the median duration of therapy was 8 days. Ceftazidime was administered from 5 to 13 days. The mean duration of therapy was 8.2 days, the median duration of therapy was 8 days. There were no significant differences between the two treatment groups with regard to duration of therapy.

Clinical Efficacy: Table 081E.6 summarizes the applicant's and the medical officer's assessment of the clinical efficacy. The applicant's data is presented in shaded boxes. Because of the small number of patients involved, the clinical efficacy for each infection type (e.g. cellulitis, abscess, etc.) is not presented.

Table 081E.6
Clinical Efficacy Table

Clinical Response	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
BMS	5	6		
Satisfactory	4 (80)	4 (67)		
Unsatisfactory	1 (20)	2 (33)		
Medical Officer	7	6	0	2
Cure	5 (71)	5 (83)	-	2 (100)
Failure	2 (29)	1 (17)	-	0

Medical Officer's Comments: Due to the small number of evaluable patients in this study, no formal statistical analysis can be performed. However, in the medical officer's evaluable population, there was a trend toward greater clinical efficacy in the ceftazidime treatment group.

Medical Officer's Comments: No single infection type contributed disproportionately to the clinical failures in either treatment group.

Microbiologic Efficacy: According to the applicant, In the cefepime group, 6 pathogens susceptible to cefepime and ceftazidime were isolated and identified in cultures from the 5 evaluable SSTI patients. Five (83%) pathogens were eradicated by cefepime treatment. One pathogen (Streptococcus agalactiae) relapsed after cefepime treatment. In the ceftazidime group, 8 pathogens susceptible to both study drugs were isolated and identified in cultures from the 6 evaluable SSTI patients. Six (75%) pathogens were eradicated by ceftazidime treatment and 2 (2 cases of Staphylococcus aureus) persisted after ceftazidime treatment.

There were only two patients who were considered to be microbiologically evaluable by the medical officer. Both microbiologically evaluable patients were in the ceftazidime treatment group. The pathogens involved (S. aureus and Group-G Streptococcus) were eradicated.

Efficacy Conclusions: Study #081E was designed to evaluate the safety and efficacy of cefepime 1 gram every 12 hours versus ceftazidime 1 gram every 8 hours in the treatment of mild to moderate infections of the skin and soft tissues.

Thirty-two patients were enrolled into the cefepime treatment group and 15 patients were enrolled into the ceftazidime treatment group. According to the applicant, 5 patients in the cefepime treatment group and 6 patients in the ceftazidime treatment group were considered evaluable for efficacy. According to the medical officer, 7 patients in the cefepime treatment group and 6 patients in the ceftazidime treatment group were evaluable for clinical efficacy. No patients in the cefepime group and 2 patients in the ceftazidime group were evaluable for microbiologic efficacy.

The primary determinant of efficacy in SSTI is the clinical efficacy. According to the medical officer, the clinical cure rate in the cefepime treatment group was 5/7 (71%), the clinical cure rate in the ceftazidime treatment group was 5/6 (83%). Although the number of patients involved is too small for meaningful statistical analysis there is a trend toward greater efficacy in the ceftazidime treatment group.

Since no patients in the cefepime treatment group and only two patients in the ceftazidime treatment group were evaluable for microbiologic efficacy it is not possible to draw conclusions concerning the microbiologic efficacy of cefepime based on the results of this study.

In conclusion, although the number of evaluable patients is very small, study #081 at the European centers seems to support the finding of study #081 at the North American centers where cefepime at a dose of 1.0 grams every 12 hours was not found to be equivalent to ceftazidime at a dose of 1000 mg every 8 hours for the treatment of SSTI.

Section V.2.1.3 - 2.0 grams every 12 hours.**North American Protocol #097:**

Protocol Description: Study #097 was a randomized (1:1, cefepime:ceftazidime), comparative, North American study. At the majority of study centers the protocol was conducted in an open manner, however, at three study centers (I-042, I-055, I-056) the study was conducted in a double-blind manner. (one blinded center (I-056 did not enroll any patient with SSTI)

The study used the common inclusion and exclusion criteria described previously. Protocol #097 specifically sought to recruit patients with serious SSTI including: infected decubitus ulcers, postoperative wound infections, diabetic ulcers, or "SSTI which usually produce systemic toxicity". Study #097 used the common pre-, during-, and post-treatment procedures described previously. Evaluability criteria and efficacy outcome definitions described previously for the common protocol were employed.

Enrollment: Patients were enrolled in study #097 between October 12, 1988 and September 29, 1991. In total, 882 patients were enrolled: 439 were treated with cefepime and 443 were treated with ceftazidime. All enrolled patients received at least one dose of study medication and therefore were evaluable for the assessment of safety.

Of the 882 patients enrolled, 420 were diagnosed with SSTI by the principal investigator: 214 were treated with cefepime and 206 were treated with ceftazidime.

Table 097.1 summarizes the principal investigator, the location and the enrollment at each of the study centers.

Medical Officer's Comments: None of the principal investigator's involved in study #097 are listed in the Division of Scientific Investigation's Restricted Investigator List.

Medical Officer's Comments: According to the applicant, for center #27 "due to inadequate records of pre-study cultures, no efficacy claims will be made on the basis of the data from this center" (vol.1.207, page 08-041132).

Table 097.1
Enrollment by Study Center
(BMS Table)

Infection Type/ Study Center	Principal Investigator*	Location	Number of Patients Enrolled (Evaluable)	
			Cefepime	Ceftazidime
UNBLINDED CENTERS				
I-004	Young, Byron and Rapp, Robert*	Lexington, KY	1	-0
I-006	Wlodaver, Clifford	Oklahoma City, OK	4	5
I-007	Neu, Harold	New York, NY	2	1
I-008	Schlossberg, David	Philadelphia, PA	3	5
I-010	Rytel, Michael	Milwaukee, WI	2	0
I-012	Christou, Nicolas	Montreal, Canada	0	1
I-013	Markowitz, Arnold	Pontiac, MI	13	18
I-015	Palmer, Darwin	Albuquerque, NM	0	1
I-017	Bohnen, John	Toronto, Canada	0	2
I-019	John, Joseph	Charleston, SC	0	1
I-020	Cone, Lawrence	Rancho Mirage, CA	4	5
I-025	Paladino, Joseph*	Buffalo, NY	1	0
I-026	Sachs, Mark	Philadelphia, PA	1	0
I-028	Holloway, William	Wilmington, DE	16	16
I-029	Schwartz, Robert	Fort Myers, FL	32	25
I-030	Schlech, Walter	Nova Scotia, Canada	1	1
I-033	LeFrock, Jack	Sarasota, FL	11	6
I-036	Slama, Thomas	Indianapolis, IN	3	3
I-041	Everett, E. Dale	Columbia, MO	3	5
I-043	Rotstein, Coleman	Buffalo, NY	5	2
I-049	Pachucki, Constance	Hines, IL	4	3
I-053	Smith, David	Kansas City, MO	1	0
I-054	Ramirez-Ronda, Carlos	San Juan, PR	18	19
I-059	Gainer, R. Brooks	Morgantown, WV	1	0
I-063	Stone, Judy	Cumberland, MD	1	0
I-078	Algozzine, Gary* and Andrews, Robert and Scoggins, William	Bradenton, FL	1	0
I-079	Ho, Hoi	El Paso, TX	2	0
I-080	Joseph, Patrick	Oakland, CA	0	1
I-087	Deery, H. Gunner	Petoskey, MI	1	0
I-088	Greenman, Richard	Miami, FL	2	0
TOTAL SSTI			133	120
BLINDED CENTERS				
I-042	Levine, Donald	Detroit, MI	7	9
I-055	Schwartz, Robert	Fort Myers, FL	18	25
TOTAL			25	34
I-027	Gentry, Layne	Houston, TX	56	52
TOTAL SSTI			214	206

Medical Officer's Comments: The majority of patients in both treatment groups were enrolled at 6 of the 33 centers participating (027, 028, 029, 054, and 055).

03,
7/20/44

Evaluability: Table 097.2 presents both the applicant's and the medical officer's assessment of the evaluability at each study center. For the medical officer's evaluable population, both those patients who were considered fully evaluable (i.e. both clinically and microbiologically evaluable) and tho. - patients who were considered clinically evaluable only are presented.

Table 097.2
Evaluability by Study Center and Treatment Group

Center	Enrollment		BMS Evaluability		M.O. Clinically Eval.		M.O. Fully Eval.	
	Cefep.	Ceftaz.	Cefep.	Ceftaz.	Cefep	Ceftaz.	Cefep.	Ceftaz.
004	1	0	0	0	0	0	0	0
006	4	5	1(1)	1(1)	1(1)	1(1)	1(2)	0
007	2	1	0	0	1(1)	0	0	0
008	3	5	0	1(1)	2(2)	1(1)	1(2)	1(1)
010	2	0	2(3)	0	2(2)	0	1(2)	0
012	0	1	0	0	0	0	0	0
013	13	18	8(11)	8(12)	6(8)	8(10)	2(4)	5(10)
015	0	1	0	0	0	0	0	0
017	0	2	0	0	0	0	0	0
019	0	1	0	1(1)	0	1(1)	0	1(2)
020	4	5	1(1)	1(1)	2(2)	2(2)	1(1)	0
025	1	0	0	0	0	0	0	0
026	1	0	0	0	0	0	0	0
0	56	52	0	0	0	0	0	0
028	16	16	3(4)	8(8)	3(4)	9(11)	3(6)	7(15)
029	32	25	26(35)	19(28)	26(33)	18(23)	20(42)	10(21)
030	1	1	0	0	1(1)	0	0	0
033	11	6	2(3)	3(4)	2(2)	2(2)	0	0
036	3	3	1(1)	2(2)	3(4)	2(2)	2(4)	1(2)
041	3	5	1(1)	1(1)	2(2)	3(4)	0	0
042	7	9	0	0	1(1)	1(1)	0	0
043	5	2	2(3)	0	1(1)	1(1)	0	0
049	4	3	1(1)	0	1(1)	1(1)	1(2)	1(2)
053	1	0	0	0	0	0	0	0

Table Continued on Next Page

Table 097.2-Continued
Evaluability by Study Center and Treatment Group

Center	Enrollment		BMS Evaluability		M.O. Clinically Eval.		M.O. Fully Eval.	
	Cefep.	Ceftaz.	Cefep.	Ceftaz.	Cefep	Ceftaz.	Cefep.	Ceftaz.
054	18	19	9 (12)	7 (10)	9 (11)	9 (11)	5 (10)	6 (13)
055	18	25	15 (20)	17 (25)	14 (17)	20 (25)	9 (19)	16 (33)
059	1	0	0	0	1 (1)	0	0	0
062	1	0	0	0	0	0	0	0
078	1	0	1 (1)	0	0	0	0	0
079	2	0	0	0	0	0	0	0
080	0	1	0	0	0	0	0	0
087	1	0	1 (1)	0	1 (1)	0	1 (1)	0
088	2	0	0	0	0	0	0	0
Total	214	206	74 (35)	69 (38)	79 (38)	79 (38)	47 (23)	48 (23)

Exclusions from the Efficacy Analysis: According to the applicant, there was no statistically significant difference between the two groups in the rate of evaluability ($p=0.884$). In the cefepime treatment group the most common reasons for exclusion from the analysis of efficacy were: no pathogen isolated (8%), no susceptibility testing (8%), and post-treatment visit out of window (8%). In the ceftazidime treatment group, the most common reason for exclusion from the efficacy analysis was post-treatment visit out of window (10%).

As in other studies reviewed for this indication, the medical officer attempted to define the most significant reason for which a patient was considered not evaluable. In both treatment groups, the most frequent reason for exclusion from the analysis of efficacy was the failure to complete the prescribed treatment course. (See table 097.4 for reasons for termination of therapy).

In one center (#27) the applicant's medical monitors were not able to corroborate the information presented on the case report forms by an inspection of on-site records. The applicant, therefore, did not consider any of these patients evaluable. The medical officer concurred with the applicant's decision to exclude the patients from center #27 from the analysis of efficacy.

Table 097.3 summarizes the reasons that patients were excluded from the efficacy analysis by the medical officer.

Table 097.3
Reasons for Exclusion from the Analysis of Efficacy
(M.O. Table)

Reason	Cefepime	Ceftazidime
Exclusions from The Clinically Evaluable Population		
Diagnosis not established ¹	8 (6)	7 (7)
Incomplete treatment	30 (22)	20 (16)
Other antimicrobial administered	13 (10)	11 (9)
Fatal Protocol Violation ²	1 (1)	6 (5)
Insufficient Follow-Up	17 (13)	15 (12)
Dx Not Appropriate for Protocol ³	10 (7)	16 (13)
Unable to Verify Information ⁴	56 (41)	52 (41)
Total Excluded	135	127
Exclusions from The Fully Evaluable Population		
No Pathogen Isolated	6 (19)	6 (19)
Inadequate Culture ⁵	8 (25)	10 (32)
Resistant Organism	1 (3)	2 (6)
No Susceptibility Testing	2 (6)	2 (6)
Inappropriate Pathogen Isolated ⁶	3 (9)	7 (23)
Antimicrob. < 24 hours Pre-Enroll	12 (38)	4 (12)
Total Excluded	32	31

¹Includes those patients who did not have a pre-treatment evaluation, or who at the pre-treatment evaluation had less than 3 signs and/or symptoms specific for SSTI.

²Includes those patients who received an improper dosage of study medication)

³Osteomyelitis or septic arthritis

⁴Patients from center #027 were medical monitors could not verify the CRF

⁵Includes those patients whose culture was not obtained by an appropriate technique (i.e. sterile aspirate, at surgery, etc.)

⁶*S. epidermidis* in an immunocompetent individual

Differences in Evaluability Between the Applicant and the M.O.: Thirteen patients in the cefepime treatment group who were considered not-evaluable by the applicant were considered evaluable by the medical officer. The majority of these patients were excluded by the sponsor for the failure to isolate a pathogen, which did not preclude them from being a part of the medical officer's clinically evaluable population.

Eight patients in the cefepime treatment group who were considered evaluable by the applicant were considered not-evaluable by the medical officer. In the majority of cases there were not a sufficient number of signs/symptoms present, directly referable to the skin, to enable the medical officer to be sure of the

diagnosis.

Fourteen patients in the ceftazidime treatment group who were considered not-evaluable by the applicant were considered evaluable by the medical officer. As with the cefepime treatment group, the majority were excluded by the sponsor for the failure to properly isolate a pathogen, which did not preclude them from being a part of the medical officer's clinically evaluable population.

Four patients in the ceftazidime treatment group who were considered evaluable by the applicant were considered not-evaluable by the medical officer. One patient was judged to have a mild infection by the principal investigator. The medical officer felt that patients with mild infections should not be studied in a protocol using high-dose, parenteral therapy. Two patients had osteomyelitis, and, therefore were not appropriate for an SSTI protocol. One patient did not have a sufficient number of signs/symptoms present, directly referable to the skin, to enable the medical officer to be sure of the diagnosis.

Completion Status: Table 097.4 summarizes the reason for which the study drug was terminated. The majority of patients completed therapy in both treatment groups. There was no statistically significant difference, between the treatment groups, in the rate of discontinuation for other causes.

Table 097.4
Reasons for Discontinuation
(M.O. Table)

Reason	Cefepime ¹	Ceftazidime ¹
N =	214	206
Treatment Completed	175 (82)	164 (80)
No Pathogen/Resistant Pathogen	10 (5)	9 (4)
Treatment Ineffective	12 (6)	15 (7)
Adverse Reaction	9 (4)	6 (3)
Physician's Decision ²	1 (<1)	2 (1)
Patient's Decision ³	6 (3)	6 (3)
Protocol Error ⁴	1 (<1)	4 (2)

¹Numbers in parenthesis are percent of total number of patients enrolled.

²Includes: "I.V. treatment no longer necessary"; "affected area amputated; and "lack of IV access".

³Includes left against medical advice

⁴Includes: no susceptibility testing; and incorrect diagnosis for protocol.

Population Demographics: Table 097.5 summarizes the demographic characteristics of the enrolled population. Table 097.6 summarizes the demographic characteristics of the evaluable populations.

Table 097.5
Demographic Characteristics of the Enrolled Population

Parameter	CEFEPIME	CEFTAZID
SEX		
FEMALE	69 (32%)	76 (37%)
MALE	145 (68%)	130 (63%)
RACE		
WHITE	166 (78%)	152 (74%)
BLACK	38 (18%)	45 (22%)
HISPANIC	8 (4%)	8 (4%)
OTHER	2 (1%)	1 (0%)
AGE (YR)		
N	214	206
MEAN	50.6	49.4
MEDIAN	52	47
RANGE		
AGE DISTRIBUTION		
< 18	1 (0%)	0 (0%)
18 - 24	17 (8%)	17 (8%)
25 - 44	64 (30%)	76 (37%)
45 - 64	80 (37%)	62 (30%)
65 - 84	49 (23%)	47 (23%)
85 +	3 (1%)	4 (2%)
WEIGHT (KGS)		
N	201	189
MEAN	77.08	72.82
MEDIAN	72.0	58.0
RANGE		

Medical Officer's Comments: There were no statistically significant differences noted between the two treatment group in the enrolled population for any of the demographic variables studied.

Table 097.6
Demographic Characteristics of the Evaluable Populations
(BMS Data in Shaded Columns)

Parameter	Cefepime			Ceftazidime		
	BMS	Clinic. Eval.	Fully Eval.	BMS	Clinic. Eval.	Fully Eval.
Female	24 (32)	25 (32)	14 (30)	27 (39)	31 (39)	19 (40)
Male	50 (68)	54 (68)	33 (70)	42 (61)	48 (61)	29 (60)
White	58 (78)	61 (77)	35 (74)	43 (62)	51 (65)	32 (67)
Black	14 (19)	15 (19)	11 (23)	23 (33)	24 (30)	15 (31)
Hispanic	2 (3)	3 (4)	1 (2)	3 (4)	4 (5)	1 (2)
Mean Age	46.6	47.5	41.5	45.4	46.3	40.7
Median Age	46	47	39	43	43	37
Age Range						
<18	1 (1)	1 (1)	1 (1)	0	0	0
18-24	12 (16)	12 (15)	11 (23)	7 (10)	8 (10)	7 (15)
25-44	23 (31)	22 (28)	16 (34)	31 (45)	34 (43)	25 (52)
45-64	23 (31)	27 (34)	12 (26)	18 (26)	19 (24)	10 (21)
65-84	14 (19)	16 (20)	7 (15)	13 (19)	17 (22)	10 (21)
85 +	1 (1)	1 (1)	0	0	1 (1)	0
Mean Weight	78	81	77	81	80	80
Median Weight	74	75	72	76	76	76
Range						

Medical Officer's Comments: The majority of patients in all treatment and evaluability groups were white males. There were no significant differences in any demographic characteristics between the two treatment groups.

Clinical Diagnosis: Table 097.7 summarizes the clinical diagnosis at study entry for the medical officer's fully evaluable and clinically evaluable populations.

Table 097.7
Clinical Diagnosis at Study Entry
(M.O. Table)

Diagnosis	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
N=	79	79	47	48
Abscess	19 (24)	26 (33)	13 (28)	19 (40)
Cellulitis	34 (43)	35 (44)	21 (44)	22 (46)
Otitis Externa	0	2 (3)	0	2 (4)
Infected Ulcer	5 (6)	6 (8)	1 (2)	0
Infected Wound	21 (27)	9 (11)	12 (26)	5 (10)
Infected Burn	0	1 (1)	0	0

Medical Officer's Comments: There were no statistically significant differences between the two treatment groups in terms of clinical diagnosis at study entry.

Severity: Table 097.8 summarizes the severity of infections in the medical officer's evaluable populations.

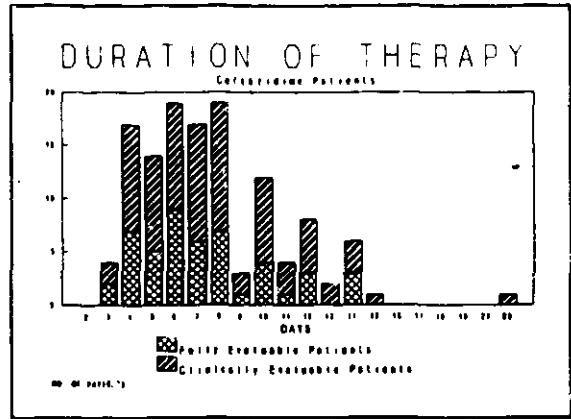
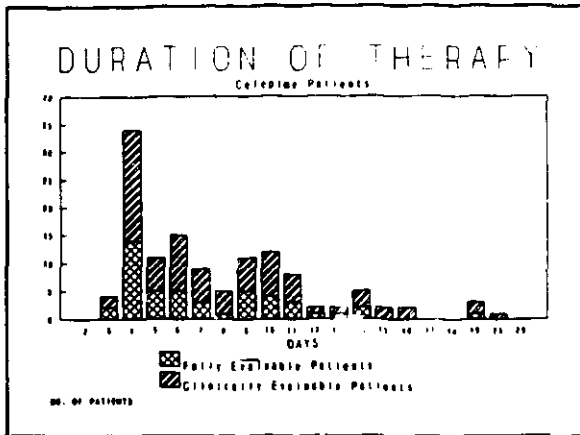
Table 097.8
Severity of Infections
(M.O. Table)

Severity	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
N=	79	79	47	48
Mild	0	0	0	0
Moderate	52 (66)	47 (59)	28 (59)	29 (60)
Severe	27 (34)	32 (41)	19 (41)	19 (40)

Medical Officer's Comments: There were no significant differences in severity of infection noted between the two treatment groups.

Duration of Therapy: According to the medical officer, the duration of therapy was comparable between the two treatment groups. In the cefepime treatment group, the clinically evaluable population had a mean duration of therapy of 8.0 days, the fully evaluable population had a mean duration of therapy of 7.2 days. Among patients in the ceftazidime treatment group, the mean duration of therapy in the clinically evaluable population was 7.9 days, the mean duration of therapy in the fully evaluable population was 7.3 days.

Figure 097.1
Duration of Therapy



Clinical Efficacy: Table 097.9 summarizes the results of the assessment of clinical efficacy for the applicant's (BMS) and the medical officer's evaluable populations. Please note, results from the applicant's data pool are presented in the shaded boxes.

Table 097.9
Clinical Efficacy Table
(M.O. Table)

Clinical Response	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
BMS	NA	NA	74	69
Satisfactory			66 (89)	61 (88)
Unsatisfactory			8 (11)	8 (12)
Overall	79	79	47	48
Cure	64 (81)	65 (82)	39 (83)	44 (92)
Failure	15 (19)	14 (18)	8 (17)	4 (8)
Cellulitis	34	35	21	22
Cure	31 (91)	29 (83)	19 (90)	21 (95)
Failure	3 (9)	6 (17)	2 (10)	1 (5)
Abscess	19	26	13	19
Cure	16 (84)	24 (92)	12 (92)	17 (89)
Failure	3 (16)	2 (8)	1 (8)	2 (11)
Wound Infection	21	9	12	5
Cure	14 (67)	8 (89)	7 (58)	5 (100)
Failure	7 (33)	1 (11)	5 (42)	0
Otitis Externa	0	2	0	2
Cure	0	1 (50)	0	1 (50)
Failure	0	1 (50)	0	1 (50)
Infected Burns	0	1	0	0
Cure	0	1 (100)	0	0
Failure	0	0	0	0
Infected Ulcers	5	6	1	0
Cure	3 (60)	2 (33)	1 (100)	
Failure	2 (40)	4 (67)	0	0

Medical Officer's Comments: The 95% confidence intervals around the true difference in the overall clinical cure rates for the evaluable populations are as follows:

	<u>Corrected</u>	<u>Uncorrected</u>
BMS:	[-11, +13]	[-10, +11]
M.O. Clinically Evaluable	[-15, +12]	[-13, +10]
M.O. Fully Evaluable	[-24, +6]	[-22, +5]

Therefore, according to the applicant's data, cefepime does fulfill the regulatory definition of equivalence. In addition, in the medical officer's clinically evaluable population, the regulatory definition of equivalence is fulfilled, however, in the fully (i.e. clinically and microbiologically) evaluable population the regulatory definition of equivalence is not fulfilled. The smaller numbers of patients in the fully evaluable population contributed to the failure to achieve statistical significance.

Of interest is the clinical results at the three center (042, 055, 056) in which the investigation was conducted in a blinded manner. Table 097. ~~111~~ ^{9A} summarizes the clinical efficacy at the blinded study centers. 9A
12/20/97

Table 097.9A
Clinical Efficacy at the Blinded Centers

	<u>Cure Rate (# Cured/# Enrolled)</u>	
	<u>Cefepime</u>	<u>Ceftazidime</u>
BMS	14/15 (93%)	17/17 (100%)
M.O. Clinically Eval.	13/15 (87%)	20/21 (95%)
M.O. Fully Eval.	9/9 (100%)	16/16 (100%)

As can be seen from the sub-group analysis, the majority of patients had either abscesses or cellulitis. Since this is a trial of a high dose (2 grams every 12 hours) of a parenteral antimicrobial drug, the more relevant population would be those persons with wound infections, burns and infected ulcers, infections generally considered to be "difficult to treat". The number of patients in these more difficult to treat categories is small. However, if we pool all patients with wound infection, infected ulcers and infected burns, the following results are obtained.

Table 097.9B
Clinical Efficacy for
Wound Infections, Infected Burns and Infected Ulcers

	<u>Eradication Rate</u>	
	<u>Cefepime</u>	<u>Ceftazidime</u>
M.O. Clinically Evaluable	17/26 (65%)	11/16 (69%)
M.O. Fully Evaluable	8/13 (63%)	5/5 (100%)

Even with pooling the categories of "difficult to treat" SSTI the numbers are still too small for a meaningful confidence interval analysis, however, a trend exists toward superior performance in the ceftazidime treatment group.

Microbiologic Efficacy: Table 097.10 summarizes the results of the microbiologic assessment of efficacy for the applicant's and the medical officer's evaluable populations. The results that are tabulated are the microbiologic response per patient.

Table 097.10
Microbiologic Response in Evaluable Patients
(M.O. Table)

Population Outcome	Microbiologically Evaluable Patients (%)			
	Cefepime		Ceftazidime	
BME	74		69	
Eradication:				
Documented	5		4	
Presumed	61		58	
Total	66	(89)	62	(90)
Persistence:				
Documented	7		7	
No Culture Performed	1 ¹		0	
Total	8	(11)	7	(10)
Medical Officer	47		48	
Eradication	41	(87)	43	(90)
Persistence				
Documented	5		4	
Presumed	1		1	
Total	6	(13)	5	(10)

1-Patient was a clinical failure

Medical Officer's Comment: Both the applicant and the medical officer found similar eradication rates in both treatment groups. The uncorrected 95% confidence interval for the true difference in eradication rates between the two treatment groups was [-11, +9] for the applicant's evaluable population and [-17, +13] for the M.O. evaluable population.

Microbiologic Response by Infecting Organism and Infection Type

As would be expected, *S. aureus* was the most frequently isolated pathogen in the medical officer's fully evaluable population; it was eradicated in 27/30 infections (90%) in the cefepime treatment group and in 30/34 infections (88%) in the ceftazidime treatment group.

Table 097.10A summarizes the microbiologic response by organism and infection type.

Medical Officer's Comments: The microbiologic response by pathogen, at the dose level studied was virtually indistinguishable between the two treatment groups. The (corrected) 95% confidence interval around the true difference in eradication rates is [-9, +10].

Table 097.10A
Microbiologic Response for Evaluable Pathogens
M.O. Fully Evaluable Population

Parameter	CEFEPIME	CEFTA2ID
SSTI/ABSCSS		
A. LWOFFI	0	1/ 1 (100%)
B. CORRODENS	1/ 1 (100%)	3/ 3 (100%)
E. CLOACAE	1/ 1 (100%)	0
H. INFLUENZAE	1/ 1 (100%)	0
P. AERUGINOSA	1/ 1 (100%)	0
P. MIRABILIS	1/ 1 (100%)	0/ 1 (0%)
S. AUREUS	6/ 7 (86%)	12/ 13 (92%)
S. FAECALIS	1/ 1 (100%)	0
STREP. (ALPHA HEMOLYTIC)	0	1/ 1 (100%)
STREP. (GROUP A)	5/ 5 (100%)	6/ 6 (100%)
STREP. (GROUP B)	1/ 1 (100%)	1/ 1 (100%)
STREP. (GROUP C)	0	2/ 2 (100%)
STREP. (GROUP F)	1/ 1 (100%)	1/ 1 (100%)
TOTAL ABSCSS	19/ 20 (95%)	27/ 29 (93%)
SSTI/CELLULITIS		
E. CLOACAE	0/ 1 (0%)	1/ 2 (50%)
M. MORGANII	0	1/ 1 (100%)
P. AERUGINOSA	0	1/ 1 (100%)
P. MIRABILIS	1/ 1 (100%)	0
S. AUREUS	14/ 14 (100%)	15/ 17 (88%)
S. EPIDERMIDIS	0	1/ 1 (100%)
S. EPIDERMIDIS (MR)	1/ 1 (100%)	0
STREP. (GROUP A)	10/ 10 (100%)	11/ 12 (92%)
STREP. (GROUP B)	0	1/ 1 (100%)
TOTAL CELLULITIS	26/ 27 (96%)	31/ 35 (89%)
SSTI/OTITIS EXTERNA		
P. AERUGINOSA	0	1/ 1 (100%)
S. AUREUS	0	0/ 1 (0%)
TOTAL OTITIS EXTERNA	0	1/ 2 (50%)
SSTI/INFECTED ULCER		
STREP. (GROUP A)	1/ 1 (100%)	0
TOTAL INFECTED ULCER	1/ 1 (100%)	0
SSTI/INFECTED WOUND		
B. CORRODENS	1/ 1 (100%)	0
E. COLI	1/ 1 (100%)	0
M. MORGANII	0	1/ 1 (100%)
P. AERUGINOSA	0/ 1 (0%)	2/ 2 (100%)
S. AUREUS	7/ 9 (78%)	3/ 3 (100%)
S. CAPITIS	1/ 1 (100%)	0
S. MARCESCENS	1/ 1 (100%)	0
STREP. (ALPHA HEMOLYTIC)	1/ 1 (100%)	0
STREP. (GROUP A)	2/ 3 (67%)	2/ 2 (100%)
TOTAL INFECTED WOUND	14/ 18 (78%)	8/ 8 (100%)
TOTALS	60/ 66 (91%)	67/ 74 (91%)

Organisms Persisting: According to the medical officer, six organisms persisted after treatment with cefepime: Group-A beta-hemolytic Streptococcus(1), *P. aeruginosa*(1), *S. aureus*(3), and *E. cloacae*(1). Seven organisms persisted after treatment with ceftazidime: Group-A beta-hemolytic Streptococcus(1), *S. aureus*(4), *E. cloacae*(1), and *P. mirabilis*(1).

New Infections: No symptomatic new infections occurred among the fully evaluable population in either treatment group.

Efficacy Conclusions: The objective of study #097 was to compare the safety and efficacy of cefepime and ceftazidime for the treatment of serious bacterial infections including serious SSTI. The dose of cefepime studied was 2 grams IV twice daily. In most centers the investigation was conducted in an open fashion, however in two center (#042, #055) the investigation was conducted in a double-blind fashion.

The study enrolled 414 patients (cefepime=208, ceftazidime=206) with SSTI. According to the medical officer, of the 208 patients enrolled in the cefepime treatment group, 79 (38%) were clinically evaluable and 47 (23%) were microbiologically and clinically evaluable. Of the 206 patients enrolled in the ceftazidime treatment group, 79 (38%) were clinically evaluable and 48 (23%) were microbiologically and clinically evaluable.

The primary determinant of efficacy for SSTI is the clinical response. For both the applicant's evaluable population and the medical officer's clinically evaluable population, the lower bound of the 95% confidence interval around the true difference in eradication was less than or equal to -15%. (Please see page 60 for confidence intervals). Since the ~~expected~~ ^{observed} (control) cure rate is between 80-89%, the study fulfills the current regulatory definition of equivalence between the two drugs studied.

With regard to microbiological efficacy, the overall eradication rates were equivalent between the two treatment groups. *S. aureus* was the most frequently encountered pathogen; it was eradicated well by both drugs studied. The number of patients with infection due to *P. aeruginosa* was small (cefepime=2, ceftazidime=4) therefore no conclusions can be drawn regarding the efficacy of the studied drugs in treating infections caused by this organism.

In conclusion, study #097 supports the applicant's claim of efficacy for cefepime at a dose of 2 grams IV every 12 hours for the treatment of patients with moderate to severe SSTI.

European Protocol #111:

Protocol Description: Study #111 was an open, randomized (1:1, cefepime, ceftazidime), comparative, European study. The protocol used many of the common inclusion and exclusion criteria described previously. This protocol specifically called for the enrollment of patients with serious SSTI such as: extensive or deep infected decubitus ulcers, post-surgical wounds, diabetic ulcers, and other infections which might be expected to produce systemic toxicity. Many patients in this study suffered from neoplasia and the side effects of antineoplastic chemotherapy. The study used the common pre-, during-, and post-treatment procedures described previously. Cefepime was administered at a dose of 2 grams every 12 hours by intravenous infusion. Ceftazidime was administered at a dose of 2 grams every 8 hours by intravenous infusion. Evaluability and efficacy outcome definitions described previously for the common protocol were employed.

Enrollment: Patients were enrolled in study #111 between March 14, 1989 and

March 22, 1991. A total of 348 patients were enrolled in this study. Of the 348 enrolled, 38 patients were diagnosed with SSTI on enrollment. Of the 38 patients enrolled with SSTI, 23 were randomized to receive cefepime and 15 were randomized to receive ceftazidime. Table 111.1 summarizes the enrollment at each of the study centers.

Table 111.1
Enrollment by Study Center
(BMS Table)

----- PROTOCOL=411-111 -----			
CENTER	INVESTIGATOR	CEFEPIME ENROLLED	CONTROL ENROLLED

003	A. HOEPELMAN	3	1
004	F. MEUNIER	15	13
006	T. STRAND	2	
003	GILLESPIE	3	1
		--	--
TOTAL PATIENTS		23	15

Evaluability: Table 111.2 presents both the applicant's and the medical officer's assessment of the evaluability at each study center. For the medical officer's evaluable population, both those patients who are fully evaluable (i.e. both clinically and microbiologically evaluable) and those patients who are clinically evaluable only are presented.

Table 111.2
Evaluability by Study Center and Treatment Group

Center	Enrollment		BMS Evaluability		M.O. Clinically Eval.		M.O. Fully Eval.	
	Cefep.	Ceftaz.	Cefep.	Ceftaz.	Cefep.	Ceftaz.	Cefep.	Ceftaz.
003	3	1	0	0	0	0	0	0
004	15	13	4 (80)	4 (100)	4 (67)	6 (100)	0	3 (100)
006	2	0	1 (20)	0	2 (33)	0	1 (100)	0
008	3	1	0	0	0	0	0	0
Total	23	15	5	4	6	6	1	3

Exclusions from the Efficacy Analysis: According to the applicant, in the cefepime treatment group, the most common reason for exclusion from the efficacy analysis was the failure to isolate a pathogen at the pre-treatment evaluation. In the ceftazidime treatment group, the most common reason for exclusion from the efficacy analysis was the isolation of a resistant pathogen.

According to the medical officer, the majority of patients in both treatment groups (cefepime=14, ceftazidime=5) were excluded from the efficacy analysis for the failure to adequately document the infection. (Less than three signs and/or symptoms specific to skin infections were documented).

Medical Officer's Comments: According to both the applicant and the medical officer there were no significant differences between the two treatment groups in the rate of non-evaluability.

Differences in Evaluability Between the Applicant and the Medical Officer:

Most of the differences in evaluability between the applicant and the medical officer stemmed from two issues. Study #111 was designed to establish the safety and efficacy of cefepime for multiple indications (UTI, SSTI, etc.), thus, many patients were enrolled with more than one infected site. Since multiple simultaneous infections might be present in a given patient the presence of systemic signs of infection such as fever or tachycardia, were not considered supportive of the specific diagnosis of SSTI. Therefore, in order to be sure that cefepime was efficacious in SSTI the medical officer required that at least three signs and/or symptoms specific for infections of the skin and soft tissue be present in order to consider a patient evaluable (please refer to Section V.1.2 of this review for a list of acceptable signs and symptoms). Four patients in the cefepime treatment group and one patient in the ceftazidime treatment group were excluded from the analysis of efficacy by the medical officer for the failure to meet this requirement.

An enrolled patient was required to be both clinically and microbiologically evaluable in order to be considered evaluable by the applicant, thus, the applicant excluded many patients from the efficacy analysis for deficiencies in the microbiological documentation such as "no pathogen recovered", or "no susceptibility testing performed". Since the medical officer considered clinical and microbiologic evaluability separately, five patients in the cefepime treatment group and three patients in the ceftazidime treatment group who were excluded from the efficacy analysis by the applicant were considered clinically evaluable by the medical officer.

Completion Status: The majority of patients in both treatment groups completed therapy. Table 111.3 summarizes the reasons for which therapy was discontinued.

Table 111.3
Reasons for Discontinuation of Therapy

Reason	Cefepime ¹	Ceftazidime ¹
N =	23	15
Treatment Completed	13 (57)	11 (73)
No Pathogen/Resistant Pathogen	3 (12)	1 (7)
Treatment Ineffective	5 (22)	2 (14)
Adverse Reaction	1 (4)	1 (7)
Physician's Decision ²	1 (4)	0

1- Numbers in parenthesis are percent of total number of patients enrolled.
2- Includes IV treatment no longer necessary.

Population Demographics: Table 111.4 summarizes the demographic characteristics of the enrolled population and table 111.5 summarizes the demographic characteristics of the evaluable populations.

Table 111.4
Demographic Characteristics of the Enrolled Population

Parameter	CEFPIME	CEFTAZID
SEX		
FEMALE	8 (35%)	8 (53%)
MALE	15 (65%)	7 (47%)
RACE		
WHITE	20 (87%)	13 (87%)
BLACK	1 (4%)	0 (0%)
ORIENTAL	1 (4%)	2 (13%)
OTHER	1 (4%)	0 (0%)
AGE (YR)		
N	23	15
MEAN	60.4	58.9
MEDIAN	62	62
RANGE		
AGE DISTRIBUTION		
25 - 44	4 (17%)	2 (13%)
45 - 64	8 (35%)	7 (47%)
65 - 84	10 (43%)	6 (40%)
85 +	1 (4%)	0 (0%)
WEIGHT (KGS)		
N	20	15
MEAN	63.85	60.13
MEDIAN	61.0	58.6
RANGE		
HEIGHT (CM)		
N	18	14
MEAN	168.94	160.93
MEDIAN	170.0	163.5
RANGE		

Medical Officer's Comments: A greater proportion of the patients enrolled into the cefepime treatment group are males, the difference between the treatment group is not statistically significant.

Table 111.5
Demographic Characteristics of the Evaluable Populations
(BMS Data in Shaded in Columns)

Parameter	Cefepime			Ceftazidime		
	BMS	Clinic. Eval.	Fully Eval.	BMS	Clinic. Eval.	Fully Eval.
Female	2 (40)	1 (17)	0	2 (50)	2 (33)	1 (33)
Male	3 (60)	5 (83)	1 (100)	2 (50)	4 (67)	2 (67)
White	5 (100)	6 (100)	1 (100)	2 (50)	4 (67)	1 (33)
Oriental	0	0	0	2 (50)	2 (33)	2 (67)
Mean Age	62.6	58.8	77	63.8	57.2	62.7
Median Age	66	58	NA	66	59	64
Age Range						
18-24	0	0	0	0	0	0
25-44	1 (20)	0	0	0	1 (17)	0
45-64	1 (20)	3 (50)	0	2 (50)	4 (67)	2 (67)
65-84	3 (60)	3 (50)	1 (100)	2 (50)	1 (17)	1 (33)
Mean Weight	61.73	67.1	72.9	65.1	67.2	67.8
Median Weight	65	71	NA	63	67	69
Range						

Medical Officer's Comments: No major differences were observed between the two treatment groups in any of the evaluability categories with respect to any demographic variables measured.

Clinical Diagnosis: Table 111.6 summarizes the clinical diagnosis at study entry for the medical officer's fully evaluable and clinically evaluable population.

Table 111.6
Clinical Diagnosis at Study Entry

Diagnosis	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftaz.	Cefepime	Ceftaz.
N=	6	6	1	3
Abscess	1 (17)	0	1 (100)	0
Cellulitis	1 (17)	0	0	0
Infected Ulcer	1 (17)	0	0	0
Wound Infection	3 (50)	6 (100)	0	3 (100)

Medical Officer's Comments: As opposed to most of the other studies reviewed for this application where the majority of patients were enrolled for cellulitis or abscess, the majority of patients in study #111 were enrolled for the treatment of wound infections.

Severity: The majority of infections in both treatment groups were judged to be "severe" by the principal investigators. There were no significant differences in the severity of infections between the two treatment groups.

Duration of Therapy: Cefepime was administered for 6 to 15 days. The mean duration of therapy for patients in the cefepime treatment group was 11 days, the median duration of therapy was 12 days.

Ceftazidime was administered from 3 to 14 days. The mean duration of therapy for patients in the ceftazidime treatment group was 8.7 days, the median duration of therapy was 8 days.

Medical Officer's Comments: The difference in mean administration rates is not significant ($p > 0.05$, paired t-test).

Clinical Efficacy: Table 111.7 summarizes the results of the assessment of clinical efficacy for the applicant's (BMS) and the medical officer's evaluable populations.

Table 111.7
Clinical Efficacy
(M.O. Table)

Clinical Response	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
BMS	5	4		
Satisfactory	4 (80)	3 (75)		
Unsatisfactory	1 (20)	1 (25)		
Overall	6	6	1	3
Cure	2 (33)	4 (67)	1 (100)	3 (100)
Failure	4 (67)	2 (33)	0	0
Cellulitis	1	0	0	0
Cure	1 (100)	0		
Failure	0	0		
Abscess	1	0	1	0
Cure	1 (100)	0	1 (100)	0
Failure	0	0	0	0
Wound Infection	3	6	0	3
Cure	0	4 (67)	0	3 (100)
Failure	3 (100)	2 (33)	0	0
Infected Ulcers	1	0	0	0
Cure	0	0	0	0
Failure	1 (100)	0	0	0

Medical Officer's Comments: Because of the small numbers of patients involved, the 95% confidence intervals around the true difference are too wide to be meaningful.

Medical Officer's Comments: At issue is the disparity in the clinical outcome for the cefepime treatment group between the applicant's and the medical officer's evaluable population. The reader will recall that several patients were considered evaluable by the medical officer that were considered not-evaluable by the applicant, the majority of these patients were clinical failures. Also, the medical officer excluded several patients from the cefepime treatment group for the failure to adequately substantiate the diagnosis of SSTI, the majority of these patients were clinical successes. Therefore, the inclusion of additional failures and the exclusion of clinical successes account for the discrepancy in outcome between the medical officer

and the applicant, rather than any difference in interpretation of the outcome data. In addition, it should be recalled, that due to the small numbers of patients involved, the large differences in cure rates seen are in reality due to a difference in a very small absolute number of patients.

Microbiologic Efficacy: According to the applicant, in the cefepime treatment group, a total of 6 pathogens were isolated from the 5 evaluable SSTI patients. Four (67%) of the 6 pathogens were eradicated and 2 (33%) persisted. Pathogens that persisted in the cefepime group included *E. coli*(1) and *K. pneumoniae*(1).

Six pathogens were isolated from the 4 evaluable SSTI in the ceftazidime treatment group. Four (67%) of the organisms were eradicated and 2 (33%) persisted. Organisms which persisted in the ceftazidime group included *K. pneumoniae*(1) and *Salmonella* spp (1).

According to the medical officer, only one patient in the cefepime treatment group was evaluable for microbiologic efficacy. The patient was infected with *S. aureus*. The pathogen was eradicated.

In the ceftazidime treatment group, 5 pathogens (*E. coli*(1), *K. pneumoniae*(2), *P. aeruginosa*(1), and *P. vulgaris*(1)) were recovered from 3 patients. Two patients (67%) were assigned the microbiologic outcome or eradication and in 1 (33%) patient a persistence was documented. The only organism that persisted in the ceftazidime treatment group was *K. pneumoniae*.

No new infections were documented in evaluable patients in either treatment group.

Efficacy Summary: The objective of study #111 was to assess the safety and efficacy of cefepime at a dose of 2 grams every 12 hours in patients with serious bacterial infections. Patient enrolled in study #111 were frequently suffering from neoplasia and often were receiving chemotherapy. Cefepime was compared to ceftazidime at a dose of 2 grams every 8 hours. The study was performed at multiple centers in Europe. A large proportion of the patients enrolled were treated for wound infections.

According to the applicant, 5/23 (22%) patients in the cefepime and 4/15 (27%) patients in the ceftazidime group were evaluable for efficacy. The clinical cure rate for cefepime was 4/5 (80%); the clinical cure rate for ceftazidime was 3/4 (75%). The applicant concluded that there was no difference between the two therapy with regard to clinical efficacy. A total of 6 pathogens were isolated from patients in the cefepime treatment group; 4/6 (67%) were eradicated. A total of 6 pathogens were isolated from patients in the ceftazidime treatment group 4/6 (67%) were eradicated. Again the applicant concludes that there is no difference between the two therapies with regard to microbiologic efficacy.

According to the medical officer, 6/23 patients (26%) in the cefepime treatment group and 6/15 patients (40%) in the ceftazidime treatment group were evaluable for clinical efficacy. The clinical cure rate for the cefepime treatment group was 2/6 (33%); the clinical cure rate for ceftazidime was 4/6 (67%). The number of evaluable patients is too small for meaningful statistical analysis. According to the medical officer, one patient in the cefepime treatment group was evaluable for microbiologic efficacy; the microbiologic response in that patient was eradication. Three patients in the ceftazidime treatment group were evaluable for efficacy. The eradication rate in the ceftazidime treatment group was 2/3 (67%). Again, the number of evaluable patients involved is too small to draw conclusions based on these results.

In conclusion, the small number of patients who were evaluable for efficacy makes it impossible to draw meaningful conclusion from the results of this single study.

Section V.2.2 - The Non-Comparative Trials

The safety and efficacy of cefepime in SSTI was studied in three non-comparative studies. The studies differed only in the dose of cefepime administered and the location of the study. All non-comparative studies used the same inclusion and exclusion criteria described in the common protocol. The procedures and observations described under the common protocol were also used for the non-comparative studies. Finally, the evaluability criteria and efficacy outcome definitions described previously were also used for the non-comparative studies. The results of the non-comparative studies will be presented in tabular form in this section.

Protocol Description: Table NC.1 summarizes the study location and dose of cefepime used in each of the non-comparative trials.

Table NC.1
Study Design - Non-Comparative Studies

Study Number	Location	Cefepime Dose	Dosing Interval
061	North American	1 gram ¹	Every 12 Hours
140	North American	2 grams	Every 12 Hours ²
067-LD	European	1 gram	Every 12 Hours
067-HD	European	2 grams	Every 12 Hours

¹Patients with severe infections could receive 2 grams BID

²Patients with severe infections could receive 2 grams TID

Enrollment: Table NC.2 summarizes the enrollment at each study center within the non-comparative trials.

Table NC.2
Enrollment - Non-Comparative Studies

Study/ Center	Investigator	Location	BMS		Med. Officer	
			Enrol	Eval	Clin. Eval	Full Eval
#061						
I-002	Timothy Sorg	Dayton, OH	2	0	0	0
I-004	R. Schwartz	Ft. Myers, FL	31	22	8	6
I-005	Harold Neu	New York, NY	2	2	0	0
I-006	Bienvenido Yangco	Tampa, FL	6	2	2	2
I-007	Jack LeFrock	Sarasota, FL	11	2	4	0
I-010	Charles Hanna	Spartanburg, SC	25	3	4	3
I-011	Carlos Ramirez-Ronda	San Juan, PR	17	12	5	5
I-012	Timothy Lane	Greensboro, NC	6	5	2	2
I-013	Robert McCabe	Martinez, CA	21	8	2	0
I-015	Sandra Handwerger	New York, NY	3	2	0	0
I-016	Michael Gelfand	Memphis, TN	27	13	1	1
I-020	William Hall	S. Portland, ME	3	0	0	0
I-023	William Mogabgab	New Orleans, LA	20	9	0	0
I-028	Richard Greenberg	St. Louis, MO	6	3	1	1

Table NC.2 - Continued
Enrollment - Non-Comparative Studies

Study/ Center	Investigator	Location	BMS		Med. Officer	
			Enrol	Eval	Clin. Eval	Full Eval
#061						
I-030	Susan Forlenza	East Meadow, NY	1	1	1	1
I-031	Gary Wormser	Valhalla, NY	7	1	1	1
I-035	R. Brooks Gainer II	Morgantown, WV	3	3	0	0
I-037	Paul Iannini	Danbury, CT	5	2	1	1
I-038	Lawrence Dall	Kansas City, MO	2	0	0	0
I-042	Nicolas Christou	Montreal, Quebec	3	0	1	0
I-043	Joseph G. Jemsek	Charlotte, NC	11	1	1	0
I-048	Stephen Green	Hampton, VA	6	4	1	1
I-050	Richard Olans	Malden, MA	2	0	1	0
TOTAL	061		220	95	36	24
140						
I-003	Hooker, K. Dale	Kansas City, MO	5	1	1	1
I-005	Hunt, Robert	South Bend, IN	6	2	2	1
I-007	Lerner, Charles	San Antonio, TX	6	0	1	0
I-009	Tan, James	Akron, OH	1	0	0	0
I-010	Hofstetter, Mark	Pittsburgh, PA	1	0	0	0
I-011	VanWay, Charles	Kansas City, MO	3	0	1	0
I-012	Yangco, Bienvenido	Tampa, FL	13	4	5	1
I-014	Butler, Thomas	Lubbock, TX	8	0	0	0
I-019	Neu, Harold	New York, NY	7	0	1	0
I-020	Brooks, Robert/ Sieger, Barry	Orlando, FL	19	9	9	8
I-022	Najem, Ahmad	East Orange, NJ	5	0	2	0
I-023	McCloskey, Richard	Philadelphia, PA	2	1	1	1
I-024	Glefand, Michael	Memphis, TN	2	1	0	0
I-026	Melcher, Gregory	Lackland AFB, TX	1	0	0	0
I-030	Jauregui, Luis	Toledo, OH	3	1	1	0
I-031	Smith, David	Kansas City, MO	3	1	1	1
I-040	Sorbello, Alfred Turnersville, NJ/ Stratford, NJ	Cherry Hill, NJ/				
TOTAL	140		86	20	25	13
*I-021	Gentry, Layne	Houston, TX San Jose, C.R.	38	0	0	0
067-LD						
I-004	H. Giamarellou	Athens, Greece	10	4	1	0
I-009	Y. Mouton	Tourcoing, France	6	1	2	1
I-011	P. Veyssier	Compiègne, France	2	1	2	1
TOTAL	067-LD		18	6	6	2
067-HD						
I-009	Y. Mouton	Tourcoing, France	2	0	0	0
I-011	P. Veyssier	Compiègne, France	4	2	4	2
I-012	J. Modai	Paris, France	1	0	0	0
I-021	Micoud/Stahl	Grenoble, France	5	0	4	0
TOTAL	067-HD		12	2	8	2

*-See Medical Officer's Comment on next page.

Medical Officer's Comments: During routine data verification, BMS medical monitors could not verify the results of pre-treatment cultures reported on the case report form for center #021 in study #140. Therefore, the applicant chose to exclude all patients from this center for the evaluation of efficacy. The M.O. concurs with the applicant's decision.

Population Characteristics: Table NC.3 summarizes the demographic characteristics of the enrolled population in the non-comparative studies.

Table NC.3
Demographic Characteristics

Parameter	Cefepime			
	Enroll.	BMS Eval.	Clinic. Eval.	Fully Eval.
Female	114 (30)	27 (22)	24 (32)	11 (27)
Male	260 (70)	96 (78)	51 (68)	30 (73)
White	268 (72)	86 (70)	55 (73)	29 (71)
Black	91 (24)	33 (27)	18 (24)	11 (24)
Hispanic	14 (4)	4 (3)	2 (3)	2 (5)
Other	1 (0)	-	-	-
Mean Age	48.0	49.0	50.1	48.7
Median Age	48	84	50	49
Age Range				
18-24	34 (9)	10 (8)	3 (4)	2 (4)
25-44	133 (36)	41 (33)	26 (35)	15 (37)
45-64	137 (37)	49 (49)	32 (43)	17 (41)
65-84	65 (17)	22 (18)	12 (16)	6 (15)
85 +	5 (1)	1 (1)	2 (3)	1 (2)
Mean Weight	80.4	82.8	84.9	87.2
Median Weight	75.9	79	79	81
Range				

Medical Officer's Comments: There were no significant differences noted between the enrolled and evaluable groups with respect to any demographic variable observed.

Clinical Efficacy: Table NC.4 summarizes the clinical efficacy observed in each of the non-comparative studies of cefepime.

Table NC.4
Clinical Efficacy in Non-Comparative Studies

Study Outcome	BMS (Percent)	Clinically Evaluable (Percent)	Fully Evaluable (Percent)
North American Studies			
061 (1 gram BID)			
Success	86/95 (91%)	18/36 (50%)	12/24 (50%)
Failure	9/95 (9%)	17/36 (47%)	11/24 (46%)
Indeterminate ¹		1/36 (3%)	1/24 (4%)
140 (2 grams BID)			
Success	18/20 (90%)	22/25 (88%)	11/13 (85%)
Failure	2/20 (10%)	3/25 (12%)	2/13 (15%)
European Studies²			
067-LD (1 gram BID)			
Success	6/6 (100%)	4/6 (67%)	0/2 (0%)
Failure	0/0 (0%)	2/6 (33%)	2/2 (100%)
067-HD (2 grams BID)			
Success	2/2 (100%)	8/8 (100%)	2/2 (100%)
Failure	0/2 (0%)	0/8 (0%)	0/2 (0%)

1- This patients was placed on ciprofloxacin for the persistence of *P. aeruginosa* during treatment, however, at the time that the antimicrobial was changed the patients had no signs or symptoms of disease.

Medical Officer's Comments: Although the results of non-comparative studies must be interpreted with caution, it can be inferred from the results of both the North American and European studies that 2 grams BID gives superior efficacy in SSTI than 1 gram BID dosing.

Medical Officer's Comments: The non-comparative studies seem to confirm the results of the comparative studies indicating the efficacy of the 2 gram BID dose in SSTI but the lack of efficacy of lower doses.

Microbiologic Efficacy: Table NC.5 summarizes the microbiologic efficacy.

Table NC.5
Microbiologic Efficacy by Patient

Study # Outcome	BMS (Percent)	Medical Officer (Percent)
North American Studies		
061 (1 gram BID)	95	24
Eradication	73 (77%)	13 (54%)
Persistence	22 (23%)	11 (46%)
140 (2 grams BID)	20	13
Eradication	18 (90%)	11 (85%)
Persistence	2 (10%)	2 (15%)
European Studies		
067-LD (1 gram BID)	6	2
Eradication	4 (67%)	1 (50%)
Persistence	2 (33%)	1 (50%)
067-HD (2 grams BID)	2	2
Eradication	2 (100%)	2 (100%)
Persistence	0	0

Medical Officer's Comment: Similar eradication rates were seen in both the applicant's and the medical officer's evaluable populations. In both North American and European non-comparative trials, higher eradication rates were seen in those patients who received high-dose cefepime therapy.

Microbiologic Response by Infecting Organism: Table NC.6 lists the microbiologic response by infecting organism in the non-comparative studies for the medical officer's fully evaluable population.

Table NC.6
Microbiological Response by Infecting Organism

Parameter	CEFEPIME

Study #061	
E. CLOACAE	0/ 1 (0%)
E. COLI	1/ 2 (50%)
K. PNEUMONIAE	0/ 1 (0%)
P. AERUGINOSA	2/ 4 (50%)
P. MIRABILIS	0/ 1 (0%)
P. MULTOCIDA	0/ 1 (0%)
S. AUREUS	9/ 16 (56%)
S. MARCESCENS	0/ 1 (0%)
STREP. (GROUP A)	6/ 7 (86%)
STREP. (GROUP B)	0/ 2 (0%)
STREP. SP.	0/ 1 (0%)

TOTALS Study #061	18/ 37 (49%)

Study # 140	
B. FRAGILIS	0/ 1 (0%)
N. CONORRHOEAE	1/ 1 (100%)
P. AERUGINOSA	0/ 1 (0%)
P. MIRABILIS	1/ 2 (50%)
S. AUREUS	2/ 2 (100%)
S. AUREUS (MS)	5/ 6 (83%)
STREP. (GROUP A)	4/ 4 (100%)
STREP. (GROUP B)	1/ 1 (100%)
STREP. (GROUP G)	1/ 1 (100%)

TOTAL (Study #140)	15/ 19 (79%)

Study #067-LD	
S. AUREUS	1/ 2 (50%)

TOTAL (Study #067LD)	1/ 2 (50%)

Study #067-HD	
FUSOBACTERIUM SP.	1/ 1 (100%)
PEPTOSTREPTOCOCCUS SP.	1/ 1 (100%)
S. AUREUS	1/ 1 (100%)

TOTAL (Study 067HD)	3/ 3 (100%)

TOTAL NON-COMPARATIVE	37/ 61 (61%)

Organisms Persisting: The following organism persisted after treatment with low-dose cefepime (1.0 grams every 12 hours): *E. cloacae*(1), *E. coli*(1), *K. pneumoniae*(1), *P. aeruginosa*(2), *P. mirabilis*(1), *P. multocida*(1), *S. aureus*(8), Group-A Streptococci(1), Group-B Streptococci(2), other Streptococcal species (2).

The following organisms persisted after treatment with high-dose cefepime (2.0 grams every 12 hours). *B. fragilis*(1), *P. aeruginosa*(1), *P. mirabilis*(1), and *S. aureus*(1).

Efficacy Conclusions: Cefepime was studied in three non-comparative studies. Study #061, conducted in North America, studied the efficacy of a low-dose cefepime (1.0 grams every 12 hours). Although the study enrolled over 200 patients, the medical officer considered only 36 patients to be clinically evaluable and 24 patients to be microbiologically evaluable. The principal reason for which the medical officer considered patients to be not-evaluable in this study was that many patients had their post-therapy assessment on the day of completion of therapy. For reasons stated earlier, the medical officer required that patients be assessed at least five days after the completion of therapy.

75/95 (77%)

13/24
(54%)
12/14/H

According to the applicant, the clinical cure rate seen in this low-dose study was 86/95 (90%), however according to the medical officer, the clinical cure rate was 18/36 (50%). There was a similar disparity in the microbiologic eradication rate, the applicant reporting 95% eradication and the medical officer reporting a 24% eradication rate. The reader will recall that the dose used in this study 1.0 grams every 12 hours was not shown to be equivalent to a similar dose of ceftazidime in comparative studies. The medical officer believes that the low clinical cure rates and microbiologic eradication rates seen in this non-comparative study confirm the lack of efficacy of this dose demonstrated in the comparative studies.

Study #140 was also conducted in several North American centers. Study #140 assessed the efficacy of a high-dose of cefepime (2.0 grams every 12 hours) in patients with severe infections. According to the applicant, the clinical cure rate was 18/20 (90%), according to the medical officer the clinical cure rate was 22/25 (88%). With respect to microbiologic efficacy, the applicant determined that the infection was eradicated in 18/20 patients (90%), the medical officer determined that the infection was eradicated in 11/13 patients (85%). Again, the reader will recall that in comparative studies cefepime, at a dose of 2.0 grams every 12 hours was shown to be equivalent to a similar dose of ceftazidime. It is the opinion of the medical officer that the results of study #140 confirms the efficacy of cefepime at a dose of 2.0 grams every 12 hours, that was seen in the comparative studies.

Study #067 was conducted at multiple centers in Europe. Study #067 had two arms. A low-dose arm studied the safety and effectiveness of cefepime at a dose of 1.0 grams every 12 hours; the high dose arm studied the safety and effectiveness of cefepime at a dose of 2.0 grams every 12 hours. According to both the applicant and the medical officer only small numbers of patients were evaluable from either of the two arms. The clinical and microbiological efficacy demonstrated in study #067 are reported in tables NC.5 and NC.6. In general, although the numbers are small, clinical and microbiological success rates were similar to those seen in the two North American non-comparative studies discussed previously (#061 and #140).

In conclusion, the results of the non-comparative seem to be supportive of conclusions reached in the analysis of the comparative studies.

Section V.3 - Integrated Efficacy Summary for Skin and Soft Tissue Infections

Section V.3.1 - Enrollment and Evaluability: In total, the results from 1331 patients were submitted by the applicant in support of their claim of efficacy for cefepime in patients with SSTI. Of the 1331 patients, 571 were treated with cefepime and 386 were treated with ceftazidime in comparative clinical trials. There were 374 patients treated with cefepime in non-comparative trials.

146 patients (cefepime=94, ceftazidime=52) were studied at a center where information was not available to verify the data entered on the case report form. The applicant chose to exclude these patients, a-priori, from any analysis of efficacy. The medical officer concurs with the applicant's approach regarding these patients.

Among patients in the comparative clinical trials, the applicant determined that 214/571 cefepime patients (37%) and 136/386 ceftazidime patients (35%) were evaluable for the assessment of efficacy. The medical officer determined that 227/571 cefepime patients (40%) and 142/386 ceftazidime patients (37%) were evaluable for the determination of clinical efficacy. In addition, the medical officer determined that 140/571 cefepime patients (25%) and 90/386 ceftazidime patients (23%) were evaluable for the determination of both clinical and microbiological efficacy.

The applicant determined that an additional 123/374 cefepime patients (33%) enrolled in non-comparative trials were also evaluable for the assessment of efficacy. The medical officer determined that an additional 75/374 cefepime patients (20%) enrolled in non-comparative trials were evaluable for the determination of clinical efficacy and an additional 41/374 (11%) of cefepime patients enrolled in non-comparative trials were evaluable for the determination of both clinical and microbiological efficacy.

Table ES.1, on the following page, lists the enrollment and evaluability in each of the nine studies submitted in support of this application.

Table ES.1
Enrollment and Evaluability in SSTI Studies
as Determined by Both the Applicant (BMS) and the Reviewing Medical Officer

Dose	Dose		Enrollment		BMS		Med. Officer		Med. Officer	
	Cefep. ¹	Ceftaz. ¹	Cefep.	Ceftaz.	Evaluable		Clinically Evaluable		Fully Evaluable	
					Cefep.	Ceftaz.	Cefep.	Ceftaz.	Cefep.	Ceftaz.
075/NA	0.5 grams	0.5 grams	104	50	37	20	35	15	27	15
081/NA	1.0 grams	1.0 grams	198	100	93	37	100	36	65	22
081/Eur	1.0 grams	1.0 grams	32	15	5	6	7	6	0	2
097/NA ⁴	2.0 grams	2.0 grams	214	206	74	69	79	79	47	48
111/Eur	2.0 grams	2.0 gram	23	15	5	4	6	6	1	3
Total Compar.			571	386	214 (37%)	136 (35%)	227 (40%)	142 (37%)	140 (25%)	90 (23%)
061/NA	1.0 grams ³	NA	220	NA	95	NA	36	NA	24	NA
067/LD/Eu	1.0 grams	NA	18	NA	6	NA	6	NA	2	NA
140/NA ⁵	2.0 grams ³	NA	124	NA	20	NA	25	NA	13	NA
067/HD/Eu	2.0 grams	NA	12	NA	2	NA	8	NA	2	NA
Total Non-Comp			374	NA	123 (33%)	NA	75 (20%)	NA	41 (11%)	NA
Total			945	386	337 (36%)	136 (35%)	302 (32%)	142 (37%)	181 (19%)	90 (23%)

1- Cefepime was administered every 12 hours except where noted.

2- Ceftazidime was administered every 8 hours in all cases.

3- 22 enrolled patients were treated with doses other than 1.0 gram BID including: 750 mg BID(1); 1.0 gram TID(1); 1.5 gram TID(1); 2.0 gram BID(13); and 2.0 gram TID(5).

4- Includes the 108 patient (cefepime=56, ceftazidime=52) from center #027 excluded by the BMS medical monitors (See page-50).

5- Includes the 38 patients from center #021 excluded by BMS medical monitors (See page-73).

Section V.3.2 - Demographics: The majority of patients in all evaluability and treatment groups were white males. There were no significant differences noted between the two treatment groups with respect to any demographic parameter in either the applicant's or the medical officer's evaluable populations. There was a trend toward lower weights in the ceftazidime treatment group. Table ES.2 summarizes the demographic characteristics of the enrolled and evaluable populations.

Table ES.2
Demographic Characteristics
Patients Enrolled in Comparative Studies

Parameter	Enrolled ¹		BMS		Med. Officer		Med. Officer	
	Cefep	Ceftaz	Evaluable		Clinically Eval.		Fully Eval.	
			Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz
Female	178(35)	119(36)	73(34)	50(37)	70(31)	51(36)	35(25)	32(36)
Male	337(65)	215(64)	141(66)	86(63)	157(69)	91(64)	105(75)	58(64)
White	340(66)	214(64)	145(68)	84(62)	159(70)	89(63)	99(71)	56(62)
Black	151(29)	102(31)	57(27)	45(33)	56(25)	45(31)	35(25)	30(33)
Hispanic	21(4)	12(4)	11(5)	4(3)	11(5)	5(3)	6(4)	1(1)
Oriental	1(0)	4(1)	0(0)	3(2)	0(0)	3(2)	0(0)	3(3)
Other	2(1)	2(1)	1(0)	0(0)	1(0)	0(0)	0(0)	0(0)
Mean Age	49.2	49.4	48.6	46.5	49.3	48.1	45.6	42.7
Median Age	47	46	47	44	48	46	44	40
Age Range								
< 18	1(0)	0(0)	1(0)	0(0)	1(0)	0(0)	1(1)	0(0)
18-24	57(11)	33(10)	28(13)	15(11)	25(11)	15(11)	22(16)	12(13)
25-44	174(34)	123(37)	70(33)	56(41)	71(31)	53(37)	50(36)	41(46)
45-64	156(30)	91(27)	61(29)	36(26)	72(32)	40(28)	39(28)	24(26)
65-84	111(22)	75(22)	50(23)	26(19)	53(24)	29(20)	27(19)	13(14)
85 +	16(3)	12(4)	4(2)	3(2)	5(2)	5(5)	1(1)	0(0)
Mean Weight	79.1	75.9	79.6	77.9	80.5	78.2	82.6	79.1
Median Weight	76	73	77	75	77	76	77	75
Range								

1- Does not include the 108 patients (cefepime=56, ceftazidime=52) that were excluded a-priori by the sponsor for inadequate documentation of results.

Section V.3.3 - Clinical Diagnosis: The medical officer assigned a clinical diagnosis to each patient based on a review of the investigator comment pages of the case report form. The following diagnosis were assigned: cellulitis, abscess, furuncle, otitis externa, wound infection, and superinfection of a chronic ulcer. Cellulitis was the most commonly assigned diagnosis, present in over 50% of the evaluable patients. Table ES.3 summarizes the medical officer's assignment of clinical diagnoses.

Table ES.3
Clinical Diagnosis at Study Entry
(M.O. Table)

Diagnosis	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
N=	227	142	140	90
Cellulitis	117 (51%)	68 (48%)	75 (54%)	49 (54%)
Abscess	44 (19%)	38 (27%)	34 (24%)	28 (31%)
Wound Infection	41 (18%)	17 (12%)	24 (17%)	9 (10%)
Superinfected Ulcer	22 (10%)	15 (10%)	5 (4%)	2 (2%)
Infected Burns	1 (0%)	1 (0%)	0	0
Fasciitis	0 (0%)	1 (0%)	0	0
Furuncle	2 (1%)	0 (0%)	2 (1%)	0
Otitis Externa	0 (0%)	2 (1%)	0	2 (2%)

Section V.3.4 - Severity: In all cases, the medical officer accepted the principal investigator's assessment of the severity of the infection. The medical officer felt that patients with "mild" infections were not appropriate for study in trials of parenteral agents, therefore, the medical officer only considered patients with moderate or severe infections to be evaluable. There were no significant differences between the two treatment groups with respect to severity of infection. Table ES.4 summarizes the severity of infection in the medical officer's evaluable populations.

Table ES.4
Severity of Infection
(M.O. Table)

Severity	Clinically Evaluable		Fully Evaluable	
	Cefepime	Ceftaz.	Cefepime	Ceftaz.
N=	227	142	140	90
Moderate	153 (67%)	90 (63%)	96 (69%)	57 (63%)
Severe	74 (33%)	52 (37%)	44 (31%)	33 (37%)

Section V 1.5 - Clinical Efficacy/Comparative Studies: The Clinical Efficacy is the primary determinant of efficacy for antimicrobial agents in SSTI. The next five tables will summarize the clinical efficacy observed in the SSTI trials for cefepime.

Table ES.5 reports the clinical efficacy by sex, race, and age. There were no marked differences noted in efficacy between males and females. There were no differences in efficacy between patients in different racial groups. In the medical officer's evaluable population there was a trend observed toward decreased efficacy for cefepime but not for ceftazidime in older individuals. This trend was not seen in the applicant's evaluable population.

Table ES.5
Clinical Efficacy by Demographic Variable

Population	BMS		Medical Officer			
			Clinically Eval.		Fully Eval.	
	Cefep.	Ceftaz.	Cefep.	Ceftaz.	Cefep.	Ceftaz.
All	189/214 (88%)	120/136 (88%)	173/227 (76%)	120/142 (85%)	115/140 (82%)	85/90 (95%)
Males	129/141 (91%)	79/86 (92%)	121/157 (77%)	79/91 (87%)	86/105 (82%)	55/58 (95%)
Females	60/73 (82%)	41/50 (82%)	52/70 (74%)	41/51 (80%)	29/35 (83%)	30/32 (94%)
White	130/145 (90%)	73/84 (87%)	123/159 (77%)	71/89 (80%)	83/99 (84%)	53/56 (95%)
Black	49/57 (86%)	40/45 (89%)	40/56 (71%)	41/45 (91%)	26/35 (74%)	28/30 (93%)
Other Races	10/12 (83%)	7/7 (100%)	10/12 (83%)	8/8 (100%)	6/6 (100%)	4/4 (100%)
< 65 years	143/160 (89%)	95/107 (89%)	135/169 (80%)	94/108 (87%)	96/112 (86%)	72/77 (93%)
≥ 65 years	46/54 (85%)	25/29 (86%)	38/58 (66%)	26/34 (76%)	19/28 (68%)	13/13 (100%)

Table ES.6 reports the clinical efficacy by study location. There was a trend toward lower clinical success rates in European studies compared with North American studies. This trend was evident in the applicant's evaluable population and the medical officer's clinically evaluable population.

Table ES.6
Clinical Efficacy by Study Location

Population	BMS		Medical Officer			
			Clinically Eval.		Fully Eval.	
	Cefep.	Ceftaz.	Cefep.	Ceftaz.	Cefep.	Ceftaz.
All	189/214 (89%)	120/136 (88%)	173/227 (76%)	120/142 (85%)	115/140 (82%)	85/90 (95%)
North American	181/204 (89%)	113/126 (90%)	166/214 (78%)	111/130 (85%)	114/139 (82%)	80/85 (94%)
European	8/10 (80%)	7/10 (70%)	7/13 (54%)	9/12 (75%)	1/1 (100%)	5/5 (100%)

Table ES.7 reports the clinical efficacy by study design. There was a trend toward lower comparative efficacy of cefepime compared with ceftazidime at the blinded centers. No conclusions can be drawn from this trend because of the small number of patients studied at blinded centers.

Table ES.7
Clinical Efficacy by Study Design

Population	BMS		Medical Officer			
			Clinically Eval.		Fully Eval.	
	Cefep.	Ceftaz.	Cefep.	Ceftaz.	Cefep.	Ceftaz.
All	189 (89%)	120/136 (88%)	173/227 (76%)	120/142 (85%)	115/140 (82%)	85/90 (95%)
Unblinded	175/199 (88%)	103/119 (87%)	160/212 (75%)	100/121 (83%)	106/131 (81%)	69/74 (93%)
Blinded	14/15 (93%)	17/17 (100%)	13/15 (87%)	20/21 (95%)	9/9 (100%)	16/16 (100%)

Table ES.8 summarizes the clinical efficacy by dose of cefepime received.

Cefepime 500 mg BID was studied in one study of patients with SSTI (Study No. 075); Cefepime was compared with ceftazidime 500 mg TID. According to the applicant, the clinical cure rate seen among patients with SSTI treated with cefepime 500 mg BID was 33/37 (89%), the clinical cure rate seen among patients with SSTI treated with ceftazidime 500 mg TID was 19/20 (95%). According to the medical officer, the clinical cure rate seen among patients with SSTI treated with cefepime 500 mg BID was 26/35 (74%), the clinical cure rate seen among patients with SSTI treated with ceftazidime 500 mg TID was 15/15 (100%). Given the observed clinical cure rates, a lower bound of the 95% confidence interval around the true difference in cure rates that is closer to zero than -10% would be required to demonstrate equivalence. The observed lower bound of the corrected 95% confidence interval was -24% for the applicant's data and -45% for the medical officer's data. Therefore the applicant failed to demonstrate equivalence between cefepime at a dose of 0.5 grams every 12 hours and ceftazidime at a dose of 0.5 grams every 8 hours by the 95% confidence interval approach. The medical officer's analysis of the data for the dose of 0.5 grams every 12 hours also failed to demonstrate equivalence between the two treatment regimens.

Cefepime 1.0 gram BID was studied in one comparative study of patients with SSTI (study #081); Cefepime was compared with ceftazidime 1.0 mg TID. Study #081 included both U.S. and European centers. According to the applicant, the clinical cure rate seen among patients with SSTI treated with cefepime 1.0 g BID was 86/98 (88%), the clinical cure rate seen among patients with SSTI treated with ceftazidime 1.0 g TID was 37/43 (86%). According to the medical officer, the clinical cure rate seen among patients with SSTI treated with cefepime 1.0 g BID was 81/107 (76%), the clinical cure rate seen among patients with SSTI treated with ceftazidime 1.0 g TID was 36/42 (86%). Given the observed clinical cure rates, a lower bound of the 95% confidence interval around the true difference in cure rates that is closer to zero than -15% would be required to demonstrate equivalence. The observed lower bound of the corrected 95% confidence interval was -12% for the applicant's data and -25% for the medical officer's data. Therefore, the applicant demonstrated equivalence between cefepime at a dose of 1.0 gram every 12 hours and ceftazidime at a dose of 1.0 grams every 8 hours by the 95% confidence interval approach. However, the medical officer was not able to confirm the applicant's finding of equivalence between cefepime and ceftazidime at a dose of 1.0 gram every 12 hours.

Cefepime 2.0 grams BID was studied in two studies of patients with SSTI (study nos: 097, 111); Cefepime was compared with ceftazidime 2.0 grams TID. Because of differences in design and population, the studies will be considered separately.

In study #097, according to the applicant, the clinical cure rate seen among patients with SSTI treated with cefepime was 66/74 (89%), the clinical cure rate seen among patients with SSTI treated with ceftazidime was 61/69 (89%). According to the medical officer, the clinical cure rate seen among patients with SSTI treated with cefepime was 64/79 (81%), the clinical cure rate seen among patients with SSTI treated with ceftazidime was 65/79 (82%). Given the observed clinical cure rates, a lower bound of the 95% confidence interval around the true difference in cure rates that is closer to zero than -15% would be required to demonstrate equivalence. The observed lower bound of the corrected 95% confidence interval was -11% for the applicant's data and -15% for the medical officer's data. Therefore, the applicant's and the medical officer's analysis has demonstrated equivalence of the two treatment groups by the 95% confidence interval approach.

In study #111, according to the applicant, 4/5 (80%) patients in the cefepime treatment group and 3/5 (75%) patients in the ceftazidime treatment group had satisfactory clinical outcomes. According to the medical officer, 2/6 patients (33%) in the cefepime treatment group and 4/6 (67%) patients in the ceftazidime treatment group were clinically cured of their infection. Because of the small numbers of evaluable patients in this trial, a meaningful confidence interval analysis can not be performed.

Table ES.8
Clinical Efficacy by Dose Received

Dose	Studies	BMS		Medical Officer			
		Cefep.	Ceftaz.	Clinically Eval.		Fully Eval.	
				Cefep.	Ceftaz.	Cefep.	Ceftaz.
All Doses		189/214 (88%)	120/136 (88%)	173/227 (76%)	120/142 (85%)	115/140 (82%)	85/90 (95%)
0.5 grams	075	33/37 (89%)	19/20 (95%)	26/35 (74%)	15/15 (100%)	22/27 (81%)	15/15 (100%)
	95% CI	[-24%, +12%]		[-45%, +7%]		[-38%, +1%]	
1.0 grams	081/NA	82/93 (88%)	33/37 (89%)	76/100 (76%)	31/36 (86%)	53/65 (82%)	21/22 (96%)
	081/EU	4/5 (80%)	4/6 (67%)	5/7 (71%)	5/6 (83%)	0	2/2 (100%)
	All 1.0 Grams	80/98 (82%)	37/43 (86%)	81/107 (76%)	36/42 (86%)	53/65 (82%)	23/24 (96%)
	95% CI	[-12%, +16%]		[-25%, +6%]		[-29%, +1%]	
2.0 Grams	097	66/74 (89%)	61/69 (89%)	64/79 (81%)	65/79 (82%)	39/47 (83%)	44/48 (92%)
	95% CI	[-11%, +13%]		[-15%, +12%]		[-24%, +7%]	
	111	4/5 (80%)	3/4 (75%)	2/6 (33%)	4/6 (67%)	1/1 (100%)	3/3 (100%)
	95% CI	[-73%, +83%]		[-103%, +37%]		[-67%, +67%]	
All 2.0 grams		70/79 (89%)	64/73 (88%)	66/85 (78%)	69/85 (81%)	40/48 (83%)	47/51 (92%)

Medical Officer's Comment: In study #097, the pivotal study at the 2.0 gram dose, equivalent clinical efficacy was observed in patients treated with both cefepime and ceftazidime in the applicant's evaluable population and in the medical officer's clinically evaluable population. However, in the medical officer's fully evaluable population, there is a discrepancy in clinical outcome between the two treatment groups. 39/47 fully evaluable patients (83%) who were treated with cefepime were cured of their infection. In contrast, 44/48 fully evaluable patients (92%) who were treated with ceftazidime were cured of their infection.

Further analysis of the data from study #097 reveals that similar eradication rates were observed in the two treatment groups for fully evaluable patients with cellulitis (cefepime:19/21(83%), ceftazidime:21/22(95%)) and abscess (cefepime:12/13(92%), ceftazidime(17/19(89%)). However, in patients with wound infections, a smaller proportion of patients in the cefepime group were cured of their infection (7/12, 58%) compared with the ceftazidime group (5/5, 100%).

The fully evaluable patients with wound infection were analyzed in additional detail to determine the cause of the observed discrepancy in clinical outcome. There were 17 fully evaluable patients with wound infection, 12 were treated with cefepime and 5 were treated with ceftazidime. 10/12 patients (83%) in the cefepime treatment group and 3/5 patients (60%) in the ceftazidime treatment groups were male. The mean age in the two treatment groups was similar (cefepime=45.8, ceftazidime=41.1). Two patients in the cefepime treatment group were diabetics, however, no patients in the ceftazidime treatment group were diabetics.

In the cefepime treatment group, one patient (8%) was treated for a post-traumatic wound, 8 patients (67%) for post-operative wounds, and 3 patients (25%) for bite wounds. In the ceftazidime treatment group, there was 1 post-traumatic wound (20%), 3 post-operative wounds (60%) and 1 bite wound (20%). In the cefepime treatment group 9 wounds (75%) involved the extremities while 4 wounds (25%) involved the face or trunk. In the ceftazidime treatment group, 4/5 wounds (80%) involved the extremities while 1/5 wounds (20%) involved the face or trunk.

Adjunctive surgical procedures (debridement, incision and drainage) were performed, during therapy, for 1 cefepime patient (8%) and for 2 ceftazidime patients (40%).

The causative organisms were *S. aureus* and Group-A Streptococci in the majority of cases in both treatment groups.

A brief description of the involved patients follows:

Cefepime Patients There were twelve fully evaluable patients with wound infection that were treated with cefepime.

Cefepime Failures Five of 12 patients (42%) with wound infection were considered clinical failure by the medical officer.

P.I.D. 23 y.o. female; DX: Post-traumatic wound, ankle; Organism: Group-A Streptococcus; BMS Clinical Response: Satisfactory; Course: The patient received 12 doses of cefepime (6 days). The last evaluation occurred one day post-therapy. Pain, erythema and edema were improved but still present. The causative organism persisted. M.O. Clinical Response: Unsatisfactory.

P.I.D. 69 y.o. male; DX: Post-op wound, abdominal; Organism: *S. aureus*; BMS Clinical Response: Satisfactory; Course: The patient received 27

doses of cefepime (14 days). The last evaluation occurred 11 days post-therapy. Erythema and exudate were improved but still present. The organism was eradicated. M.O. Clinical Response: Unsatisfactory.

P.I.D.: 63 y.o. male, diabetic; DX: Post-op wound, leg; Organism: *S. aureus*, *P. aeruginosa*; BMS Clinical Response: Unsatisfactory Course: The patient received 7 doses of cefepime (4 days). The last evaluation occurred on the fourth day of therapy. Cefepime was discontinued and the patient was placed on vancomycin and ciprofloxacin (treatment ineffective). One organism (*P. aeruginosa*) persisted. M.O. Clinical Response: Unsatisfactory

P.I.D.: 57 y.o. male; DX: Post-op wound, leg; Organism: *S. aureus*; BMS Clinical Response: Unable to determine; Course: The patient received 7 doses of cefepime (4 days). The last evaluation occurred on the fourth day of therapy. Cefepime was discontinued and the patient was placed on vancomycin (other antibiotic wanted by physician). The causative organism persisted. M.O. Clinical Response: Unsatisfactory.

P.I.D.: 19 y.o. male; DX: Post-op wound, hip; Organism: *S. aureus*; BMS Clinical Response: Unsatisfactory; Course: The patient received 21 doses of cefepime (11 days). The last evaluation occurred 6 days post-therapy. The patient was placed on Timentin, tobramycin and nafcillin for persistent positive culture. M.O. Clinical Response: Unsatisfactory.

Cefepime Successes Seven of 12 fully evaluable patients (58%) were considered cured of their infection by the medical officer.

P.I.D.: 67 y.o., male; DX: Post-op wound, leg; Organism: *S. aureus*; BMS Clinical Response: Satisfactory. M.O. Clinical Response: Satisfactory.

P.I.D.: 69 y.o., male, diabetic; DX: Post-op wound, groin; Organism: *S. marcescens*; BMS Clinical Response: Satisfactory. M.O. Clinical Response: Satisfactory.

P.I.D.: 52 y.o., female; DX: Post-op wound, leg; Organism: *E. coli*; Course: Debridement on day #13; BMS Clinical Response: Satisfactory. M.O. Clinical Response: Satisfactory.

P.I.D.: 54 y.o., male; DX: Post-op wound, face; Organism: *S. aureus*, Group-A Streptococcus; BMS Clinical Response: Satisfactory. M.O. Clinical Response: Satisfactory.

P.I.D.: 22 y.o. male; DX: Dog Bite, hand; Organism: *S. aureus*; BMS Clinical Response: Satisfactory. M.O. Clinical Response: Satisfactory.

P.I.D.: 28 y.o., male; DX: Human Bite, hand; Organism: Streptococcus (alpha-hemolytic), *E. corrodens*; BMS Clinical Response: Satisfactory. M.O. Clinical Response: Satisfactory.

P.I.D.: 27 y.o. male; DX: Human Bite, hand; Organism: Group-A Streptococcus, *S. aureus*; BMS Clinical Outcome: Satisfactory. M.O. Clinical Response: Satisfactory.

Ceftazidime Patients - There were five fully evaluable patients with wound infection.

Ceftazidime Failures - No fully evaluable patients were considered to be clinical failures by the medical officer.

Ceftazidime Successes - Five of five fully evaluable patients (100%) were considered to be clinical successes by the medical officer.

P.I.D.: 44 y.o., female; DX Post-op wound, face; Organism: *P. aeruginosa*; BMS Clinical Outcome: Satisfactory.

P.I.D.: 22 y.o. male; DX: Post-traumatic wound (knife assault), hand; Organism: *S. aureus*; BMS Clinical Response: Satisfactory. M.O. Clinical Response: Satisfactory.

P.I.D.: 76 y.o., female; DX: Post-op wound, leg; Organism: *P. aeruginosa*, *M. morganii*; Course: Debridement day #6 and 9; BMS Clinical Outcome: Satisfactory. M.O. Clinical Response: Satisfactory.

P.I.D.: 29 y.o. male; DX: Post-traumatic wound (MVA), arm; Organism: *S. aureus*, Group-A streptococcus; BMS Clinical Outcome: Satisfactory. M.O. Clinical Response: Satisfactory.

P.I.D.: 36 y.o. male; DX: Human Bite; Organism: Group-A Streptococcus, *S. aureus*; Course: Incision and Drainage day #2 and #5; BMS Clinical Outcome: Satisfactory. M.O. Clinical Response: Satisfactory.

In conclusion, there is a notable difference in the clinical outcome between the cefepime and ceftazidime treatment groups for fully evaluable patients with wound infections. This difference is not accounted for by any differences in sex, age, organism, body site, or type of wound between the two treatment groups. There were two patients in the cefepime treatment group with diabetes mellitus. Also, more patients in the ceftazidime treatment group underwent surgical procedures during treatment (cefepime=1, ceftazidime=2) which may have elevated the success rate in the ceftazidime treatment group. These cited differences involve small numbers of patients and may not account for the observed discrepancy in clinical outcome.

Therefore, although cefepime and ceftazidime appear to be equally efficacious in patients with cellulitis and abscesses, cefepime may be less efficacious than ceftazidime in patients with ~~wound~~ infection. The final approved label for cefepime should reflect this possibility.

wound

The most common diagnoses recorded were cellulitis, abscess and wound infection. The clinical efficacy for each diagnosis paralleled the overall trends. In both treatment groups, patients with infected skin ulceration did poorly. Table ES.10 summarizes the clinical efficacy by infection type.

Table ES.9
Clinical Efficacy by Diagnosis
(According to the Medical Officer)

Diagnosis	Dose of Cefepime							
	All Doses		500 mg		1.0 grams		2.0 grams	
	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz
Cellulitis	94/118 (80%)	62/70 (89%)	9/15 (60%)	9/9 (100%)	52/67 (78%)	22/24 (92%)	32/35 (91%)	29/35 (83%)
Abscess	36/44 (82%)	35/38 (92%)	8/9 (89%)	5/5 (100%)	11/15 (73%)	6/7 (86%)	17/20 (85%)	24/26 (92%)
Wound Infection	29/41 (71%)	14/17 (82%)	8/8 (100%)	1/1 (100%)	7/9 (78%)	1/1 (100%)	14/24 (58%)	12/15 (80%)
Infected Ulcers	12/22 (55%)	9/15 (60%)	1/3 (33%)	--	8/13 (62%)	7/9 (78%)	3/6 (50%)	2/6 (33%)
Other Diagnosis*	3/3 (100%)	2/4 (50%)	--	--	3/3 (100%)	0/1 (0%)	--	2/3 (67%)

*Includes: Superinfection of burns, fasciitis, furuncles, and otitis externa.

Comment: For some diagnoses, lower clinical cure rates were seen with higher doses of cefepime. It is possible that this ~~phenomena~~ phenomenon is due to the greater severity of illness present in patients enrolled in high dose studies.

phenomenon

Section V.3.6 - Clinical Efficacy/Non-Comparative Studies: Table ES.10 reviews the clinical efficacy seen in non-comparative studies. The finding in the non-comparative studies seem to confirm the results seen in the comparative studies. At a dose of 1.0 grams every 12 hours, acceptable clinical cure rates are seen in the applicant's evaluable population (91%), however, in the medical officer's evaluable population, the clinical cure rates are much lower (50%). At a dose of 2.0 grams acceptable clinical cure rates are seen in both the applicant's evaluable populations and the medical officer's evaluable populations. (Efficacy > 85% in all populations). Thus, the results of the non-comparative studies confirms the efficacy of cefepime 2.0 grams every 12 hours for SSTI.

Table ES.10
Clinical Efficacy in Non-Comparative Studies

Study Outcome	BMS (Percent)	Clinically Evaluable (Percent)	Fully Evaluable (Percent)
North American Studies			
061 (1 gram BID)			
Success	86/95 (91%)	18/36 (50%)	12/24 (50%)
Failure	9/95 (9%)	17/36 (47%)	11/24 (46%)
Indeterminate		1/36 (3%)	1/24 (4%)
140 (2 grams BID)			
Success	18/20 (90%)	22/25 (88%)	11/13 (85%)
Failure	2/20 (10%)	3/25 (12%)	2/13 (15%)
European Studies			
067-LD (1 gram BID)			
Success	6/6 (100%)	4/6 (67%)	0/2 (0%)
Failure	0/0 (0%)	2/6 (33%)	2/2 (100%)
067-HD (2 grams BID)			
Success	2/2 (100%)	8/8 (100%)	2/2 (100%)
Failure	0/2 (0%)	0/8 (0%)	0/2 (0%)

Section V.3.7 - Microbiologic Efficacy: The results of the applicant's and the medical officer's determination of microbiologic efficacy will be presented in the following tables for each dosage group.

According to the applicant, 48/57 pathogens (84%) were eradicated after treatment with cefepime 500 mg BID and 28/29 pathogens (97%) were eradicated after treatment with ceftazidime 500 mg TID. The 95% confidence interval around the true difference in eradication rates for the 500 mg group is [-27%, +2%] (Corrected). Therefore, since the lower bound of the 95% confidence interval around the true difference in eradication rates falls below -10%, the applicant was not able to demonstrate equivalence in terms of the bacteriologic outcome.

According to the applicant, 129/141 pathogens (91%) were eradicated after treatment with cefepime 1.0 grams BID and 61/66 pathogens (92%) were eradicated after treatment with ceftazidime 1.0 grams TID. The 95% confidence intervals around the true difference in eradication rates is [-10%, +8%] (Corrected). Therefore, since the lower bound of the 95% confidence intervals around the true difference is within the limit of -10%, the applicant was able to demonstrate equivalence in terms of bacteriologic outcome.

According to the applicant, 101/113 pathogens (89%) were eradicated after treatment with cefepime 2.0 grams BID and 112/123 pathogens (91%) were eradicated after treatment with ceftazidime 2.0 grams TID. The 95% confidence interval around the true difference in eradication rates is [-10%, +7%] (Corrected). Since the lower bound of the 95% confidence interval around the true difference is within the limit of -10%, the applicant was able to demonstrate equivalence between the two treatment groups in terms of bacteriologic outcome.

Please note in the tables that follow, the microbiologic response for each evaluable pathogen is presented.

Table ES.11 presents the applicant's analysis of the bacteriologic data.

Table ES.11
Bacteriologic Response Table
According to the Applicant

Parameter	CEFEPIME		CEFTAZID	
	500 MG BID		500 MG TID	
A. ANITRATUS	1/	1 (100%)	0	
B. CORRODENS	1/	1 (100%)	1/	1 (100%)
E. AEROGENES		0	2/	2 (100%)
E. CLOACAE	2/	2 (100%)	0	
E. COLI	2/	2 (100%)	0	
E. TARDA	1/	1 (100%)	0	
K. OXYTOCA	2/	2 (100%)	0	
K. PNEUMONIAE	1/	3 (33%)	0	
LACTOBACILLUS SP.	1/	1 (100%)	0	
M. MORGANII	1/	1 (100%)	0	
P. AERUGINOSA	2/	3 (67%)	2/	2 (100%)
P. MICROS	1/	1 (100%)	0	
P. MIRABILIS	1/	2 (50%)	1/	1 (100%)
PEPTOSTREPTOCOCCUS SP.		0	1/	1 (100%)
S. AUREUS	19/	20 (95%)	11/	12 (92%)
S. EPIDERMIDIS	1/	1 (100%)	0	
S. INTERMEDIUS	1/	1 (100%)	0	
S. MARCESCENS	1/	1 (100%)	0	
S. SANGUIS		0	1/	1 (100%)
STAPH. COAGULASE (-)	1/	2 (50%)	1/	1 (100%)
STREP. (ALPHA HEMOLYTIC)	2/	2 (100%)	1/	1 (100%)
STREP. (BETA HEMOLYTIC)		0	1/	1 (100%)
STREP. (GROUP A)	2/	3 (67%)	3/	3 (100%)
STREP. (GROUP B)	3/	5 (60%)	2/	2 (100%)
STREP. (GROUP C)		0	1/	1 (100%)
STREP. (GROUP F)	1/	1 (100%)	0	
STREP. (GROUP G)	1/	1 (100%)	0	
TOTALS 500 mg	48/	57 (84%)	28/	29 (97%)

Table ES.11 - Continued
Bacteriologic Response Table
According to the Applicant

Parameter	CEFEPIME 1.0 G BID		CEFTAZID 1.0 G TID	
A. ANITRATUS	2/	2 (100%)	1/	1 (100%)
A. HYDROPHILA		0	1/	1 (100%)
C. DIVERSUS		0	1/	1 (100%)
E. CLONACAE	2/	2 (100%)	1/	1 (100%)
E. COLI	6/	7 (86%)	1/	1 (100%)
E. TARLIA		0	1/	1 (100%)
K. OXYTOCA	1/	1 (100%)		0
K. PNEUMONIAE	5/	5 (100%)	2/	2 (100%)
M. MORGANII	1/	2 (50%)		0
P. AERUGINOSA	9/	10 (90%)	4/	5 (80%)
P. FLUORESCENS	1/	1 (100%)		0
P. MIRABILIS	8/	11 (73%)	4/	5 (80%)
P. MULTOCIDA	1/	1 (100%)		0
P. STUARTII	2/	3 (67%)		0
P. VULGARIS		0	1/	1 (100%)
S. AGALACTIAE	3/	4 (75%)	1/	1 (100%)
S. ANGINOSUS		0	1/	1 (100%)
S. AUREUS	48/	50 (96%)	19/	21 (90%)
S. AUREUS (MR)	0/	1 (0%)		0
S. EPIDERMIDIS	8/	8 (100%)	4/	5 (80%)
S. HAEMOLYTICUS	2/	2 (100%)		0
S. HOMINIS	1/	1 (100%)		0
S. MARCESCENS	1/	1 (100%)	2/	2 (100%)
S. MILLERI		0	1/	1 (100%)
S. MITIS		0	1/	1 (100%)
S. SALIVARIUS	1/	1 (100%)		0
STAPH. COAGULASE (-)	1/	1 (100%)		0
STREP. (ALPHA HEMOLYTIC)	1/	2 (50%)		0
STREP. (BETA HEMOLYTIC)	1/	1 (100%)		0
STREP. (GROUP A)	20/	20 (100%)	12/	12 (100%)
STREP. (GROUP B)	3/	3 (100%)	2/	2 (100%)
STREP. (GROUP G)		0	1/	1 (100%)
STREP. SP.	1/	1 (100%)		0
TOTALS 1.0 grams	129/	141 (91%)	61/	66 (92%)

Table ES.1: - Continued
Bacteriologic Response Table
According to the Applicant

Parameter	CEFEPIME 2.0 G BID	CEFTAZID 2.0 G TID
A. ANITRATUS	0	2/ 2 (100%)
A. CALCOACETICUS	0	1/ 1 (100%)
A. LWOFFI	0	1/ 1 (100%)
B. CORRODENS	2/ 2 (100%)	4/ 4 (100%)
C. FREUNDII	1/ 1 (100%)	0
E. AGGLOMERANS	1/ 1 (100%)	0
E. CLOACAE	5/ 6 (83%)	4/ 5 (80%)
E. COLI	2/ 4 (50%)	3/ 3 (100%)
H. INFLUENZAE	1/ 1 (100%)	0
K. PNEUMONIAE	3/ 5 (60%)	4/ 5 (80%)
M. MORGANII	2/ 2 (100%)	3/ 3 (100%)
P. AERUGINOSA	7/ 10 (70%)	9/ 9 (100%)
P. MIRABILIS	4/ 4 (100%)	4/ 5 (80%)
P. RETTGERI	0	1/ 1 (100%)
P. VULGARIS	0	1/ 1 (100%)
PEPTOSTREPTOCOCCUS SP.	0	1/ 1 (100%)
S. AGALACTIAE	0	1/ 1 (100%)
S. AUREUS	36/ 38 (95%)	32/ 38 (84%)
S. AUREUS (MR)	0	1/ 1 (100%)
S. CAPITIS	1/ 1 (100%)	0
S. EPIDERMIDIS	5/ 5 (100%)	7/ 7 (100%)
S. EPIDERMIDIS (MR)	1/ 2 (50%)	0
S. EPIDERMIDIS (MS)	0	1/ 1 (100%)
S. FAECALIS	1/ 1 (100%)	0
S. MARCESCENS	3/ 3 (100%)	1/ 1 (100%)
SALMONELLA SP.	0	0/ 1 (0%)
STAPH. COAGULASE (-)	1/ 1 (100%)	0
STREP. (ALPHA HEMOLYTIC)	1/ 1 (100%)	3/ 3 (100%)
STREP. (GROUP A)	21/ 22 (95%)	19/ 20 (95%)
STREP. (GROUP B)	2/ 2 (100%)	4/ 4 (100%)
STREP. (GROUP C)	0	2/ 2 (100%)
STREP. (GROUP F)	1/ 1 (100%)	1/ 1 (100%)
STREP. (GROUP G)	0	1/ 1 (100%)
STREP. SP.	0	1/ 1 (100%)
TOTALS	101/113 (89%)	112/123 (91%)

According to the medical officer, 31/35 pathogens (89%) were eradicated after treatment with cefepime 500 mg BID and 19/19 pathogens (100%) were eradicated after treatment with ceftazidime 500 mg TID. The observed difference in eradication rates was -11%. The 95% confidence interval around the true difference in eradication rates was [-26%, +3%] (Corrected). Thus, like the applicant, the medical officer was not able to demonstrate equivalence between the two treatment groups at the 500 mg dosage level.

According to the medical officer, 82/89 pathogens (92%) were eradicated after treatment with cefepime 1.0 grams BID and 34/35 pathogens (97%) were eradicated after treatment with ceftazidime 1.0 grams TID. The difference in eradication rates was -5%. The 95% confidence interval around the true difference in eradication rates was [-15%, +5%] (Corrected). Therefore, the medical officer was not able to demonstrate equivalence between the two treatment groups at the 1.0 gram dosage level.

According to the medical officer, 61/67 pathogens (91%) were eradicated after treatment with cefepime 2.0 grams BID and 71/79 pathogens (90%) were eradicated after treatment with ceftazidime 2.0 grams TID. The difference in eradication rates was +1%. The 95% confidence interval around the true difference in eradication rates was [-10%, +12%] (Corrected). Therefore, the medical officer was able to corroborate the applicant's conclusion of equivalent efficacy between the two treatment groups at the 2.0 gram dose.

Table ES.12 summarizes the medical officer's determination of the bacteriologic efficacy in comparative trials.

Table ES.12
Bacteriologic Response Table
According to the Medical Officer

Parameter	CEFEPIME 500 MG BID	CEFTAZID 500 MG TID
A. ANITRATIS	1/ 1 (100%)	0
E. AEROGENES	0	1/ 1 (100%)
E. CLOACAE	1/ 1 (100%)	0
E. TARDA	1/ 1 (100%)	0
K. OXYTOCA	1/ 1 (100%)	0
K. PNEUMONIAE	0/ 1 (0%)	0
M. MORGANII	1/ 1 (100%)	0
P. AERUGINOSA	1/ 1 (100%)	1/ 1 (100%)
P. MIRABILIS	1/ 1 (100%)	1/ 1 (100%)
PEPTOSTREPTOCOCCUS SP.	0	1/ 1 (100%)
S. AUREUS	14/ 16 (88%)	10/ 10 (100%)
S. INTERMEDIUS	1/ 1 (100%)	0
S. MARCESCENS	1/ 1 (100%)	0
STAPH. COAGULASE (-)	1/ 1 (100%)	0
STREP. (ALPHA HEMOLYTIC)	1/ 1 (100%)	0
STREP. (GROUP A)	1/ 2 (50%)	3/ 3 (100%)
STREP. (GROUP B)	3/ 3 (100%)	2/ 2 (100%)
STREP. (GROUP F)	1/ 1 (100%)	0
STREP. (GROUP G)	1/ 1 (100%)	0
TOTALS 500 mg	31/ 35 (89%)	19/ 19 (100%)

Table ES.12 - Continued
 Bacteriologic Response Table - According to the Medical Officer

Parameter	CEFEPIME 1.0 G BID	CEFTAZID 1.0 G TID
A. ANITRATUS	2/ 2 (100%)	1/ 1 (100%)
C. DIVERSUS	0	1/ 1 (100%)
E. CLOACAE	2/ 3 (67%)	0
E. COLI	2/ 2 (100%)	0
K. OXYTOCA	1/ 1 (100%)	0
K. PNEUMONIAE	1/ 1 (100%)	0
M. MORGANII	1/ 1 (100%)	0
P. AERUGINOSA	3/ 3 (100%)	2/ 2 (100%)
P. ANAEROBIUS	1/ 1 (100%)	0
P. FLUORESCENS	1/ 1 (100%)	0
P. MALTOPHILIA	1/ 1 (100%)	0
P. MIRABILIS	3/ 4 (75%)	1/ 1 (100%)
P. MULTOCIDA	1/ 1 (100%)	0
S. AGALACTIAE	4/ 4 (100%)	0
S. ANGINOSUS	0	1/ 1 (100%)
S. AUREUS	38/ 41 (93%)	13/ 14 (93%)
S. EPIDERMIDIS	1/ 1 (100%)	0
S. MARCESCENS	0	2/ 2 (100%)
S. MILLERI	0	1/ 1 (100%)
S. VIRIDANS	0/ 1 (0%)	0
STREP. (ALPHA HEMOLYTIC)	0/ 1 (0%)	0
STREP. (BETA HEMOLYTIC)	1/ 1 (100%)	0
STREP. (GROUP A)	18/ 18 (100%)	10/ 10 (100%)
STREP. (GROUP B)	2/ 2 (100%)	1/ 1 (100%)
STREP. (GROUP G)	0	1/ 1 (100%)
TOTALS 1 gram	82/ 89 (92%)	34/ 35 (97%)

Table ES.12 - Continued
 Bacteriologic Response Table - According to the Medical Officer

Parameter	CEFEPIME 2.0 G BID	CEFTAZID 2.0 G TID
A. LWOFFI	0	1/ 1 (100%)
B. CORRODENS	2/ 2 (100%)	3/ 3 (100%)
E. CLOACAE	1/ 2 (50%)	1/ 2 (50%)
E. COLI	1/ 1 (100%)	1/ 1 (100%)
H. INFLUENZAE	1/ 1 (100%)	0
K. PNEUMONIAE	0	1/ 2 (50%)
M. MORGANII	0	2/ 2 (100%)
P. AERUGINOSA	1/ 2 (50%)	5/ 5 (100%)
P. MIRABILIS	2/ 2 (100%)	0/ 1 (0%)
P. VULGARIS	0	1/ 1 (100%)
S. AUREUS	28/ 31 (90%)	30/ 34 (88%)
S. CAPITIS	1/ 1 (100%)	0
S. EPIDERMIDIS	0	1/ 1 (100%)
S. EPIDERMIDIS (MR)	1/ 1 (100%)	0
S. FAECALIS	1/ 1 (100%)	0
S. MARCESCENS	1/ 1 (100%)	0
STREP. (ALPHA HEMOLYTIC)	1/ 1 (100%)	1/ 1 (100%)
STREP. (GROUP A)	18/ 19 (95%)	19/ 20 (95%)
STREP. (GROUP B)	1/ 1 (100%)	2/ 2 (100%)
STREP. (GROUP C)	0	2/ 2 (100%)
STREP. (GROUP F)	1/ 1 (100%)	1/ 1 (100%)
TOTALS 2.0 grams	61/ 67 (91%)	71/ 79 (90%)

Table ES.12 summarizes the comparative efficacy of cefepime and ceftazidime for patients infected with *S. aureus*, Group-A Beta-Hemolytic Streptococci and *P. aeruginosa*. *S. aureus* and Group-A Streptococci were the most frequently isolated pathogens; both were well treated by cefepime. *P. aeruginosa* was infrequently isolated. Although both drugs seems to perform similarly with respect to *P. aeruginosa*, the small number of patients studied precludes reliable conclusions.

Table ES.13
Bacteriologic Efficacy for Selected Pathogens

Pathogen	BMS		Medical Officer	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
<i>S. aureus</i>	103/108 (95%)	62/71 (87%)	80/88 (91%)	53/58 (91%)
<i>Strep., Gp. A</i>	44/45 (98%)	34/35 (97%)	37/39 (95%)	32/33 (97%)
<i>P. aeruginosa</i>	18/23 (78%)	15/16 (94%)	5/6 (83%)	8/P (100%)

Bacteriologic Response/Non-Comparative Studies: Table ES.13 summarizes the bacteriologic response observed in the non-comparative studies. As was the case with the comparative studies, in both the applicant's and the medical officer's evaluable population a superior eradication rate was seen in studies using 2 grams Q12h compared with studies at lower doses.

Table ES.14
Bacteriologic Response
Non-Comparative Studies

Study	Dose	Cefepime	
		BMS	Med. Officer
North American Non-Comparative Studies			
061	1 gram Q12H	124/152 (82%)	18/37 (49%)
140	2 grams Q12H	27/29 (93%)	15/19 (79%)
European Non-Comparative Studies			
067-LD	1 gram Q12H	5/7 (71%)	2/6 (33%)
067-HD	2 grams Q12H	3/3 (100)	3/3 (100%)

Efficacy Conclusions:

The primary determinant of efficacy in SSTI is the clinical response demonstrated in comparative studies. Three doses of cefepime were studied in comparative studies of patient with SSTI: 500 mg Q12H, 1.0 grams Q12H, and 2.0 grams Q 12H.

Cefepime 500 mg Q12H was studied in one comparative study of patients with SSTI (#075). The applicant has not requested to include the 500 mg Q12H dosing regimen in their approved product label. Indeed this decision seems to be corroborated by the evidence, as neither the applicant nor the medical officer was able to demonstrate comparable efficacy of cefepime at this dose with ceftazidime.

The applicant proposes that the dose of 1 gram Q12H be approved for the treatment of mild to moderate SSTI. Cefepime 1.0 gram Q12H was studied in one comparative study of patients with SSTI (#081), the study had both European and North American centers. According to the applicant, 86/98 evaluable patients (88%) in the cefepime group and 37/43 evaluable patients (86%) in the ceftazidime group had a satisfactory response to therapy. The difference in outcome between the two treatment groups is +2%, the 95% confidence interval around the true difference in outcomes is [-12%, +16%]. Therefore, the applicant demonstrated clinical efficacy for this dose that is equivalent to the clinical efficacy of ceftazidime by the 95 % confidence interval approach. In addition, the applicant has also shown that the bacteriologic responses are equivalent (by the 95% confidence interval approach) for this dosing regimen.

The medical officer, however, questions the appropriateness of using a broad-spectrum, parenteral anti-microbial agent for patients with "mild" skin infections. The medical officer, therefore, considered patients with mild skin infections to be not-evaluable. In the medical officer's analysis, 81/107 (76%) clinically evaluable cefepime patients and 36/42 (86%) clinically evaluable ceftazidime patients were clinically cured of their SSTI. The difference in outcome is -10%, the 95% confidence interval around the true difference in outcome is [-25%, +6%]. Therefore, the medical officer's analysis did not confirm the applicant's finding of equivalence. In addition, the medical officer was not able to demonstrate bacteriologic equivalence between the two treatment groups at the 1.0 gram Q12h dosing level (the 95% confidence interval around the true difference in bacteriologic eradication rates was [-15, +5]).

Cefepime 1.0 gram Q12H was studied in two non-comparative studies of patients with SSTI (#061, #067-LD). According to the applicant, in non-comparative studies using a dose of 1.0 grams every 12 hours, an overall (combining studies #061 and #67LD) clinical cure rate of 92/101 (91%) was observed. According to the medical officer, in the same non-comparative studies, a clinical cure rate of 22/42 (52%) was observed. The medical officer feels that the results of the non-comparative studies are consistent with the data from the comparative studies and together point to a lack of efficacy of the dose of 1.0 grams every 12 hours in patient with moderate to severe SSTI.

The applicant proposes that the dose of cefepime, 2.0 grams Q12 be indicated for the treatment of severe SSTI and in fact, both the applicant and the medical officer formed evaluable population where the majority of patients had moderate to severe infections. Cefepime 2.0 grams Q12H was studied in two comparative studies of patients with SSTI (#97 and #111). Study #97 was a large, domestic, multi-center trial. Study #111 was a small European trial. Because of differences in the enrolled patient population, a meta-analysis of the two studies using the 2.0 gram dose would not be appropriate, therefore, each study will be considered separately.

In study #97, according to the applicant, 66/74 (89%) evaluable cefepime patients and 61/69 (89%) evaluable ceftazidime patients had a satisfactory clinical outcome. There was no observed difference in clinical outcome, the 95% confidence interval around the true difference in outcome is [-11%, +13%]. Therefore, the applicant concludes that equivalent clinical outcomes were seen in both treatment groups. In the medical officer's analysis of study #097 a clinical cure was observed in 64/79 (81%) of clinically evaluable cefepime patients and in 65/79 (82%) of clinically evaluable ceftazidime patients. The observed difference in outcomes was -1%, the 95% confidence interval around the true difference in clinical outcomes is [-15%, +12%]. Therefore, the medical officer corroborated the findings of the applicant in study 097.

It should be noted, that although equivalent clinical efficacy was demonstrated for the two treatment groups in the clinically evaluable population, there was a discrepancy in the clinical outcomes for the fully evaluable population. In the cefepime treatment group 39/47 fully evaluable patients (83%) were cured of their infection, in contrast, in the ceftazidime treatment group, 44/48 evaluable patients (92%) were cured of their infection.

The observed difference was primarily due to a difference in clinical outcome in patients with wound infections. In the cefepime treatment group, 7/12 (58%) fully evaluable patients with wound infection were cured of their infection, in the ceftazidime treatment group, 5/5 (100%) fully evaluable patients with wound infection were cured of their infection. The observed difference could not be accounted for by differences in the demographic characteristics or characteristics of the infection between the two treatment groups. Therefore, the medical officer can not exclude the possibility that cefepime may not perform as well as ceftazidime in the treatment of patients with wound infection.

According to the medical officer, in study #097, 60/66 pathogens (91%) were eradicated in the cefepime treatment groups and 57/74 pathogens (91%) were eradicated in the ceftazidime treatment group. Cefepime performed well in treatment of infections caused *S. aureus* and Group-A Beta-Hemolytic *Streptococci*, the two most important pathogens in skin and skin structure infections. The number of patients with SSTI due to *P. aeruginosa* was too small to form valid conclusions. No other pathogens were studied in greater than 10 evaluable patients.

In study #111, neither the applicant nor the medical officer considered a sufficient number of enrolled patients to be evaluable for meaningful confidence interval analysis.

Cefepime 2.0 grams Q12H was studied in two non-comparative studies of patients with SSTI (140, 067-HD). According to the applicant, in non-comparative studies using a dose of 2.0 grams every 12 hours, an overall (combining studies #140 and #67HD) clinical cure rate of 20/22 (91%) was observed. According to the medical officer, in the same non-comparative studies, a clinical cure rate of 30/33 (91%) was observed. The medical officer feels that the results of the non-comparative studies are supportive of the data from the comparative studies.

In conclusion, according to both the applicant and the medical officer the efficacy of cefepime at a dose of 2.0 grams every 12 hours has been shown to be equivalent to ceftazidime 2 grams Q12H, by the 95% confidence interval approach, in study #097. However, there is a suggestion that cefepime may be inferior to ceftazidime in the treatment of patients with wound infection at the 2.0 gram dosage level. The findings of study #097 have been corroborated by a high clinical cure rate observed in the non-comparative studies #067-HD and #140. It is the opinion of the medical officer that the combination of the comparative

multi-center study (#097) and the non-comparative multi-center studies (#067 and #140) fulfills the regulatory requirement for adequate and well controlled studies.

Therefore, the efficacy of cefepime for the treatment of moderate to severe skin and soft tissue infections due to susceptible strains of *S. aureus* and Group-A Beta-Hemolytic Streptococci at a dose of 2.0 grams administered every 12 hours has been established.

*see Response Memorandum
in 7/2/14*

The efficacy for cefepime at a dose of 1.0 grams every 12 hours for the treatment of mild to moderate SSTI has not been established.

No claims for the efficacy of the 500 mg Q12H dose were made by the sponsor.

Section V.4 - Integrated Safety Summary for Skin and Soft Tissue Infections

The assessment of safety is based on the experience in 985 patients with skin or soft tissue infections treated with cefepime in clinical trials. 945 patients were studied in protocols specifically designed to assess the safety and efficacy of cefepime in patients with SSTI, an additional 45 patients who were enrolled in other protocols not specifically designed to assess SSTI but who nevertheless had an SSTI and were treated with cefepime are included. 900 patients were studied in the United States, 85 patients were studied in Europe.

The cefepime treated patients were compared with 386 patients with SSTI that were treated with ceftazidime. 356 patients were studied in the United States and 30 patients were treated in Europe.

Table SS.1 catalogues the patients considered in the analysis of safety.

Table SS.1
Population Evaluable for the Safety Assessment

Study Number	#Evaluable for Safety	
	Cefepime	Ceftazidime
North American Comparative Studies		
411-075	104	50
411-081	198	100
411-097	214	206
North American Non-Comparative Studies		
411-061	220	NA
411-140	124	NA
Other North American Studies ¹	40	0
European Comparative Studies		
411-081	32	15
411-111	23	15
European Non-Comparative Studies		
411-067	30	NA
Totals	985	386

1- Includes patients from 411-123, 129, 135, 157 not designed to assess SSTI.

Section V.4.1 - Deaths

Table SS.2 summarizes the deaths which occurred among patients with SSTI enrolled in comparative and non-comparative studies designed to demonstrate the safety and efficacy of cefepime. Overall, there was no difference in mortality rate between the two treatment groups among patients enrolled in comparative clinical trials. At the lower dose levels (500 mg, 1.00 grams), however, there was a trend toward increased deaths in the cefepime treatment group. The trend, however, did not reach statistical significance.

Table SS.2
Deaths in SSTI Patients

Dose	Study	#Deaths/#Enrolled		P-Value*
		Cefepime	Ceftazidime	
Comparative Studies				
500 mg	075	1/104 (1%)	0/50 (0%)	1.0
1.0 grams	081 NA	5/198 (3%)	0/100 (0%)	
	081 EU	0/32 (0%)	0/15 (0%)	
Total 1.0 grams		5/230 (2%)	0/115 (0%)	0.17
2.0 grams	097 NA	3/214 (2%)	6/206 (4%)	
	111 EU	6/23 (26%)	4/15 (27%)	
Total 2.0 grams		9/237 (4%)	10/221 (5%)	0.82
Non-Comparative Studies				
1.0 grams	061 NA	2/220 (1%)	NA	NA
	067-LD EU	0/16 (0%)	NA	NA
2.0 grams	140 NA	3/124 (2%)	NA	NA
	067-HD EU	0/14 (0%)	NA	NA
	Other Studies	0/40 (0%)	NA	NA
All Studies		17/985 (2%)	10/384 (3%)	0.39

*Fisher's Exact Test

Medical Officer's Comments: Study #111 enrolled many patients with neoplasms who were neutropenic secondary to chemotherapy. The high mortality rate seen is thus not unexpected in such a population.

The following sections provide brief descriptions of each patient who died during a cefepime clinical trial. Most patients who died were elderly and severely ill at the time of their enrollment into the cefepime trials. In no cases did death appear to be attributable to a direct toxic effect of the drug.

Section V.3.1.1 - Comparative Studies

CEFEPIME DEATHS**Dose: 500 mg Every 12 Hours****Protocol #075 (North American)**

One death occurred among patients in the cefepime treatment group.

Patient _____ The patient was a 65 year old female with diabetes mellitus and a history of congestive heart failure. The patient was enrolled for cellulitis of the right foot due to *E. coli* and *S. faecalis*. The patient was randomized to cefepime and received two days of treatment. The patient failed to improve and her antibiotics were changed to mezlocillin and tobramycin. Ultimately the patient required both amputation of the affected toe and a below the knee amputation of the affected leg. The patient tolerated the procedures well. On 4/25/88 (11 days after enrollment) the patient suffered a myocardial infarction and died. The investigator did not believe that the death was related to the study drug.

Medical Officer's Comments: The medical officer concurs that death in this patient was, most likely, due neither to a toxic effect of the drug or a lack of therapeutic response.

Dose: 1.0 grams Every 12 Hours**Protocol #081 (North American)**

Five deaths occurred among patients in the cefepime treatment group.

Patient _____ The patient was a 98 year old female with an infected decubitus ulcer who was treated with cefepime from 9/9-9/15/88. The patient was reported to have complete resolution of signs and symptoms of infection and there was no source to culture at the end of therapy. One day post-therapy, the patient died. The patient had a history of arteriosclerotic heart disease and had signs of congestive heart failure on admission. The patient suffered an unexpected cardio-pulmonary arrest. The investigator felt that the death was not related to cefepime therapy.

Patient _____ The patient was an 88 year old female who was treated with cefepime from 1/21-1/22/89 for an infected decubitus ulcer. Cefepime was discontinued after 3 doses when the infecting pathogen was identified as methicillin resistant *S. aureus*. The patient also had septicemia with *Enterococci* and *Bacteroides* spp. Vancomycin and metronidazole were substituted for cefepime. The patient had a progressive deterioration and died on 1/28/89. The cause of death was felt to be systemic infection.

Medical Officer's Comments: Although this patient died of systemic infection, since she received only three doses of cefepime, and since therapy was discontinued for resistance to cefepime, this patient's death was not considered a result of, treatment failure by the medical officer.

Patients _____ ^{unexpected} The patient was an 83 year old female who was treated from 1/9-1/13/89 with cefepime for cellulitis. All signs and symptoms of infection resolved and there was no source to culture at the conclusion of therapy. On admission the patient was noted to have atrial fibrillation and congestive heart failure thought to be secondary to arteriosclerotic heart disease. On 1/23/89 the patient experienced an acute myocardial infarction and died. The death was felt to be due to an underlying disease process and not related to cefepime therapy.

Patient The patient was a 64 year old female who was treated from 11/24-12/1/89 with cefepime for cellulitis. All signs and symptoms of infection resolved and there was no source to culture at the end of therapy. Nine days (12/9/89) after the completion of therapy the patient developed mild gastrointestinal complaints which abruptly worsened to gastrointestinal hemorrhage. The patient died of hypovolemic shock on 12/11/89. AT autopsy, ischemic necrosis of the small bowel and torsion of the mesentery were noted.

Patient The patient was a 69 year old male who was treated with cefepime from 3/6/89 to 3/16/89 for cellulitis. A methicillin resistant *S. aureus* was isolated and the patient was removed from the study. On 3/21 the patient underwent a revision of a left BKA to a left AKA. On the first post-operative day, the patient suffered an acute myocardial infarction and a cerebrovascular accident. The patient was placed on "do not resuscitate" status. The patient died on 3/27. The findings at autopsy were consistent with acute myocardial infarction.

Medical Officer's Comments: In the opinion of the medical officer, none of the deaths among patients in the cefepime treatment group were due to a direct toxic effect of the drug or to a lack of therapeutic effect.

Protocol #081 (European)

There were no deaths among patients in the cefepime treatment group.

Dose: 2.0 grams Every 12 Hours:

Protocol #097 (North American)

Patient The patients was an 88 year old white female with a history of NIDDM who was admitted for surgical repair of a right hip fracture. The patients developed a surgical wound infection 20 days after her operative procedure. Cultures from the wound yielded *P. mirabilis* and *E. coli*. The patient was randomized to the cefepime treatment group. The patient received 14 days of therapy with poor clinical response. X-rays showed that the infection had progressed on therapy to involve the bone (osteomyelitis). A repeat culture yielded a persistence of *E. coli* and a new infection with *Enterococcus* spp. Cefepime was discontinued at this time. Ampicillin and gentamicin were started, however, the patient expired 20 days after the discontinuation of cefepime therapy. The cause of death was (according to the investigator) was septic shock.

Medical Officer's Comments: This patient death was contributed to by a lack of therapeutic effectiveness of cefepime.

Patient The patient was a 51 year old white male with a history of malignant lymphoma. The patient was enrolled in the study for treatment of a cellulitis around a Gashrong catheter exit site. Culture of the drainage from the affected area yielded *S. marcescens*. The patient was randomized to cefepime. The patient received 7 days of cefepime therapy with clinical resolution of the subject infection. The patient died seven days after the completion of cefepime therapy from gross involvement of the mesentery with lymphoma. The patient was not considered to be infected at the time of death.

Medical Officer's Comments: This patient's death was unrelated to cefepime.

Patient The patient was a 39 year old white male with a history of intravenous drug abuse, cirrhosis and hepatitis. The patients was hospitalized for treatment of a traumatic hip dislocation. During the hospitalization, the

patient developed skin ulceration. A cellulitis developed surrounding the site of the ulcer. An aspiration of the involved skin yielded a methicillin-resistant *S. aureus* that was susceptible to cefepime. The patient was randomized to the cefepime treatment group. The patient was treated with cefepime for 7 days. Clinical improvement was noted. The patient died from a gastrointestinal hemorrhage from pre-existing esophageal varices while still on cefepime therapy.

Medical Officer's Comments: This patient's death was unrelated to cefepime.

Protocol #111 (European)

Six deaths occurred among the 23 patients in the cefepime treatment group. The mortality rate in the cefepime treatment group was 26%. (See previous comment)

Patient The patient was a 59 year old female with a history of carcinoma of the breast with osseous and cutaneous metastasis. The patient was hospitalized for lower back pain and was found to have a retroperitoneal mass. During the hospitalization the patient developed septicemia, pneumonia and cellulitis. The patient was treated with cefepime from 3/27/89 to 4/12/89. The patient was clinically and microbiologically improved by the end of therapy. The patient died on 5/6/89, almost one month after the completion of cefepime therapy due to complications of her pancreatic tumor.

Medical Officer's Comments: This patient's death is not considered to be related to cefepime by either the investigator or the medical officer.

Patient The patient was a 62 year old female with a history of epithelioma of the breast with bone and peritoneal metastasis. The patient was enrolled into the cefepime study on 2/16/90 for suspected LRTI and SSTI involving the tongue. The patient was treated from 2/18 to 2/28/90 with cefepime. The patient showed clinical improvement on therapy. The patient died on 3/2/90, four days after completing cefepime therapy. The cause of death was not recorded on the CRF.

Medical Officer's Comments: Given the close proximity of this patient's death to cefepime therapy and the absence of information as to the cause of death, it is difficult to determine if this patient's death was in any way related to cefepime. The investigator felt that the patient's death was related to her underlying malignancy.

Patient The patient was 68 year old male with progressive small cell carcinoma of the lung and carcinomatous meningitis. The patient was enrolled in the cefepime study for a UTI due to *E. coli* and infected decubitus ulcers due to *E. coli* and *B. fragilis*. The patient was treated from 4/13/90 to 4/18/90. The patient was considered to be a clinical failure and was placed on alternative therapy. The patient died on 4/23/93, five days after the conclusion of cefepime therapy. The cause of death was recorded as "progressive small cell carcinoma of the lung".

Patient The patient was an 80 year old male with a history of surgical resection of a bladder tumor. The patient was enrolled in the cefepime study for the treatment of a post-operative wound infection. The patient was treated from 9/11/90 to 9/18/90. While on therapy the patient developed fungemia with *C. albicans*. The patient died while still on-therapy. The cause of death was thought to be due to complications of her underlying bladder neoplasm.

Patient The patient was a 67 year old male with a history of epidermoid epithelioma, COPD, intermittent claudication, laryngectomy and

tracheostomy. The patient was enrolled in the cefepime study for a post-operative wound infection due to *E. coli* at the laryngectomy site. The patient also had *E. coli* UTI and bacteremia. The patient was treated with cefepime from 1/1/91 to 1/2/91. While on therapy the patient developed cholecystitis due to a resistant *E. faecalis*. Cefepime was discontinued and the patient was started on vancomycin, ceftazidime and metronidazole. A cholecystectomy was performed. The patient died 9 days after the discontinuation of cefepime therapy from renal insufficiency and complication of his neoplasm.

Patient _____ The patient was a 62 year old male with a history of acute myeloid leukemia. The patient was enrolled in the cefepime study for the treatment of a scrotal ulcer infected with *X. maltophilia*. The organism was found to be resistant to cefepime, therefore, cefepime was discontinued after 2 days of therapy. The patient was placed on azlocillin, vancomycin and augmentin as alternative therapy. The patient died approximately 2 months after the last dose of cefepime due to congestive heart failure secondary to chemotherapy induced cardiomyopathy.

CEFTAZIDIME DEATHS

Dose: 500 mg Every 8 Hours

Protocol #075 (North American)

There were no deaths among patients in the ceftazidime treatment group.

Dose: 1.0 grams Every 8 Hours

Protocol #081 (North American)

There were no deaths among patients in the ceftazidime treatment group.

Protocol #081 (European)

There were no deaths among patients in the ceftazidime treatment group.

Dose: 2.0 grams Every 8 Hours

Protocol #097 (North American)

Patient _____ The patient was a 70 year old white female with a history of atherosclerotic vascular disease. The patient was enrolled in study 097 for a toe abscess. The patient was treated with ceftazidime for four days. Ceftazidime was discontinued for lack of response. Bactrim, penicillin-G and nafcillin were substituted. The patient expired 10 days after removal from ceftazidime from ventricular tachycardia and resultant congestive heart failure.

Medical Officer's Comments: This patient's death was unrelated to ceftazidime therapy.

Patient _____ The patient was a 40 year old black female with a history of diabetes, depression and malnutrition. The patient was enrolled in study 097 for treatment of a ischio-rectal abscess. Cultures of the abscess yielded *P. aeruginosa* and *E. aerogenes*. The patient was randomized to the ceftazidime treatment group. While on therapy, the patient developed a UTI and pneumonia. The pneumonia progressed, eventually resulting in ARDS. The patient died while still on therapy. The principal investigator felt that septic shock was the cause of death.

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Medical Officer's Comments: This patient's death was contributed to by a lack of therapeutic effectiveness of ceftazidime.

Patient _____: The patient was a 74 year old female with a history of rheumatoid arthritis. The patient was enrolled in study 097 for treatment of an infected ulcer. A culture of the ulcer yielded *P. aeruginosa*. The patient was randomized to the ceftazidime treatment group. The ulcer responded both clinically and microbiologically to treatment. After 10 days of therapy, ceftazidime was discontinued due to the occurrence of nausea, eight days later the patient expired from a gastrointestinal hemorrhage.

Medical Officer's Comments: Retrospectively, it would seem that the patient's nausea represented underlying gastrointestinal pathology and not a reaction to ceftazidime. In a patient with a history of rheumatoid arthritis, NSAID induced gastritis and/or peptic ulcer disease may occur. The medical officer does not consider this patient's death to be related to ceftazidime therapy.

Patient _____: The patient was an 88 year old male with a history of cholecystitis, hypertension, gastritis, pancreatitis, prostate enlargement, pneumonia and alcoholism. The patient was enrolled in study 097 for treatment of an infected surgical wound (post-cholecystectomy). Cultures from the wound yielded *P. aeruginosa* and *E. cloacae*. The patient received nine doses of ceftazidime. Ceftazidime was discontinued at that time because of a poor clinical response. While on therapy the patient developed a suspected intra-abdominal infection and pneumonia. After discontinuation of ceftazidime, the patient was treated with ceftriaxone, metronidazole and amphotericin-B. The patient expired 8 days after the last dose of ceftazidime was given. The principal investigator felt that the cause of death was complications of hospital acquired pneumonia.

Medical Officer's Comments: A lack of therapeutic effectiveness of ceftazidime may have contributed to this patient's death.

Patient _____: The patient was a 27 year old male with a history of Hodgkin's disease. The patient was enrolled in study 097 for treatment of a cellulitis surrounding a Gashrong catheter exit site. A culture of the affected area yielded *S. aureus* and *P. aeruginosa*. The patient was randomized to the ceftazidime treatment group and was treated for 13 days with clinical improvement of the area. The patient expired 22 days after completion of therapy from an esophageal hemorrhage secondary to esophageal candidiasis.

Medical Officer's Comments: This patient's death was unrelated to ceftazidime therapy.

Patient _____: The patient was a 76 year old white male with NIDDM and peripheral vascular insufficiency. The patient was enrolled in study 097 for the treatment of a right ankle abscess. A culture of the abscess yielded *S. aureus*. The patient was randomized to the ceftazidime treatment group and received 10 days of therapy. Clinical improvement was noted, however, X-rays showed the development of osteomyelitis at the affected site. The patient was removed from ceftazidime therapy and placed on alternative therapy with vancomycin and aztreonam. Ten days after the discontinuation of ceftazidime therapy the patient developed a nosocomial pneumonia. The patient died 17 days after removal from ceftazidime therapy from complications of nosocomial pneumonia.

Medical Officer's Comments: It is unclear whether the lack of therapeutic effect of ceftazidime contributed to this patient's death. However, given that symptoms of pneumonia were not apparent until 10 days after the discontinuation of therapy and symptoms progressed on vancomycin and

aztreonam the role of ceftazidime in this patient's death is doubtful.

Protocol #111 (European)

There were four deaths among patients in the ceftazidime treatment group. The mortality rate in the ceftazidime treatment group was 27%. (See previous comment).

Patient _____ The patient was an 80 year old male with a history of colectomy _____ moid neoplasia. The patient was enrolled in the cefepime study for a post-operative wound infection due to *P. aeruginosa* and *E. coli*. The patient was treated with ceftazidime from 10/19/90 to 11/3/90. While on therapy, the patient developed a new wound infection due to an *E. cloacae* that was resistant to ceftazidime. On 11/7, four days after the discontinuation of ceftazidime, the patient died while undergoing endoscopy. The findings at endoscopy were consistent with a gastrointestinal hemorrhage.

Patient _____ The patient was a 60 year old female with a past history of cervical carcinoma. The patient was enrolled in the cefepime study for asymptomatic bacteriuria, and a superinfection of a decubitus ulcer due to *P. aeruginosa* and *P. mirabilis*. The patient was treated with ceftazidime from 9/2/90 to 9/7/90. The signs and symptoms of infection worsened on therapy. The patient died on 9/9/90. The cause of death was "extensive cervical carcinoma".

Patient _____ The patient was a 67 year old female with a past history of glandular epithelioma. The patient was enrolled in the cefepime study for septicemia and cellulitis of the chest due to *Salmonella* spp. The patient was treated with ceftazidime from 9/16/90 to 6/24/90. The patient was considered a clinical and microbiological failure. The patient's death, however, was thought to be due to the patient's underlying disease.

Patient _____ The patient was a 79 year old female. The patient was enrolled in the cefepime study for treatment of a UTI due to *E. coli* and septicemia and wound infection due to *S. aureus*. The patient received one dose of ceftazidime. Ceftazidime was discontinued when it was discovered that the *S. aureus* was resistant to the drug. The patient was placed on vancomycin as alternative therapy. The patient, however, died on the next day. The cause of death was felt to be septicemia.

Section V.3.1.2 - Non-Comparative Trials

Dose: 1.0 gram Every 12 Hours

Protocol #061 (North American)

Two deaths occurred among patients with SSTI enrolled in study #061.

Patient _____ The patient was a 35 year old white male with severe cellulitis of the left foot due to *S. aureus*. The patient was treated with cefepime 1 gram BID from 3/10/88 to 3/12/88 (5 doses of cefepime were administered). Cefepime was discontinued after 5 doses due to persistent symptoms of infection. The patient was placed on vancomycin and imipenem. The patient, however, signed out against medical advice. Two days later the patient was found with a gun shot wound to the heart. The date of death was 3/14/88.

Patient _____ The patient was a 59 year old white female with a past history of congestive cardiomyopathy, pulmonary hypertension, COPD, NIDDM,

hypertension, and peptic ulcer disease. The patient was admitted for worsening shortness of breath. Upon admission, a cellulitis of the left leg due to *K. pneumoniae* and *P. mirabilis* was observed. The patient was treated with cefepime, 1 gram BID, from 3/13/88 to 3/21/88 (17 doses of cefepime were administered). The signs and symptoms of infection improved on therapy. Subsequent to treatment, the patient became febrile. The patient was found to have bacteremia due to MRSA. The patient was started on vancomycin, however, the patient clinically deteriorated. The patient died of cardio-pulmonary arrest on 4/20/88 (approximately 1 month after completion of cefepime therapy).

Medical Officer's Comment: Neither of the two deaths that occurred in this study are directly attributable to cefepime.

Protocol #067-LD (European)

No deaths occurred among patients in protocol #067-LD

Dose: 2.0 grams Every 12 Hours

Protocol #140 (North American)

There were three deaths among patients with SSTI enrolled in study #140.

Patient _____: The patient was a 70 year old male with a history of diabetes mellitus, gastric ulcer, pancreatic ulcer and chronic renal failure. The patient was believed to have an entero-cutaneous fistula. The patient received cefepime for a post-operative wound infection. Despite the patient's history of renal failure, the dose of cefepime was not adjusted. The creatinine on randomization was 2.6 mg/dL. The creatinine rose to 5.1 mg/dL by day #13 of therapy. Cefepime was discontinued at that time due to the patient's deteriorating renal status. Four days after the discontinuation of cefepime, the patient expired. The causes of death included: renal insufficiency; pancreatic ulcer; and infection.

Patient _____ The patient was a 75 year old male with a past history of diabetes mellitus, severe pneumonia, and hypotension. The patient was admitted for the treatment of a severe pneumonia due to multiple organisms. The patient was enrolled in the SSTI protocol for the treatment of infected decubitus ulcers. The patient was removed from the study after one dose of cefepime because, in the opinion of the principal investigator, the severity of the patient's illness warranted broad spectrum antimicrobial therapy. The patient died 13 days after the last dose of cefepime. The cause of death was pneumococcal sepsis.

Patients _____ The patient was an 80 year old female. The patient was a nursing home resident with a history of congestive heart failure, cerebrovascular accident, hemiparesis, depression, and multiple decubitus ulcers. The patient was admitted for the treatment of lobar pneumonia, urinary tract infection, and infected decubitus ulcers. The patient was removed from the cefepime study after one dose because, in the opinion of the principal investigator the severity of the patient's illness warranted broad spectrum antimicrobial therapy. The patient died 17 days after the last dose of cefepime. The cause of death was aspiration pneumonia.

Protocol #067-HD (European)

No death occurred among patient in protocol #067-HD.

Section V.4.2 - Discontinuations

Twenty-two of 985 patients (2%) who were treated with cefepime were removed from participation because of adverse clinical or laboratory events. Seven of 386 patients (2%) who were treated with ceftazidime were removed from therapy because of adverse clinical or laboratory events. There was no significant difference in the overall percentage of patients removed due to adverse events.

Table SS.3 summarizes the numbers of patients in whom therapy was discontinued due to adverse events by dose of drug received. In the high dose (2 grams Q12H) trials, there was a trend toward a larger number of patients removed for adverse events in the cefepime treatment group. The difference, however, is not statistically significant (p=0.18).

Table SS.3
Patients Discontinued from SSTI Protocols

Dose	Study	#Discontinued/#Enrolled		P-Value*
		Cefepime	Ceftazidime	
Comparative Studies				
500 mg	075	2/104 (2%)	1/ 50 (2%)	1.0
1.0 grams	081 NA	1/198 (<1%)	1/100 (1%)	
	081 EU	0/ 32 (0%)	0/ 15 (0%)	
Total 1.0 grams		1/230 (<1%)	1/115 (<1%)	1.0
2.0 grams	097 NA	10/214 (6%)	5/206 (3%)	
	111 EU	1/ 23 (4%)	0/ 15 (0%)	
Total 2.0 grams		11/237 (5%)	5/221 (2%)	0.21
Non-Comparative Studies				
1.0 grams	061 NA	4/220 (2%)		
	067-LD EU	1/ 16 (6%)		
2.0 grams	140 NA	1/124 (1%)		
	067-HD EU	2/ 14 (14%)		
Other Studies		0/40 (0%)	NA	NA
All Studies		22/985 (2%)	7/384 (2%)	0.68

*Fisher's Exact Test

Table SS.4 reports the specific adverse event that resulted in the discontinuation of the study medication. In both the cefepime and ceftazidime treatment groups, adverse events related to the skin most often resulted in discontinuation of the study medication. Of note, six patients in the cefepime

treatment group were removed from therapy for laboratory test abnormalities, while no patients in the ceftazidime treatment group were removed from therapy for this reason.

Table SS.4
Events Resulting in Discontinuation of Study Medication

Reason	# Cefepime	# Ceftazidime
Clinical Adverse Events		
Rash/Urticaria	0	2
Pruritus	3	2
Diarrhea	0	2
Abdominal Upset	1	0
Nausea	0	1
Encephalopathy	1	0
Candidal Infection	1	0
Laboratory Test Abnormalities		
Hyperbilirubinemia	1	0
Elevation of LFT	2	0
Renal Failure	1	0
Anemia	1	0
Granulocytopenia	1	0
Local Reactions at the Infusion Site		
Phlebitis	1	0

Section V.4.3 - Clinical Adverse Events

Tables SS.5 and SS.6 on the following pages summarizes information regarding the occurrence of clinical adverse events.

Among patients in comparative clinical trials, 116/571 patients (20.3%) in the cefepime treatment group reported at least one clinical adverse event. In contrast, 88/386 patients (22.8%) in the ceftazidime treatment group reported at least one clinical adverse event. The difference in the incidence of clinical adverse events between the two treatment groups was not significant ($X^2=0.85$, $p>>0.05$).

Among patients in comparative clinical trials, 85/571 patients (15%) in the cefepime treatment group and 91/386 patients (16%) in the ceftazidime treatment group reported a clinical adverse event that was considered of probable or unknown relationship to the study drug. The difference in the incidence rates of clinical adverse events of probable or unknown relationship to the study drug,

between the two treatment groups, was not significant ($X^2=0.15$, $p>>0.05$).

Considering patients in both comparative and non-comparative trials the overall rate of clinical adverse events for patients treated with cefepime was 168/945 (17%); 119/985 (13%) reported an adverse event that was of probable or unknown relationship to cefepime.

Table SS.5 presents the incidence rates of clinical adverse events for selected relevant sub-groups. There was no significant difference between the two treatment groups in terms of the incidence of clinical adverse events in either North American or European studies, although overall the incidence of clinical adverse events in European studies was lower than in North American studies. There was no difference in the incidence of clinical adverse events between the two treatment groups in either the high or low dose trials, however, the incidence of clinical adverse events among renally impaired patients was higher in the cefepime treatment group than in the ceftazidime treatment group. Because of the small numbers of patients involved, this difference was not statistically significant ($p=0.33$, Fisher's Exact Test).

Table SS.5 lists all adverse events reported for either cefepime or ceftazidime. For the cefepime treatment group, any adverse event that occurred, whether in comparative or non-comparative trials is reported. Ceftazidime events only occurred in comparative clinical trials.

Clinical adverse events occurred most commonly in the digestive system in both treatment groups. Clinical adverse events were also commonly reported in the nervous and skin systems. Adverse events were common in the "body as a whole" category because of the inclusion of headache within this category. There were no significant differences in the incidence of clinical adverse events between the two treatment groups in any body system.

Clinical adverse events occurring in greater than 1% of the population exposed to cefepime included: headache(2.6%), constipation(1.4%), diarrhea(1.3%), nausea(2.9%), abdominal pain(1.4%), pruritus(2.1%) and rash(2.2%).

Table SS.5
Clinical Adverse Events
Incidence

Group	Cefepime					Ceftazidime				
	N	Prob.	Unk.	Not	Total	N	Prob	Unk	Not	Total
Comparative Studies	571	21 (3.7%)	64 (11.2%)	31 (5.4%)	116 (20.3%)	386	19 (4.9%)	42 (10.9%)	27 (7.0%)	88 (22.8%)
North American Studies	516	18 (3.5%)	64 (12.4%)	30 (5.8%)	112 (21.7%)	357	17 (4.8%)	42 (11.8%)	27 (7.6%)	86 (24.1%)
European	55	3 (5.5%)	0	1 (1.8%)	4 (7.3%)	29	2 (6.9%)	0	0	2 (6.9%)
Low Dose ¹	334	7 (2.1%)	35 (10.5%)	18 (5.4%)	60 (18.0%)	166	6 (3.6%)	15 (9.0%)	14 (8.4%)	35 (21.1%)
High Dose ²	222	13 (5.9%)	28 (12.6%)	12 (5.4%)	53 (23.9%)	204	13 (6.4%)	27 (13.2%)	12 (5.9%)	52 (25.5%)
Renally Impaired	15	1 (6.7%)	1 (6.7%)	1 (6.7%)	3 (20.0%)	16	-	-	1 (6.3%)	1 (6.3%)
All Studies (incl. non-comparative)	985	36 (3.7%)	83 (8.4%)	49 (5.0%)	168 (17.1%)	NA	NA	NA	NA	NA

¹ ≤ 2 grams per day of cefepime.

² > 2 grams per day of cefepime.

Table SS.6
Clinical Adverse Events - Listed by Body System and Relatedness
All North American Trials

Body System Event	Cefepime (N=900)				Ceftazidime (N=516)			
	Prob. Rel.	Unknown Rel.	Not Rel.	Total	Prob. Rel.	Unk. Rel.	Not Rel.	Total
Body As A Whole	5(0.6)	30(3.3)	11(1.2)	46(5.1)	5(1.4)	11(3.1)	7(2.0)	23(6.4)
Anaphylactoid Rxn.	-	-	-	-	1(0.3)	-	-	1(0.3)
Asthenia	-	1(0.1)	-	1(0.1)	-	-	-	-
Drainage	-	1(0.1)	1(0.1)	2(0.3)	-	1(0.3)	-	1(0.3)
Fever	1(0.1)	1(0.1)	1(0.1)	3(0.3)	-	-	-	-
Gangrene	-	1(0.1)	-	1(0.1)	-	-	-	-
Headache	3(0.3)	19(1.9)	4(0.4)	26(2.6)	3(0.8)	7(2.0)	5(1.4)	15(4.2)
Lesion	-	-	-	-	-	1(0.3)	-	1(0.3)
Malaise	-	1(0.1)	1(0.1)	2(0.2)	-	1(0.3)	-	1(0.3)
Moniliasis	1(0.1)	-	-	1(0.1)	-	-	-	-
Neck Rigidity	-	1(0.1)	-	1(0.1)	-	1(0.3)	-	1(0.3)
Pain	-	1(0.1)	4(0.4)	5(0.6)	-	-	2(0.6)	2(0.6)
Pain Arms	-	2(0.2)	2(0.2)	4(0.4)	-	1(0.3)	-	1(0.3)
Pain Back	-	1(0.1)	2(0.2)	3(0.3)	-	2(0.6)	-	2(0.6)
Pain Body	-	-	1(0.1)	1(0.1)	-	-	-	-
Pain, Chest	-	-	1(0.1)	1(0.1)	-	-	-	-
Pain, Feet	-	-	-	-	-	1(0.3)	-	-
Pain Hands	-	1(0.1)	-	1(0.1)	-	-	-	-
Pain Incisional	-	-	1(0.1)	1(0.1)	-	-	-	-
Pain Legs	-	1(0.1)	-	1(0.1)	1(0.3)	1(0.3)	-	2(0.6)
Pain Neck	-	2(0.2)	-	2(0.2)	-	-	-	-
Pain, Pleuritic	-	1(0.1)	-	1(0.1)	-	-	-	-
Pain Ribs	-	-	1(0.1)	1(0.1)	-	-	-	-
Pain, Thighs	-	1(0.1)	-	1(0.1)	-	-	-	-
Pain, Tooth	-	-	1(0.1)	1(0.1)	-	-	1(0.3)	1(0.3)
Pain, Wound	-	1(0.1)	-	1(0.1)	-	-	-	-
Cardiovascular System	-	2(0.2)	7(0.8)	9(1.0)	-	3(0.8)	2(0.6)	5(1.4)
Atrial Fibrillation	-	-	1(0.1)	1(0.1)	-	-	-	-
Cardiac Arrest	-	-	1(0.1)	1(0.1)	-	-	-	-
Hemorrhage	-	-	1(0.1)	1(0.1)	-	-	-	-
Hypertension	-	-	-	-	-	2(0.6)	-	2(0.6)
Hypotension	-	-	3(0.3)	3(0.3)	-	1(0.3)	-	1(0.3)
Pain, Chest	-	1(0.1)	2(0.2)	3(0.3)	-	-	1(0.3)	1(0.3)
Syncope	-	1(0.1)	-	1(0.1)	-	-	-	-
Tachycardia	-	1(0.1)	-	1(0.1)	-	-	-	-
Vent. Fibrillation	-	-	-	-	-	-	1(0.3)	-
Vent. Tachycardia	-	-	-	-	-	-	1(0.3)	1(0.3)
Digestive System	10(1.1)	35(3.9)	29(3.2)	74(8.2)	10(2.8)	24(6.7)	7(2.0)	41(11.5)
Anorexia	-	-	1(0.1)	1(0.1)	-	-	-	-
Colitis	1(0.1)	-	-	1(0.1)	-	-	-	-
Constipation	1(0.1)	9(1.0)	3(0.3)	13(1.4)	1(0.3)	7(2.0)	1(0.3)	9(2.5)
Diarrhea	3(0.3)	5(0.6)	4(0.4)	12(1.3)	4(1.1)	8(2.2)	2(0.6)	14(3.9)
Dry Mouth	-	-	1(0.1)	1(0.1)	-	-	-	-
Duodenal Ulcer	-	1(0.1)	-	1(0.1)	-	-	-	-
Dyspepsia	-	4(0.4)	2(0.2)	6(0.7)	-	4(1.1)	2(0.6)	6(1.7)
GI Disorder	-	1(0.1)	-	1(0.1)	-	1(0.3)	-	1(0.3)
Hematemesis	-	-	1(0.1)	1(0.1)	-	-	-	-
Hemorrhage	-	1(0.1)	4(0.4)	5(0.6)	-	-	-	-
Intest. Obstruct.	-	-	1(0.1)	1(0.1)	-	-	-	-
Melena	-	1(0.1)	1(0.1)	2(0.2)	-	1(0.3)	-	1(0.3)
Moniliasis, Oral	-	-	1(0.1)	1(0.1)	-	1(0.3)	-	1(0.3)
Nausea	4(0.4)	11(1.2)	11(1.2)	26(2.9)	5(1.4)	7(2.0)	3(0.8)	15(4.2)
Pain, Abd.	1(0.1)	7(0.8)	5(0.6)	13(1.4)	2(0.6)	3(0.8)	-	5(1.4)
Pain, Rectal	-	-	1(0.1)	1(0.1)	-	-	-	-
Pseud. Colitis	1(0.1)	-	-	1(0.1)	-	-	-	-
Rectal Disorder	-	-	1(0.1)	1(0.1)	-	-	-	-
Thirst	1(0.1)	-	-	1(0.1)	-	-	-	-
Vomiting	1(0.1)	6(0.7)	7(0.8)	14(1.6)	-	1(0.3)	2(0.6)	3(0.8)
HAL	-	-	1(0.1)	1(0.1)	-	-	-	-
Anemia	-	-	1(0.1)	1(0.1)	-	-	-	-

Clinical Adverse Events - Continued
Listed by Body System and Relatedness
All North American Trials

Body System Event	Cefepime				Ceftazidime			
	Prob. Rel.	Unknown Rel.	Not Rel.	Total	Prob. Rel.	Unk. Rel.	Not Rel.	Total
Metabolic	1(0.1)	2(0.2)	1(0.1)	4(0.4)	-	5(1.4)	1(0.3)	6(1.7)
Edema	1(0.1)	2(0.2)	-	3(0.3)	-	5(1.4)	1(0.3)	6(1.7)
Hypoglycemia	-	-	1(0.1)	1(0.1)	-	-	-	-
Nervous	-	20(20.2)	13(1.4)	33(3.7)	3(0.8)	11(3.1)	7(2.0)	21(5.9)
Acute Brain Synd.	-	-	-	-	-	-	1(0.3)	1(0.3)
Agitation	-	-	4(0.4)	4(0.4)	-	1(0.3)	-	1(0.3)
Anxiety	-	1(0.1)	-	1(0.1)	-	-	2(0.6)	2(0.6)
Confusion	-	-	5(0.6)	5(0.6)	-	1(0.3)	-	1(0.3)
Convulsion	-	1(0.1)	-	1(0.1)	1(0.3)	-	1(0.3)	2(0.3)
Delirium	-	19(2.1)	-	1(0.1)	-	-	-	-
Depression	-	2(0.2)	-	2(0.2)	-	1(0.3)	2(0.6)	3(0.8)
Dizziness	-	7(0.8)	1(0.1)	8(0.9)	1(0.3)	5(1.4)	-	6(1.7)
Drowsiness	-	1(0.1)	-	1(0.1)	-	1(0.3)	-	1(0.3)
Hallucinations	-	-	1(0.1)	1(0.1)	-	-	-	-
Insomnia	-	3(0.3)	1(0.1)	4(0.4)	-	3(0.8)	2(0.6)	5(1.4)
Myoclonus	-	1(0.1)	-	1(0.1)	-	-	-	-
Nervousness	-	2(0.2)	2(0.2)	4(0.4)	1(0.3)	-	-	1(0.3)
Paresthesia	-	4(0.4)	1(0.1)	5(0.6)	-	-	1(0.3)	1(0.3)
Speech Disorder	-	1(0.1)	-	1(0.1)	-	-	-	-
Tremor	-	1(0.1)	1(0.1)	2(0.2)	-	-	-	-
Vertigo	-	-	-	-	-	-	1(0.3)	1(0.3)
Respiratory	-	4(0.4)	3(0.3)	7(0.8)	-	5(1.4)	3(0.8)	9(2.5)
Asthma	-	-	-	-	-	-	1(0.3)	1(0.3)
Cough	-	2(0.2)	-	2(0.2)	-	1(0.3)	2(0.6)	3(0.8)
Cough, Increas.	-	-	-	-	-	2(0.6)	-	2(0.6)
Dyspnea	-	-	3(0.3)	3(0.3)	-	1(0.3)	-	1(0.3)
Hiccup	-	1(0.1)	-	1(0.1)	-	1(0.3)	-	1(0.3)
Pain, Throat	-	-	-	-	-	1(0.3)	-	1(0.3)
Rhinitis	-	-	-	-	-	1(0.3)	-	1(0.3)
Sputum	-	1(0.1)	-	1(0.1)	-	-	-	-
Skin	14(1.6)	23(2.6)	6(0.7)	43(4.8)	6(1.7)	10(2.8)	6(1.7)	22(6.2)
Contact Derm.	-	-	-	-	-	-	1(0.3)	1(0.3)
Erythema	-	2(0.2)	-	2(0.2)	1(0.3)	2(0.6)	-	3(0.8)
Furunculosis	-	-	1(0.1)	1(0.1)	-	-	-	-
Pruritus	7(0.8)	11(1.2)	1(0.1)	19(2.1)	5(1.4)	2(0.6)	2(0.6)	9(2.5)
Rash	8(0.9)	11(1.2)	1(0.1)	20(2.2)	2(0.6)	4(1.1)	5(0.8)	9(2.5)
Sweating	-	4(0.4)	2(0.2)	6(0.7)	-	2(0.6)	1(0.3)	3(0.8)
Ulcer	-	-	1(0.1)	1(0.1)	-	-	-	-
Urticaria	1(0.1)	-	-	1(0.1)	-	-	-	-
Special Senses	-	2(0.2)	-	2(0.2)	-	2(0.6)	1(0.3)	3(0.8)
Blurred Vision	-	-	-	-	-	1(0.3)	-	1(0.3)
Eye Disorder	-	-	-	-	-	-	1(0.3)	1(0.3)
Nasal Discharge	-	1(0.1)	-	1(0.1)	-	-	-	-
Pain, Ears	-	-	-	-	-	1(0.3)	-	1(0.3)
Tinnitus	-	1(0.1)	-	1(0.1)	-	-	-	-
Urogenital	2(0.2)	4(0.4)	3(0.3)	9(1.0)	1(0.3)	2(0.6)	4(1.1)	7(2.0)
Blood Occult	-	-	-	-	-	-	1(0.3)	1(0.3)
GU Pain	-	1(0.1)	-	1(0.1)	-	-	-	-
Hematuria	-	-	-	-	-	-	1(0.3)	1(0.3)
Infection	-	1(0.1)	-	1(0.1)	-	-	-	-
Kidney Failure	-	-	1(0.1)	1(0.1)	-	-	-	-
Leukorrhea	-	1(0.1)	-	1(0.1)	-	-	-	-
Pain, GU	-	1(0.1)	-	1(0.1)	-	1(0.3)	-	1(0.3)
Pruritus	1(0.1)	1(0.1)	-	2(0.2)	1(0.3)	-	1(0.3)	2(0.6)
Urinary Pressure	-	1(0.1)	-	1(0.1)	-	-	-	-
Urinary Retention	-	-	1(0.1)	1(0.1)	-	1(0.3)	1(0.3)	2(0.6)
Vaginal Hemorrhage	-	-	1(0.1)	1(0.1)	-	-	-	-
Vaginal Monilias	1(0.1)	-	-	1(0.1)	-	-	-	-
Vaginitis	-	1(0.1)	1(0.1)	2(0.2)	-	-	-	-

Section V.4.4 - Local Tolerance

Most patients received either cefepime or ceftazidime via the intravenous route. In general, cefepime was well tolerated regardless of the route of administration. The incidence of adverse reactions at the administration site was similar in both the cefepime and ceftazidime treatment groups. Table SS.7 summarizes the experience at the administration site for patients enrolled in comparative studies of cefepime and ceftazidime.

Table SS.7
Local Reaction at the Site of Administration
BMS Table

Administration Tolerance	Low Dose ¹		High Dose ²	
	Cefep.	Ceftaz.	Cefep.	Ceftaz.
IV Administration	N=325	N=164	N=222	N=203
Well Tolerated	311 (96%)	161 (98%)	211 (95%)	193 (95%)
Poorly Tolerated	14 (4%)	3 (1%)	11 (5%)	10 (5%)
Infiltration	6 (2%)	2 (1%)	4 (2%)	2 (1%)
Phlebitis	2 (1%)	0	2 (1%)	3 (2%)
Pain	5 (2%)	0	4 (2%)	3 (3%)
Redness	1 (<1%)	0	5 (2%)	3 (2%)
Swelling	1 (<1%)	0	2 (1%)	1 (1%)
Other	0	1 (1%)	1 (1%)	0
IM Administration	N=6	N=1	N=0	N=0
Well Tolerated	6 (100%)	1 (100%)	NA	NA
IV & IM Administration	N=3	N=1	N=0	N=1
Well Tolerated	3 (100%)	1 (100%)	NA	1 (100%)

1- ≤2.0 grams cefepime per day

2- >2.0 grams cefepime per day

Section V.4.5 - Laboratory Test Abnormalities

The effect of cefepime on laboratory parameters was analyzed in two parts. The first parts studied the incidence of laboratory test abnormalities in patients who had normal laboratory test parameters at baseline. The second analysis studied the worsening of laboratory parameters in patients whose laboratory parameters were already abnormal at baseline.

Section V.4.5.1 - Laboratory Test Abnormalities Occurring in Patients with Normal Laboratory Test Parameters at Baseline

The medical officer classified patients with laboratory test abnormalities into two groups. The first group, labelled "abnormal" included all patients who developed a laboratory test value that was outside the normal range either during or after therapy. The second group, labelled "clinically significant" was an attempt by the medical officer to identify those patients in whom the observed laboratory test abnormality was sufficiently severe to warrant action in a clinical setting. Table SS.8 summarizes the criteria used by the medical officer to define a laboratory test result as "abnormal" or "clinically significant".

n.b.: all tables in this section generated by the medical officer.

Table SS.8
Criteria for Laboratory Test Abnormalities
(M.O. Table)

Test	Abnormal	Clinically Significant
Hematocrit	< LNL ¹	< 30%
Platelet	< LNL	< 100,000/mm ³
White Blood Count (WBC)	< LNL	< 3,000/mm ³
Abs. Neut. Count (ANC)	< LNL	< 1,000/mm ³
Abs. Eos. Count (AEC)	> UNL ²	> 600/mm ³
Prothrombin Time (PT)	> UNL	> 15.0 secs
Part. Throm. Time (PTT)	> UNL	> 45.0 secs.
Alkaline Phosphatase	> UNL	> 200% UNL
AST	> UNL	> 200% UNL
ALT	> UNL	> 200% UNL
Total Bilirubin	> UNL	> 150% UNL
Blood Urea Nit. (BUN)	> UNL	> 150% UNL
Creatinine	> UNL	> 150% UNL
Sodium (Na)	< LNL, > UNL	≤ 125, ≥ 156 mEq/dL
Potassium (K)	< LNL, > UNL	≤ 2.9 ^F , ≥ 6.0 mEq/dL
Calcium (Ca)	< LNL, > UNL	≤ 7.5, ≥ 11.5 mEq/dL
Phosphorous (PO ₄)	< LNL, > UNL	≤ 2.0, ≥ 5.0 mEq/dL

¹LNL - Lower normal limit for laboratory.

²UNL - Upper normal limit for laboratory.

In order to give perspective to any observed abnormalities, the medical officer chose to base the majority of the analysis of laboratory test abnormalities on the North American comparative studies. This approach will allow for a reasonable estimation of the comparative incidence between the two treatment groups. The

results for the European comparative studies and the non-comparative studies will be reported separately.

Table SS.9 summarizes those patients enrolled in North American comparative studies who developed laboratory abnormalities either during or post-treatment. The percentage of patients who developed any abnormality was not statistically different, between the two treatment groups for any laboratory parameter tested. With respect to clinically significant abnormalities, the only statistically significant difference observed between the two treatment groups was in the absolute eosinophil count. A greater percentage of patients in the ceftazidime treatment group developed eosinophilia compared with the cefepime treatment group ($p=0.04$, Fisher's Exact Test).

Table SS.9
Patients with Normal Laboratory Test Results at Baseline
who Developed Laboratory Test Abnormalities During or Post-Treatment
North American Comparative Studies Only

Test	#Abnormal/#Tested (%)		#Clin. Signif./#Tested (%)	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
Hematocrit	83/218 (38%)	45/141 (32%)	5/218 (<2%)	5/141 (<1%)
Platelet	15/418 (4%)	13/294 (4%)	1/418 (<1%)	2/294 (1%)
White Blood Cells	36/459 (8%)	26/313 (8%)	3/459 (1%)	3/313 (1%)
Abs Neutrophil Count	34/417 (8%)	30/285 (11%)	3/417 (1%)	1/285 (1%)
Abs. Eosinophil Count	69/330 (21%)	52/233 (22%)	13/330 (4%)	19/233 (8%)
Prothrombin Time	21/297 (7%)	14/204 (7%)	1/297 (<1%)	2/204 (<1%)
Part. Thromboplast. Time	20/329 (6%)	17/213 (8%)	7/329 (2%)	4/213 (2%)
Alkaline Phosphatase	36/289 (12%)	21/203 (10%)	3/289 (1%)	0/203 (0%)
AST	63/302 (21%)	45/211 (21%)	7/302 (2%)	7/211 (3%)
ALT	49/291 (16%)	40/201 (20%)	8/291 (3%)	10/201 (5%)
Total Bilirubin	11/370 (3%)	3/258 (1%)	4/370 (1%)	2/258 (1%)
Blood Urea Nitrogen	27/364 (7%)	15/272 (6%)	7/364 (2%)	2/272 (1%)
Creatinine	10/384 (3%)	8/261 (3%)	0/384 (0%)	0/261 (0%)
Sodium	39/342 (11%)	29/245 (12%)	1/342 (<1%)	1/245 (1%)
Potassium	39/383 (10%)	29/267 (11%)	9/383 (2%)	3/267 (1%)
Calcium	68/258 (26%)	47/182 (26%)	2/258 (<1%)	1/182 (1%)
Phosphorous	53/334 (16%)	41/237 (17%)	23/334 (7%)	11/237 (5%)

Table SS.10 summarizes the laboratory test abnormalities which occurred in patients who received low-dose cefepime therapy ($\pm$ 2.0 grams per day). The most frequently observed LTA among low-dose patients in both treatment groups was eosinophilia. Other LTA occurred at rates similar to those seen in the overall population (Table SS.9). There were no significant differences between the two treatment groups for any parameter among low dose patients.

Table SS.10
Patients with Normal Laboratory Test Results at Baseline
who Developed Laboratory Test Abnormalities During or Post-Treatment
North American Comparative Studies Only
Patients Receiving Low-Dose Therapy

Test	#Abnormal/#Tested (%)		#Clin. Signif./#Tested (%)	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
Hematocrit	45/146(31%)	17/72(24%)	2/146(1%)	0/72(0%)
Platelet	4/239(2%)	2/123(2%)	0/139(0%)	1/123(1%)
White Blood Cells	26/271(10%)	13/128(10%)	2/271(1%)	0/128(0%)
Abs Neutrophil Count	14/236(6%)	12/111(11%)	1/236(<1%)	1/111(1%)
Abs. Eosinophil Count	35/176(20%)	21/85(25%)	7/176(4%)	8/85(9%)
Prothrombin Time	14/198(7%)	9/103(9%)	1/198(<1%)	1/103(1%)
Part. Thrombo. Time	12/219(5%)	8/113(7%)	3/219(1%)	3/113(3%)
Alkaline Phosphatase	17/178(10%)	10/101(10%)	1/178(<1%)	0/101(0%)
AST	40/172(23%)	22/96(23%)	5/172(3%)	3/96(3%)
ALT	23/182(13%)	13/89(15%)	6/182(3%)	2/89(2%)
Total Bilirubin	6/208(3%)	0/109(0%)	3/208(1%)	0/109(0%)
Blood Urea Nitrogen	15/211(7%)	6/117(5%)	3/211(1%)	1/117(1%)
Creatinine	9/230(4%)	1/116(1%)	0/230(0%)	0/116(0%)
Sodium	25/197(13%)	14/100(14%)	0/197(0%)	1/100(1%)
Potassium	24/225(11%)	11/112(10%)	5/225(2%)	1/112(1%)
Calcium	33/152(22%)	17/85(20%)	1/152(<1%)	1/85(1%)
Phosphorous	25/191(13%)	15/98(15%)	12/191(6%)	4/98(4%)

Table SS.11 summarizes the incidence of LTA among patients who were treated with high-dose cefepime (> 2.0 grams per day). A greater percentage of patients in the high-dose ceftazidime group developed abnormalities in creatinine compared with the high-dose cefepime group. The difference was statistically significant ($p=0.03$, Fisher's Exact Test). However, no patients in either treatment group developed a clinically significant abnormality. There was no significant difference between the two treatment groups with respect to any other laboratory parameter assessed.

Table SS.11
Patients with Normal Laboratory Test Results at Baseline
who Developed Laboratory Test Abnormalities During or Post-Treatment
North American Comparative Studies Only
High-Dose Group

Test	#Abnormal/#Tested (%)		#Clin. Signif./#Tested (%)	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
Hematocrit	38/70 (54%)	27/68 (39%)	3/70 (4%)	1/68 (1%)
Platelet	8/165 (5%)	8/159 (5%)	1/165 (1%)	1/159 (1%)
White Blood Cells	8/174 (5%)	11/171 (7%)	1/174 (<1%)	2/171 (2%)
Abs Neutrophil Count	20/168 (13%)	18/161 (11%)	2/168 (2%)	0/161 (0%)
Abs. Eosinophil Count	32/144 (22%)	28/142 (19%)	6/144 (4%)	9/142 (6%)
Prothrombin Time	6/97 (6%)	4/100 (4%)	0/97 (0%)	1/100 (1%)
Part. Thrombo. Time	8/107 (8%)	8/99 (8%)	4/107 (4%)	1/99 (1%)
Alkaline Phosphatase	18/107 (17%)	8/98 (8%)	2/107 (2%)	0/98 (0%)
AST	21/121 (18%)	20/205 (10%)	2/121 (2%)	3/105 (3%)
ALT	23/100 (23%)	24/103 (23%)	2/100 (2%)	6/103 (6%)
Total Bilirubin	4/149 (3%)	2/119 (2%)	1/149 (1%)	1/139 (1%)
Blood Urea Nitrogen	10/148 (7%)	9/151 (6%)	3/148 (2%)	1/150 (1%)
Creatinine	1/151 (1%)	7/141 (7%)	0/151 (0%)	0/140 (0%)
Sodium	13/136 (10%)	12/135 (9%)	1/136 (1%)	0/135 (0%)
Potassium	10/143 (7%)	17/144 (12%)	1/146 (1%)	2/144 (2%)
Calcium	32/101 (32%)	28/92 (30%)	0/101 (0%)	0/92 (0%)
Phosphorous	24/133 (19%)	25/130 (20%)	7/133 (6%)	7/130 (6%)

Table SS.12 summarizes the LTA observed in patients in whom the dose of study drug was adjusted due to renal failure. In general, the numbers of patients in this category was too small to draw any statistically valid conclusions from this data.

Table SS.12
Patients with Normal Laboratory Test Results at Baseline
who Developed Laboratory Test Abnormalities During or Post-Treatment
North American Comparative Studies Only
Renally Impaired Patients

Test	#Abnormal/#Tested (%)		#Clin. Signif./#Tested (%)	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
Hematocrit	0/2 (0%)	1/1 (100%)	0/2 (0%)	0/1 (0%)
Platelet	3/14 (21%)	3/12 (25%)	0/14 (0%)	0/12 (0%)
White Blood Cells	0/14 (0%)	2/14 (14%)	0/14 (0%)	1/14 (7%)
Abs Neutrophil Count	0/13 (0%)	0/13 (0%)	0/13 (0%)	0/13 (0%)
Abs. Eosinophil Count	2/10 (20%)	3/6 (50%)	0/10 (0%)	2/6 (33%)
Prothrombin Time	1/2 (50%)	1/1 (100%)	0/2 (0%)	0/1 (0%)
Part. Thrombo. Time	0/3 (0%)	1/1 (100%)	0/3 (0%)	0/1 (0%)
Alkaline Phosphatase	1/4 (25%)	3/4 (75%)	0/4 (0%)	0/4 (0%)
AST	2/9 (22%)	3/10 (30%)	0/9 (0%)	1/10 (10%)
ALT	2/9 (22%)	3/9 (33%)	0/9 (0%)	2/9 (22%)
Total Bilirubin	1/13 (8%)	1/10 (10%)	0/13 (0%)	1/10 (10%)
Blood Urea Nitrogen	2/5 (40%)	0/5 (0%)	1/5 (20%)	0/5 (0%)
Creatinine	0/3 (0%)	0/5 (0%)	0/3 (0%)	0/5 (0%)
Sodium	1/9 (11%)	3/10 (30%)	0/9 (0%)	0/10 (0%)
Potassium	5/12 (42%)	1/11 (9%)	3/12 (25%)	0/11 (0%)
Calcium	3/5 (60%)	2/5 (40%)	1/5 (20%)	0/5 (0%)
Phosphorous	4/10 (40%)	1/9 (11%)	4/10 (40%)	0/1 (0%)

Table SS.13 summarizes the patients with normal laboratory test parameters at baseline who developed laboratory test abnormalities either before or during treatment. Included in the table are those patients enrolled in all North American studies (both comparative and non-comparative) of cefepime. The incidence of laboratory test abnormalities does not significantly change when the data from the non-comparative studies is added to the data from the comparative studies.

Table SS.13
Patients with Normal Laboratory Results at Baseline
who Developed Laboratory Test Abnormalities During or Post-Treatment
All North American Studies (Including Non-comparative)

Test	#Abnormal/#Tested (%)	#Clin. Signif./#Tested (%)
Hematocrit	132/362 (36%)	10/362 (3%)
Platelet	26/715 (4%)	1/715 (<1%)
White Blood Cells	66/792 (8%)	6/792 (<1%)
Abs Neutrophil Count	65/714 (9%)	7/714 (1%)
Abs. Eosinophil Count	140/600 (23%)	34/600 (<1%)
Prothrombin Time	49/491 (10%)	4/491 (1%)
Part. Thrombo. Time	34/528 (6%)	11/528 (2%)
Alkaline Phosphatase	64/485 (13%)	5/485 (1%)
AST	107/536 (20%)	15/536 (3%)
ALT	87/504 (17%)	15/504 (3%)
Total Bilirubin	17/648 (3%)	7/648 (1%)
Blood Urea Nitrogen	50/648 (8%)	12/648 (2%)
Creatinine	22/682 (3%)	1/682 (<1%)
Sodium	72/579 (12%)	2/579 (<1%)
Potassium	94/673 (14%)	15/673 (2%)
Calcium	100/365 (27%)	2/365 (<1%)
Phosphorous	84/467 (18%)	40/461 (9%)

Table SS.14 summarizes the LTA that developed in patients with normal laboratory parameters at the baseline who were enrolled in European comparative studies. In general, the number of patients involved was too small for significant differences to be observed, however, a significantly greater percentage patients in the ceftazidime treatment group experienced a clinically significant rise in alkaline phosphatase compared with the cefepime treatment group (p=0.05).

Medical Officer's Comments: Although an elevation of alkaline phosphatase was observed in the ceftazidime treatment group, a concurrent elevation of the other indicators of liver function (AST, ALT, etc) was not observed. Also, this effect was not seen in the North American comparative studies. The medical officer, therefore, questions the true significance of the finding.

Table SS.14
Patients with Normal Laboratory Test Results at Baseline
who Developed Laboratory Test Abnormalities During or Post-Treatment
European Comparative Studies Only

Test	#Abnormal/#Tested (%)		#Clin. Signif./#Tested (%)	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
Hematocrit	1/21 (5%)	3/10 (30%)	0/21 (0%)	0/10 (0%)
Platelet	4/34 (12%)	1/19 (5%)	3/34 (9%)	0/19 (0%)
White Blood Cells	4/36 (11%)	0/20 (0%)	1/36 (3%)	0/20 (0%)
Abs Neutrophil Count	8/30 (27%)	5/15 (33%)	1/30 (3%)	0/15 (0%)
Abs. Eosinophil Count	5/35 (14%)	3/15 (20%)	2/35 (6%)	1/15 (7%)
Prothrombin Time	1/1 (100%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
Prothrombin Ratio	4/25 (16%)	3/16 (19%)	0/25 (0%)	0/16 (0%)
Part. Thrombo. Time	5/30 (17%)	2/17 (12%)	0/30 (0%)	0/17 (0%)
Alkaline Phosphatase	4/22 (18%)	6/13 (46%)	1/22 (5%)	4/13 (31%)
AST	4/27 (15%)	1/13 (8%)	1/27 (4%)	0/13 (0%)
ALT	8/28 (29%)	5/14 (36%)	2/28 (7%)	2/14 (14%)
Total Bilirubin	3/27 (11%)	0/11 (0%)	3/27 (11%)	0/11 (0%)
Blood Urea Nitrogen	2/16 (13%)	0/8 (0%)	0/16 (0%)	0/8 (0%)
Blood Urea	3/18 (17%)	2/13 (15%)	2/18 (11%)	1/13 (8%)
Creatinine	2/40 (5%)	0/21 (0%)	1/40 (3%)	0/21 (0%)
Sodium	10/38 (26%)	3/21 (14%)	0/38 (0%)	1/21 (5%)
Potassium	6/34 (18%)	2/19 (11%)	1/34 (3%)	0/19 (0%)
Calcium	7/23 (30%)	1/8 (13%)	1/23 (4%)	0/8 (0%)
Phosphorous	9/22 (41%)	1/9 (11%)	1/22 (5%)	0/9 (0%)

Section V.4.5.2 - Laboratory Test Abnormalities Occurring in Patients with Abnormal Values for Laboratory Parameters at Baseline

Table SS.15 summarizes the percentage of patients, enrolled in North American Comparative Studies, in whom an abnormality in a laboratory parameter was noted at baseline, and, in whom the observed abnormality worsened during or after treatment.

Medical Officer's Comments: There is difficulty drawing conclusion from this sub-population because of the small numbers of patients involved and the variability of the data. There was a trend observed in multiple indices of liver function (Alkaline phosphatase, AST, ALT and Bilirubin) and renal function (BUN, Creatinine) toward greater percentages of patients in the cefepime treatment group worsening during therapy compared with the ceftazidime treatment group. This trend, however, did not achieve statistical significance. There were no other differences that were considered to be either statistically or clinically relevant by the medical officer.

Table SS.15
Patients with Abnormalities of Laboratory Test Parameters at Baseline
Whose Abnormalities Worsened Either During or Post Treatment
Patients Enrolled in North American Comparative Studies

Test	Cefepime		Ceftazidime	
	N	Worse (%)	N	Worse (%)
Hematocrit	222	26 (12%)	157	26 (17%)
Platelet Count	24	5 (21%)	16	3 (19%)
White Blood Cells	9	4 (44%)	7	1 (14%)
Abs. Neutrophil Count	7	0 (0%)	5	1 (20%)
Abs. Eosinophil Clout	49	5 (10%)	38	8 (21%)
Prothrombin Time	106	9 (8%)	79	7 (9%)
Part. Thromboplastin Time	23	3 (13%)	13	1 (8%)
Alkaline Phosphatase	106	3 (8%)	75	5 (7%)
AST	92	18 (21%)	35	6 (13%)
ALT	72	18 (25%)	47	8 (17%)
Total Bilirubin	30	4 (13%)	22	0 (0%)
Blood Urea Nitrogen	73	19 (26%)	30	3 (10%)
Creatinine	50	7 (14%)	29	1 (3%)
Sodium	90	0 (0%)	52	1 (2%)
Potassium	50	3 (6%)	30	1 (3%)
Calcium	129	4 (3%)	96	6 (6%)
Phosphorous	49	3 (8%)	37	2 (5%)

Section V.4.5 - Safety Summary

The mortality rates observed in comparative studies were not significantly different between the two treatment groups (cefepime=2.9, ceftazidime=2.9%). The mortality rates observed in the non-comparative studies of cefepime were consistent with those observed in the comparative studies.

In comparative studies, there was no significant difference observed in the rate of discontinuation for treatment related adverse events (cefepime=3.3%, ceftazidime=2.7%). The majority of adverse events that resulted in discontinuation were related to the skin (rash, pruritus) in both treatment groups. Six patients in the cefepime treatment group and no patients in the ceftazidime treatment group were removed from study therapy because of laboratory test abnormalities.

With regard to clinical adverse events, overall, the rate of occurrence of any adverse event was 20.3% in the cefepime treatment group and 22.8% in the ceftazidime treatment group. The difference was not significant. There were no significant differences noted between the two treatment groups with respect to the incidence of clinical adverse events when the data was analyzed according to location (North American vs. European); Dose administered (high-dose vs. low-dose); or renal impairment.

Clinical adverse events occurred most commonly in the digestive system in both treatment groups. Clinical adverse events occurring in greater than 1% of the population exposed to cefepime included: headache(2.6%); constipation(1.4%); diarrhea(1.3%), nausea(2.9%), abdominal pain(1.4%), pruritus(2.1%), and rash(2.2%).

The rate of local reaction at the infusion site was virtually identical for both treatment groups (cefepime=4.5%, ceftazidime=3.5%).

Among patients with normal values for laboratory parameters at baseline, there was no significant difference between the two treatment groups in the percentage of patients who developed any abnormality during or post-treatment. However, a statistically larger percentage of patients in the ceftazidime group developed "clinically significant" eosinophilia during or post-treatment. There were no other significant differences between the two treatment groups. Again, when the data was analyzed with regard to dose received (high-dose versus low-dose) and location of study center (North American versus European) the two treatment groups remained comparable. The incidence of abnormalities in laboratory test did not change when the data from the non-comparative studies was included along with the data from the comparative studies.

Among patients with abnormal values for laboratory parameters at baseline, again, no significant differences were observed between the two treatment groups. A trend, however, was noted toward a greater percentage of patients in the cefepime treatment group experiencing a worsening of liver function test (alkaline phosphatase, AST, ALT, and Bilirubin) as well as renal function tests (BUN, creatinine) compared with the ceftazidime treatment group. This trend was not statistically significant.

In conclusion, no significant safety issues were seen in patients with SSTI enrolled in clinical trials of cefepime.

Section VI - Overall Conclusions

The applicant has demonstrated the safety and efficacy of cefepime hydrochloride for the treatment of moderate to severe skin and soft-tissue infections due to *Staphylococcus aureus* and Group-A Beta Hemolytic Streptococci at a dose of 2.0 grams every 12 hours. The application for this dosage and indication should be approved.

The following should be placed in the approved package insert for Maxipime:

In the Indications and Usage section:

SKIN AND SKIN STRUCTURE INFECTIONS:

Skin and Skin Structure Infections caused by *Staphylococcus aureus* (penicillinase producing, methicillin-susceptible strains), and *Streptococcus pyogenes*. Cefepime may be less efficacious than comparable agents in wound infections (see clinical studies).

The following should be placed in the Clinical Studies section:

In comparative clinical trials, ^{wound} 12 patients with clinically and microbiologically documented (would) infection were treated with cefepime, the infection was cured in 7/12 patients (58%). Five patients with clinically and microbiologically documented wound infection were treated with ceftazidime, the infections was cured in 5 patients (100%).

The application for cefepime hydrochloride at a dosage level of 1.0 grams every 12 hours for the treatment of mild to moderate SSTI is not approvable for the following reasons:

1. It is not appropriate to treat mild infections of the skin and soft tissues with a broad spectrum parenteral drug.
2. According to the medical officer's analysis, the efficacy of cefepime, at a dose of 1.0 grams every 12 hours, was not shown to be equivalent to ceftazidime for the treatment of moderate to severe skin and soft tissue infections by the 95% confidence interval approach.

William A. Erhardt

William A. Erhardt, M.D.
MO/HFD-520

Concurrence Only:
HFD-520/DepDir/LGavrilovich

cc:orig. NDA
HFD-340
HFD-520
HFD-520/MO/WErhardt
HFD-520/MO/LSherman
HFD-520/SMO/RAlbrecht
HFD-520/Pharm/Mainigi
HFD-520/Micro/Soprey
HFD-520/Chem/Roy
HFD-520/CSO/DeBellis

3/8/94 ra
See addendum
6/17/94

Medical Officer's Review of New Drug Application

Applicant: Bristol-Myers Squibb Company
Wallingford, CT 06492

Submitted: June 30, 1992

Received by Agency: July 1, 1992

Received by Medical Officer: March 1, 1993

First Draft Submitted: July 8, 1993

Material Reviewed:

This review contains the safety and efficacy data generated in nine studies of patients with urinary tract infections. The studies reviewed were 411-061, -067, -071, -083, -097, -097(Blinded), -108, -111, -140.

COMMENT: Studies submitted in support of this new drug application were designed in a manner such that patients with multiple infections (e.g. pneumonia, and UTI) could be evaluable for each of those indication. Therefore, patients appearing in this review may also appear in reviews of other indications.

Section I - GENERAL INFORMATION

Generic Drug Name: Cefepime

Trade Name Requested: MAXIPIME®

Manufacturer's Identifier: BMY-28142

Chemical Name: Pyrrolidinium, 1-[[7-[[[(2-amino-4-thiazolyl(methoxyimino)acetyl)-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl]-1-methyl]-chloride, monohydrochloride, monohydrate, [6R-[6 α , 7 β (Z)]]

Structural Formula:

Molecular Formula: C₁₉H₂₃N₄O₅S₂·Cl·HCl·H₂O.

Molecular Weight: 571.5

Route of Administration: Parenteral

Dosage Form: 500 mg, 1g, and 2g Vials

COMMENT: Maxipime® is supplied as a sterile dry mixture of cefepime

hydrochloride and L-arginine. The L-arginine, at an approximate concentration of 725 mg/g of cefepime, is added to control the pH of the reconstituted solution.

Pharmacologic Category:

Cefepime is a parenterally administered semisynthetic cephalosporin. According to the applicant, cefepime has the following unique characteristics: The in-vitro activity of cefepime against methicillin-sensitive staphylococci was four-fold greater than the activity of ceftazidime, yet, the in-vitro potency of cefepime against *Pseudomonas aeruginosa* was comparable to ceftazidime. In addition, cefepime has increased potency against *Enterobacter* when compared with other cephalosporins. The sponsor claims that when *P. aeruginosa* and *Enterobacter* were exposed to cefepime, ceftazidime and ceftriaxone in-vitro, cefepime-resistance was selected at a lower rate than was ceftriaxone-resistance or ceftazidime resistance.

Approval Status

At the time the NDA was submitted, cefepime had not been approved for sale in any country. Applications have been filed in France, Japan and Belgium.

Proposed Labelling

The applicant proposes the following text concerning urinary tract infections, for inclusion in the approved product labelling for cefepime hydrochloride.

INDICATIONS AND USAGE

Complicated Urinary Tract Infections - Including Pyelonephritis caused by *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Enterobacter* species.

Uncomplicated Urinary Tract Infections due to *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species and *Enterobacter* species.

DOSAGE AND ADMINISTRATION

The usual adult dosage and route of administration is 1 g administered intravenously or intramuscularly every 12 hours. However, the dosage and route vary according to the susceptibility of the causative organisms, the severity of the infection and the condition and renal function of the patients. Guidelines for dosage of MAXIPIME® are provided in the following table. The usual duration of therapy is 7-10 days; however, more severe infections may require longer treatment.

Table
Recommended Dosage Schedule for MAXIPIME®

Site and Type of Infection	Dose	Frequency
Mild to moderate urinary tract infections (complicated and uncomplicated)	500 mg - 1g IV or IM	Q12h
Severe infections including pneumonia, septicemia, urinary tract infections, complicated intra-abdominal infections, skin and skin-structure infections	2 g IV	Q12h

Section II - MANUFACTURING AND CONTROLS

The reader is referred to the microbiologist's manufacturing and controls review.

The drug substance is manufactured by Bristol-Myers Squibb at its facilities in Syracuse, New York and Latina, Italy:

Bristol Myers Squibb Co.
Bio/Chem Division
315 N. Thompson Road
P.O. Box 4755
Syracuse, New York 13221-4755

Bristol-Myers Squibb S.p.A.
Bio/Chem Division
Sermoneta
Latina, Italy

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Section III - PHARMACOLOGY:

The reader is referred to the pharmacologist's review.

PHARMACOKINETICS:

The reader is referred to the pharmacokineticist's review.

The following table summarizes the result of tissue penetration studies after intravenous administration of cefepime. Serum and urine concentration of cefepime observed after intravenous doses of 500 mg, 1 g, and 2 g are presented.

Table - 1
Mean Concentration of Cefepime in Urine and Plasma

Tissue	Dose	Number of Patients	Sample Collection Time (hrs)	Urine Concn. ($\mu\text{g/mL}$)	Plasma Concn. ($\mu\text{g/mL}$)
Urine	500 mg	8	0-4	292	4.9
	1 g	12	0-4	926	10.5
	2 g	12	0-4	3120	20.1

Section IV - MICROBIOLOGY:

The reader is referred to the microbiologist's review.

The applicant has proposed the following guidelines to be used in interpretation of the zones of inhibition produced by a 30 mcg cefepime disk.

Table - 2
Interpretation of Zones of Inhibition

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible
15 - 17	Intermediate
≤ 14	Resistant

Table 3, on the following page, summarizes the applicant's data of modal MIC values for Gram-negative and Gram-positive pathogens commonly encountered in urinary tract infections.

COMMENT: For all commonly encountered pathogens, the urinary concentration of cefepime exceeds the modal MIC_{90} . After a 500 mg dose the, plasma cefepime concentration does not exceed the modal MIC_{90} for many *Pseudomonas* species. Even after a 2 g dose, the MIC_{90} may not be exceeded for some *Pseudomonas* species. The serum concentration may be relevant in complicated UTI patients with such entities as prostatitis or pyelonephritis.

Table - 3
Cefepime MIC for Gram-Positive and Gram-Negative Bacteria

Organism	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)
<u>Gram Negative</u>		
<i>E. coli</i>	0.03	0.06
<i>K. pneumoniae</i>	0.03	0.25
<i>K. oxytoca</i>	0.03	0.25
<i>K. ozaenae</i>	0.13	0.25
<i>E. cloacae</i>	0.06	0.5
<i>E. aerogenes</i>	0.06	0.25
<i>E. agglomerans</i>	0.03	0.25
<i>E. sakazakii</i>	0.25	1.00
<i>S. marcescens</i>	0.13	1.00
<i>S. liquefaciens</i>	0.06	0.25
<i>C. freundii</i>	0.06	0.8
<i>C. diversus</i>	0.03	0.03
<i>C. koseri</i>	0.03	0.06
<i>C. amalonaticus</i>	<0.13	0.5
<i>P. mirabilis</i>	0.06	0.06
<i>P. vulgaris</i>	0.06	0.25
<i>M. morgani</i>	0.015	0.13
<i>P. penneri</i>	0.25	0.05
<i>H. alvei</i>	0.03	0.12
<i>Kluyvera</i> spp.	<0.13	-
<i>P. rettgeri</i>	0.03	0.50
<i>P. stuartii</i>	0.06	0.25
<i>Salmonella</i> spp.	0.03	0.06
<i>Shigella</i> spp.	0.015	0.06
<i>Aeromonas</i> spp.	0.03	0.13
<i>Vibrio</i> spp.	0.25	1.00
<i>Y. enterocolitica</i>	0.03	0.03
<i>P. aeruginosa</i>	2	8
<i>P. fluorescens</i>	2	8
<i>P. cepacia</i>	8	64
<i>P. acidovorans</i>	16	32
<i>P. putida</i>	1.00	1.00
<i>P. testosteroni</i>	0.5	1.00
<i>P. pseudomallei</i>	4	8
<i>P. acidivorans</i>	32	64
<i>P. stutzeri</i>	0.12	0.12
<i>P. paucimobilis</i>	8	-
<i>P. pickettii</i>	16	-
<i>X. maltophilia</i>	32	32
<u>Gram-Positive</u>		
<i>S. aureus</i>		
MS	2	4
MR	8	128
<i>S. epidermidis</i>	2	4
<i>S. haemolyticus</i>	>32	>32
<i>S. hominis</i>	2	2
<i>S. warneri</i>	2	-
<i>S. saprophyticus</i>	4	32
<i>S. pyogenes</i>	<0.015	0.03
<i>S. agalactiae</i>	0.06	0.06
<i>Streptococcus, Group C,F,G</i>	0.03	0.12
<i>Viridans Streptococci</i>	0.12	1
<i>S. pneumoniae</i>	0.03	0.06
<i>S. bovis</i>	0.03	0.12
<i>E. faecalis</i>	32	64
<i>E. faecium</i>	>128	>128
<i>E. avium</i>	8	-
<i>L. monocytogenes</i>	16	16, 51

Section V - CLINICAL STUDIES

The applicant is seeking approval for the treatment of uncomplicated and complicated UTI (including pyelonephritis). The proposed dosage and frequency of administration are 500 mg - 1 g Q12h for mild to moderate complicated and uncomplicated UTI; 2g Q12h for severe UTI. The applicant states that the average duration of therapy should be 7 - 10 days.

INTRODUCTION TO UTI STUDIES**Regarding the Designation of Patients as Having Complicated or Uncomplicated UTI:**

A urinary tract infection may be said to be "complicated" when one or more conditions are present that increase the risk of developing an infection or of having a persistent infection. The IDSA guidelines concerning anti-infective drugs in the treatment of urinary tract infections list the following criteria for establishing a urinary tract infections as complicated:

1. Presence of an indwelling catheter
2. > 100 mL of residual urine after voiding
3. Obstructive uropathy
4. Vesico-ureteral reflux
5. Anatomic abnormalities such as Ileal loops.
6. Azotemia due to intrinsic renal disease.
7. Renal transplantation.

After the age of 40 years, almost all men begin to develop benign prostatic hypertrophy which results in varying degrees of bladder outlet obstruction and urinary retention. UTI in men are more likely to be associated with prostatitis and pyelonephritis, thus the IDSA guidelines states that almost all UTI in men are complicated.

Pyelonephritis is another special case. The IDSA guidelines recognize the entity of "uncomplicated pyelonephritis", yet, in the DAIDP Points to Consider Document it is recommended that pyelonephritis be studied with complicated UTI because the dosage regimens for effective therapy in both conditions tend to be similar.

COMMENT: The medical officer analyzed the patients with complicated UTI and pyelonephritis separately. The medical officer did not differentiate between complicated and uncomplicated pyelonephritis. The following criteria were used by the medical officer to define complicated UTI:

- Anatomic abnormalities of the urinary tract (including congenital and surgically created).
- Presence of Benign Prostatic Hypertrophy
- Presence of an indwelling urinary catheter (including Foley catheters, nephrostomy tubes, supra-pubic catheter, and urinary stents).
- Functional abnormalities of the urinary tract including the presence of post-voiding residuals.
- Males over the age of 40 years
- The presence of obstructive uropathy whether due to stones, neoplasia, or other causes).
- A recent history of surgery on the urinary tract.

The medical officer did not consider recurrent UTI, in the absence of other complicating factors to be sufficient cause to classify a UTI as complicated.

Regarding Pyelonephritis

Pyelonephritis is a deep tissue infection that is often accompanied by bacteremia. There are both systemic and local signs and symptoms of pyelonephritis. Systemic symptoms include fever, chills and malaise. Local signs and symptoms include flank pain, back pain and tenderness at the costo-vertebral angle. Neither the systemic nor the local signs and symptoms of pyelonephritis are specific to the disease and, in fact, may be found in lower UTI, as well as diseases not related to the urinary tract. The IDSA guidelines recommend that minimal clinical diagnostic criteria for pyelonephritis include fever, chills and flank pain.

COMMENT: The medical officer concurs with the IDSA guidelines and required at least three of the above symptoms to be present to support the diagnosis of pyelonephritis. In addition, the medical officer required there to be at least one sign of systemic infection (e.g. fever, chills, etc) and one sign of kidney involvement (e.g. flank pain, costo-vertebral angle tenderness, etc.) to be present in patients presumed to have pyelonephritis.

Regarding Minimal Pre-Treatment Colony Counts

Traditionally, growth of bacteria at the level of 10^5 CFU/mL in a mid-stream clean catch urine has been required to establish the diagnosis of UTI. The IDSA guidelines have suggested that increased sensitivity may be achieved through the use of lower threshold colony counts as the criteria to establish the diagnosis of UTI. For patients with uncomplicated UTI, the IDSA guidelines recommend 10^3 CFU/mL of a single species as sufficient to establish the diagnosis, in patients with pyelonephritis, 10^4 CFU/mL is recommended and in patients with complicated UTI 10^5 CFU/mL is recommended. However, in an editorial in response to the IDSA guidelines, Kunin² recommends using the criteria of 10^5 CFU/mL for clinical trials in order to add additional specificity to the diagnosis.

COMMENT: The sponsor used the criteria of 10^5 CFU/mL to define urinary tract infection. The medical officer concurs with this approach, however, for infection with *S. saprophyticus* a colony count of 10^4 CFU/mL was considered acceptable.

Regarding organisms:

In the majority of cases of uncomplicated UTI, the organisms involved are Enterobacteriaceae, Enterococci and *S. saprophyticus*¹.

COMMENT: Patients with uncomplicated UTI due to Coagulase negative Staphylococci (except *S. saprophyticus*) or Group-B Streptococci were not considered evaluable by the medical officer, these organisms were considered to represent perineal contamination.

Overview of UTI Studies

The applicant submitted data from eight studies in support of the indication of complicated and uncomplicated UTI. All studies were multi-center studies. Five studies were performed at North American centers (411-061, -071, -097, -108, -140). Two studies were performed at European centers (411-067, -111). One study (411-083) included both European and North American centers.

Three studies were non-comparative (411-061, -067, -140). Five studies were comparative (411-071, -083, -097, -108, 111). The comparator agent in all cases was ceftazidime. Three centers in one study (411-097) and all centers in study 411-108 conducted their investigation in a blinded manner. All other studies were conducted in an open manner. The sponsor considered one study 411-083 to be pivotal.

In total, 1585 patients were enrolled in clinical trials designed to assess the efficacy of cefepime in UTI. 1034 patients received cefepime and 551 received a comparator agent (in all UTI trials the comparator agent was ceftazidime). 938 (cefepime=532, ceftazidime=406) patients were enrolled in comparative trials in North America. One patient received cefepime for a UTI under an emergency IND.

COMMENT: The North American comparative clinical trials were considered pivotal trials by the medical officer.

Most studies were conducted employing a common procedure. Deviations from the common procedure will be noted in the section of the review describing each individual study.

Study Objectives

To compare the safety and efficacy of cefepime and ceftazidime in patients with complicated and uncomplicated UTI.

Definition of Study Population

Inclusion Criteria

- If female, then only those who had a pregnancy test with negative results immediately before enrollment, were taking oral contraceptives in the prescribed manner, were surgically sterilized, or were postmenopausal.
- Had symptoms consistent with acute UTI that was suspected to be complicated (e.g., cystitis, pyelocystitis, pyelonephritis, or pyelitis), or uncomplicated.
- Were suspected to have a pathogen susceptible to both cefepime and ceftazidime.
- Participant, parent, or legal guardian agreed to the patient's participation in the study by signing the Informed Consent Form.

Exclusion Criteria

- History of a serious reaction to penicillin or a cephalosporin. (Patients with Type 1 hypersensitivity reaction to penicillin could be given study drug with caution. Study drug was to be discontinued immediately if a reaction occurred.)
 - Impaired renal function (baseline serum creatinine level of ≥ 1.7 mg/dl), or on renal dialysis.
 - Impaired hepatic function.
 - Infection not yet established (e.g., antibiotic therapy for the initial management of extensive physical trauma).
 - Likelihood of receiving other antimicrobials concomitantly.
 - Previous enrollment in the study.
 - Medically significant disease or disorder that in the opinion of the investigator could influence the results of the study.
 - Pregnancy or nursing.
 - Infection that was likely to require long-term antimicrobial therapy.
 - History of neurogenic bladder, surgical reconstruction of genitourinary system, or continuous long-term indwelling urinary catheter.
- COMMENT:** Although neurogenic bladder and surgical reconstruction of the genito-urinary system were exclusion criteria, in practice, these patients were included in all protocols. The medical officer also included these patients in his evaluable population

Procedures and Observations

The following table summarizes the procedures and observations performed during the studies.

Table - 4
Procedures and Observations
Comparative UTI Studies

Procedure	Pre-Rx Within 48 hrs	During-Rx Days 2-6	Post-Rx Days 5-9	Post-F Days 20-44 ^a
Eligibility	X	-	-	-
Informed consent	X	-	-	-
Medical history	X	-	-	-
Physical examination	X	X ^b	X	-
Clinical evaluation	X	X	X	X
Bacteriologic tests ^c	X	X	X	X
Laboratory tests ^d	X	X	X	X

a The follow-up was required only for patients with complicated UTI (classified by the investigator) whose Day 5-9 post-therapy culture was

- negative.
- b An abbreviated physical examination was conducted during the study to assess the status of the clinical signs and symptoms of infection.
 - c Bacteriologic tests include culture, subculture, and susceptibility tests. Subcultures were obtained only if a causative pathogen was present.

Pre-Treatment Procedures

In the 48 hours before treatment was to begin, patients underwent a history and physical examination to record baseline signs and symptoms of urinary tract infections.

COMMENT: Signs and symptoms were recorded as present or absent. No attempt was made to reflect the intensity of the signs and symptoms present.

Bacteriologic confirmation of the infection was to be obtained by culturing a urine specimen within 48 hours before treatment. A colony count $\geq 10^5$ colony forming units (CFU)/ml was required for each pathogen.

COMMENT: As previously stated, the medical officer also required the suspected pathogen to be present at a level of 10^5 CFU/mL except of *S. saprophyticus* which was accepted at a level of 10^4 CFU/mL

Each pathogen was to be identified and tested for susceptibility to cefepime and ceftazidime by disc or minimum inhibitory concentration (MIC) methods.

Baseline laboratory studies, to monitor for drug related adverse events were performed (See appendix I for list of standard laboratory tests).

Patients were then randomized to either cefepime or ceftazidime. The details of the randomization are described for each individual study.

During Treatment Procedures

Investigators were to observe patients at least once during therapy.

An assessment of clinical signs and symptoms was to be performed on day 2-6.

COMMENT: Signs and symptoms were recorded as "same, improved or resolved".

A urine culture was to be performed on day 2-6.

The standard laboratory tests were repeated.

Post-Treatment Procedures

Procedures for Day 5 to 9 Post-Therapy

COMMENT: Although the protocol called for the early post-therapy assessment to be performed on day 5 to 9 post-therapy, the medical officer considered patients in whom the early post-therapy evaluation was performed on day 5 to 14 post-therapy to be evaluable.

An assessment of clinical signs and symptoms of UTI was to be performed.

Urine was to be collected for culture and susceptibility testing.

The standard laboratory test were repeated.

Procedures for Day 21 to 42 Post-Therapy

A second post-treatment culture on post-treatment Day 21-42 was requested for patients who were classified by the investigator as having a complicated UTI and whose culture on post-treatment Day 5-9 was negative ($<10^5$ CFU/ml). Use of any antibiotic during the period between the first and second post-treatment cultures was to be documented in the case report form (CRF).

COMMENT: The IDSA guidelines recommend the performance of the 4 to 6 week post-therapy evaluation in all types of UTI (complicated, uncomplicated, pyelonephritis and UTI in men). Furthermore, the guidelines state that data from the 4 to 6 week evaluation should be available for $\geq 50\%$ of evaluable patients. The numbers of patients who had 4 to 6 week post-therapy evaluations was significantly lower than 50% for all protocols submitted in support of this NDA.

Drug Information and Dosage Selection

The dosage and frequency of cefepime and ceftazidime administered varied from study to study and will be described in the review of the individual studies. In general doses of cefepime ranged from 250 mg Q 12h to 2 g Q8h. Most patients were treated with 500mg to 2 g Q12h of cefepime. Most patients received cefepime-arginine, however, some patients in the earlier clinical trials received cefepime-NaCl. Doses of ceftazidime administered were between 250mg Q12h and 2 g Q8h and were consistent with the approved product label for ceftazidime.

Efficacy Assessments

Criteria for Evaluability

The applicant considered patients evaluable if they fulfilled the following set of criteria:

- An infection of the urinary tract was diagnosed clinically and confirmed by a positive pretreatment culture obtained within 48 hours before administration of study medication and after any previous antimicrobial therapy.
- The pathogens identified during pretreatment had to exhibit a colony count $\geq 10^5$ CFU/ml.

COMMENT: For patients with asymptomatic bacteriuria, the medical officer required two positive pre-treatment culture to establish the diagnosis.

- The pathogens identified during pretreatment had to be susceptible to cefepime and to ceftazidime.

- The Protocol required a during-treatment clinical assessment and culture between Day 2 and 6 of treatment, but clinical assessments and cultures were accepted from Day 2 to the last day of therapy.

COMMENT: The medical officer also accepted patients as evaluable if their during therapy assessment was performed anytime after day-2 of therapy.

- The Protocol required a post-treatment clinical assessment and culture between post-therapy Days 5 and 9, but clinical assessments and cultures were accepted from post-therapy Days 5 to 20.

COMMENT: As previously stated, the medical officer required the post-treatment assessment to occur on day 5 to 14 after the completion of therapy in order for the patient to be evaluable.

- The Protocol stated that patients were not allowed to receive any other antimicrobial between the time of the pre- and post- treatment clinical assessments and cultures. In fact, patients were allowed to receive antimicrobials which, according to official labeling in the 1990 Physicians Desk Reference (PDR), did not demonstrate activity against the genus of pathogen involved in the infection.
- The study drug had to be administered intravenously or intramuscularly at the dose, frequency, and duration specified in the Protocol.

Patients who were declared clinical or bacteriologic failures (an unsatisfactory Clinical Response or persistent pathogen, respectively) and who had at least one reason for exclusion from the efficacy analyses were considered evaluable for efficacy, if the failure preceded the reason for exclusion. If the reason for exclusion from the efficacy analyses preceded the failure, the patient was not evaluable for efficacy.

COMMENT: In particular, the medical officer considered patients who were placed on non-study antimicrobial agents for the persistence of worsening of clinical condition to be evaluable. These patients were considered clinical failures and were assigned the microbiologic outcome of "presumed" persistence.

Clinical Efficacy

The classification of UTI as complicated or uncomplicated was originally based on the individual investigator's judgment as recorded categorically on the CRF. If the investigator judged the infection to be complicated, the condition that made the infection complicated was to be recorded. All CRF were reviewed by Bristol-Myers Squibb personnel, and conditions related to the urinary tract were used to classify UTI as complicated or uncomplicated. Patients with one or more of the following conditions were classified as having a complicated UTI:

- Pyelonephritis or upper urinary tract infection
- Obstruction
- Cancer of the urinary tract
- Presence of urinary catheter except for condom catheters or catheter used only intermittently
- Urinary tract surgery
- Urinary retention
- Anatomic abnormality of the urinary tract

Patients with none of the conditions listed above were classified as having an uncomplicated urinary tract infection.

COMMENT: Please see the introduction section for the criteria used by the medical officer to classify a UTI as complicated.

If the investigator judged that the clinical signs and symptoms indicated involvement of the kidney, the diagnosis of pyelonephritis was recorded on the CRF.

After treatment was completed, each patient was to be assessed by the investigator and assigned to a clinical outcome category:

Satisfactory: All signs and symptoms of the infection that were present before therapy were improved or resolved, and no new signs or symptoms of the infection were present at the post-treatment follow-up.

Unsatisfactory: One or more signs or symptoms of the infection persisted or worsened, or one or more new signs or symptoms of the infection were evident at the post-treatment follow-up.

Undetermined: All cases where a response could not be determined (e.g., no follow-up evaluation).

COMMENT: The medical officer assigned the following clinical outcomes to UTI patients:

Cure: All signs and symptoms used to establish the diagnosis of urinary tract infection were resolved, and no new signs or symptoms were present at the 5-14 day post-treatment assessment.

Improved: All signs and symptoms used to establish the diagnosis of urinary tract infection improved and no new symptoms were present at the 5-9 days post-treatment assessment.

COMMENT: The combination of the medical officer's outcome of cure and improved roughly corresponds to the applicant outcome of satisfactory.

Failure: Any sign or symptom, used to establish the diagnosis of UTI was either the same or worsened, or, the patient developed any new signs or symptoms referable to the urinary tract at the 5-9 days post-treatment assessment.

Bacteriologic Efficacy

Bacterial isolates were tested for susceptibility to cefepime and ceftazidime by disc sensitivity or MIC method. Based on the disc sensitivity method, isolates were defined as susceptible if the zone diameter was 18 mm or greater, resistant if the zone diameter was 14 mm or less, and intermediate if the zone diameter was 15 mm to 17 mm. Based on results of MIC testing, isolates were defined as susceptible if the MIC was 8 mcg/ml or less, resistant if the MIC was 32 mcg/ml or greater, and intermediate if the MIC was 16 mcg/ml.

Based on the investigator's clinical judgment, each isolate was assigned to one of the following categories: causative pathogen, colonizer, contaminant, normal flora, or other. Isolates assigned to the category of other by the investigators

were reassigned by Bristol-Myers Squibb personnel to one of the other four categories.

Cultures obtained both during and after treatment were to be used to assess the Bacteriologic Response. Each pathogen was to be assigned a response as follows:

Assessment on Post-Treatment Day 5 - 9

Eradicated: For UTI, the urine colony count was reduced to $< 10^4$ CFU/ml in both during- and post-treatment cultures, or in the post-treatment culture if the during-treatment culture remained positive ($\geq 10^4$ CFU/ml).

COMMENT: Patients with positive "during-treatment" cultures were considered to be microbiologic failures by the medical officer regardless of the results of the post-treatment culture.

Persisted: For UTI, the post-treatment culture revealed a colony count $\geq 10^4$ CFU/ml; or the during-treatment colony count was $\geq 10^4$ CFU/ml, and the patient was removed from the study.

Undetermined: The response could not be evaluated (e.g., no follow-up evaluation).

Assessment at 4 - 6 Weeks Post-Treatment (Day 21 - 42)

Continued Eradication: The second post-therapy culture (post-treatment Day 21-42) is negative or urine colony count is $< 10^5$ CFU/ml.

Relapse with the Same Organism: The original pretreatment causative pathogen is found in the second post-therapy culture (post-treatment Day 21-42) at a colony count $\geq 10^5$ CFU/ml.

Reinfection with Different Organism: The original pretreatment causative pathogen is eradicated in the second post-treatment culture, and a new causative pathogen(s) is found at a colony count $\geq 10^5$ CFU/ml.

NOTE: For evaluable patients only, if the investigator's assessment of Clinical Response or Bacteriologic Response did not conform to the Protocol definitions, Bristol-Myers Squibb corrected the response to the Protocol specifications.

Safety Evaluation

All patients who received cefepime or ceftazidime were evaluable for safety. During administration of the study drugs, investigators were to observe their patients closely for any evidence of systemic or local adverse response, including any evidence of intolerance at the infusion or injection site.

Adverse Clinical Events

All adverse clinical events were to be reported on the CRF along with the investigator's judgment of the relationship of the event to study medication. Also to be recorded were the date of onset, duration, and severity of each ACE, and any change in a patient's treatment. All serious or alarming adverse experiences, whether associated with study therapy or not, were to be reported to Bristol-Myers Squibb. If a serious or alarming experience occurred that seemed related to cefepime or ceftazidime, investigators were to stop

administering the drug immediately and notify Bristol-Myers Squibb. Deaths that occurred during or within 30 days after the last dose of study therapy were to be reported.

Tolerance

Investigators were to record on the CRF whether the study therapy was well tolerated or poorly tolerated at the infusion site or site of injection. The occurrence of phlebitis, hematoma, infiltration, or other signs of intolerance was to be noted.

Laboratory Test Abnormalities

A panel of standard chemistry and hematology tests were repeated at intervals throughout the study. The result of a laboratory test was considered abnormal by the sponsor if it was outside the normal range used in the laboratory conducting the test. In addition, the results of laboratory studies were classified as clinically relevant, when, in the opinion of the applicant, the result might be of significance to a practicing physician. Laboratory tests for which results were abnormal were to be repeated at appropriate intervals until the values returned to the normal baseline value for the patient. The investigators were to note on the CRF the relationship of the abnormal laboratory values to study drug. Table V summarizes the individual laboratory parameter studied and the applicant's definition of "clinically relevant" for each parameter.

Table - V
Laboratory Parameters Monitored and
Definition of "Clinically Relevant" for each Parameter

Test	Clinically Relevant	Test	Clinically Relevant
Hematocrit	≤ 23.9 vol%	Alk. Phos.	≥ 3 x UNL
WBC	≤ 2000/mm ³	AST, ALT	≥ 3 x UNL
Platelet	≤ 50,000/mm ³	Tot. Bilirubin	≥ 3.0 mg/dL
Neutrophil	≤ 500/mm ³	BUN	≥ 50 mg/dL
Eosinophil	≥ 1000/mm ³	Creatinine	≥ 3.0 mg/dL
Prothrombin Time	> 15 sec.	Sodium	≤ 119 or ≥ 160 mEq/dL
PTT	> 45 sec.	Potassium	≤ 2.4 or ≥ 6.5 mEq/dL
		Calcium	≤ 7.0 or ≥ 12.0 mEq/dL
		Phosphorous	≤ 1.7 or ≥ 6.1 mEq/dL

Concomitant Therapy

Medications, except for antimicrobial agents, could be administered as indicated to enrolled patients. Use of any non-study medication was to be recorded on the CRF. The protocols excluded the use of concomitant antimicrobials. In fact, antimicrobial therapy other than the study medication was allowed during the study or in the post-treatment follow-up period, provided the concomitant agent had no known activity (as defined in the official labeling in the 1990 FDR) against the genus of organism involved in the original infection. In addition, topical antimicrobial agents could be used only when the drug would not influence the treatment of the study infections. In practice, when patients received an antimicrobial that had activity against the pathogen in question while still in the cefepime study, they were rendered unevaluable for efficacy analysis.

Early Discontinuation

The protocols allowed for early discontinuation of the study medication under the following circumstances:

- No pathogen isolated from the pretreatment culture.
- Pretreatment culture revealed the causative pathogen colony count was $< 10^5$ CFU/ml.
- *In vitro* susceptibility testing indicated that the pathogen had an MIC (or disc diffusion zone size) defined as resistant to cefepime or ceftazidime.
- A poor Clinical Response was evident after 72 hours of therapy. (If a patient was removed from the study due to poor Clinical Response, then the patient was considered evaluable as a therapeutic failure, provided all evaluability criteria were met up to the point of discontinuation from the study.)
- A serious or alarming adverse event, including an ACE, abnormal laboratory result, or severe reaction at the infusion or injection site.
- Intercurrent illness.
- Patient decision not to participate further.
- Investigator decision that it was in the best interest of the patient to discontinue study therapy.
- Administrative reasons.

NORTH AMERICAN COMPARATIVE STUDIES**PROTOCOL: 411-071****Introduction**

Study #071 provides safety and efficacy data for cefepime in treating patients with urinary tract infections (UTI).

The intent of this study was to compare a low dosage (250 mg Q12h) of cefepime to ceftazidime in a population whose clinical condition suggested that infection was limited to the urinary tract. A low dosage of cefepime was proposed as this was still expected to achieve a high concentration of cefepime in the urine.

Objectives:

- 1) To evaluate the comparative safety and therapeutic efficacy of cefepime and ceftazidime when administered intravenously or intramuscularly at 250 mg Q12h for the treatment of acute urinary tract infections (UTI).
- 2) To determine the susceptibility of specific pathogens to cefepime.

Investigational Plan:**Design Overview:**

This trial was an open, randomized (2:1, cefepime:ceftazidime), comparative clinical study at multiple centers in the United States. The anticipated duration of the study was 12 months or until a sufficient number of patients was accrued. (The study was terminated after 25 months.)

Population Studied:

The inclusion and exclusion criteria common to all other UTI protocols submitted in this application were employed in study #071. Exceptions are noted below.

Study #071 specifically sought to enroll patients with uncomplicated UTI. Patients with impaired renal or hepatic function were excluded. Patients with a history of neurogenic bladder disease, surgical reconstruction of the genitourinary system, or continuous long-term indwelling urinary catheter use were also to be excluded.

COMMENT: In the performance of the study, patient with both complicated and uncomplicated UTI were enrolled.

Study Drug Administration:

Investigators were to administer cefepime and ceftazidime by intramuscular injection or intravenous infusion over a period of 30 minutes, with repeat dosing every 12 hours (250 mg BID) for up to 14 days (Amendment 2 allowed treatment up to 30 days). Each patient was required to receive seven doses of cefepime or seven doses of ceftazidime within 96 hours to be evaluable for efficacy.

Two formulations of cefepime were used during the study. The first, a

lyophilized mixture of cefepime with NaCl was administered to patients who enrolled in the study before the new formulation became available. The second formulation, a dry-powder blend of cefepime dihydrochloride monohydrate with L-arginine developed to permit long-term (two-year) room-temperature storage. Each patient received only one formulation. According to the applicant, the pharmacokinetic properties of the two formulations are bioequivalent.

Procedures and Observations:

The procedures employed and the observations collected were consistent with those found in other UTI protocols and described in the preamble to this review.

RESULTS

Study #071 was conducted at six centers within the United States. Forty-eight patients were enrolled before the study was closed to enrollment on May 21, 1990. The study was completed on May 25, 1990.

Evaluability for the Assessment of Safety:

All 48 patients enrolled in the study received at least one dose of cefepime or ceftazidime and thus were evaluable for the assessment of safety; 32 were treated with cefepime and 16 with ceftazidime.

Evaluability for the Assessment of Efficacy:

Table-071.1 presents the enrollment, the applicant's assessment of evaluability and the reviewer's assessment of evaluability at each study center. The reviewer considered slightly more patients evaluable in each treatment group than did the applicant.

Table-071.1
Enrollment and Evaluability

Center	Principal Investigator	Location	Enrol	Number of Patients					
				Cefepime		Ceftazidime			
				BMS	MO	Enr	BMS	MO	
I-003	James McCarty	Fresno, CA	2	0	0	2	1	1	
I-004	Robert McCabe	Martinez, CA	5	3	4	2	0	0	
I-005	Stephen Farkas	Barberton, OH	21	16	17	10	9	9	
I-008	Gary Plotkin	Wilkes-Barre, PA	0	0	0	1	0	1	
I-009	Stephen Zellner	Fort Myers, FL	3	0	0	1	0	0	
I-013	Dennis Mikolich	Cranston, RI	1	0	0	0	0	0	
TOTAL			32	19	21	16	10	11	
PERCENT				59%	66%	63%	63%	69%	

COMMENT: All the principal investigators have M.D. degrees. None of the investigators involved in this protocol are listed in the Division of Scientific Investigations's Restricted Investigator List.

Summary of Non-Evaluability:

Table -2, and -3 present the major reasons that patients were considered not evaluable for the assessment of efficacy.

Table-071.2
Reasons for Exclusion from the Efficacy Analysis
(According to the Applicant)

Reason*	Number (%) of Infections	
	Cefepime	Ceftazidime
<u>UTI (Number of Infections)</u>	32	16
Total Excluded (Unevaluable)	13 (41)	6 (38)
No Pre-Rx Culture	1 (3)	0
No Pathogen Isolated	3 (9)	1 (6)
Pre-Rx Culture Out Of Window	1 (3)	0
Asymptomatic UTI	2 (6)	0
No During-Rx Clinical Assessment	1 (3)	0
Incomplete Treatment	1 (3)	0
No During-Rx culture	0	1 (6)
Improper Dosage	1 (3)	0
No Post-Rx Clinical Assessment	0	2 (13)
Post-Rx Visit Out Of Window	2 (6)	2 (13)
No Post-Rx Culture Obtained	1 (3)	0
Evaluable Infections	19 (59)	10 (63)

Table-071.3
Reasons for Exclusion from the Efficacy Analysis
(According to the Reviewer)

Reason*	Number (%) of Infections	
	Cefepime	Ceftazidime
Patients Enrolled	32	16
Total Excluded	11 (34%)	5 (31%)
Pre-treatment culture out of range	0	0
No Pathogen Isolated	5 (45%)	1 (20%)
Incomplete Treatment		
Due to ADR	0	0
Due to Death	0	0
Due to Protocol Error	1 (9%)	0
Due to Patient Request	0	0
Other Antimicrobial Administered		
Oral Continuation of Treatment	1 (9%)	4 (80%)
Post-treatment culture out of range	4 (36%)	0
Evaluable UTI	21 (66%)	11 (69%)

Applicant and Reviewer Evaluability Differences:

The reviewer and the applicant differed on the evaluability of three (cefepime=2, ceftazidime=1) patients. All three patients were considered not evaluable by the applicant because their post-therapy assessments were not performed within the specified window of 5 to 9 days post-therapy. The reviewer, however, considered patients evaluable if their post-therapy assessments occurred anytime within 5 to 14 days post-therapy.

Demographic Characteristics:

Most patients enrolled in both treatment groups were white females. The mean age for both was 65-70 years of age. Table-071.4 presents the demographic characteristics of the enrolled population.

Table-071.4
Demographic Characteristics of the Enrolled Population
(According to the Applicant)

Characteristic	Cefepime	Ceftazidime	p-value
N	32	16	
Sex: N (%)			0.712
Female	26 (81)	12 (75)	
Male	6 (19)	4 (25)	
Race: N (%)			0.531
Black	1 (3)	2 (13)	
White	30 (94)	13 (81)	
Hispanic	1 (3)	1 (6)	
Age Distribution: N (%)			
24 years	1 (3)	0	
25-44 years	2 (6)	3 (19)	
45-64 years	2 (6)	1 (6)	
65-84 years	23 (72)	9 (56)	
85-88 years	4 (13)	3 (19)	
Age: (years)			0.904
Mean	70.3	67.7	
Median	73	73	
S.D.	16.0	20.1	
Minimum	24	27	
Maximum	87	88	
Weight: (kg) ^a			0.826
Mean	72.73	75.97	
Median	67.7	72.1	
S.D.	21.13	23.99	
Minimum	34.5	53.3	
Maximum	116.8	141.5	

^a Weight was not recorded for six cefepime patients and four ceftazidime patients.

Both the applicant's and the reviewer's evaluable population had similar demographic characteristics to the enrolled population. There were no significant demographic differences between the treatment groups. Tables 071.5 and 071.6 presents the demographic characteristics of the applicant's and the reviewer's evaluable populations.

Table-071.5
Demographic Characteristics of the Evaluable Population
(According to the Applicant)

Parameter	CEFEPIME	CEFTAZID
SEX		
FEMALE	16 (84%)	9 (90%)
MALE	3 (16%)	1 (10%)
RACE		
WHITE	19 (100%)	8 (80%)
BLACK	0 (0%)	1 (10%)
HISPANIC	0 (0%)	1 (10%)
AGE (YR)		
N	19	10
MEAN	76.5	72.6
MEDIAN	81	81
RANGE		
AGE DISTRIBUTION		
25 - 44	0 (0%)	1 (10%)
45 - 64	1 (5%)	1 (10%)
65 - 84	15 (79%)	5 (50%)
85 +	3 (16%)	3 (30%)
WEIGHT (KGS)		
MEAN	74.54	68.34

Table-071.6
Demographic Characteristics of the Evaluable Population
(According to the Reviewer)

Parameter	CEFEPIME	CEFTAZID
SEX		
FEMALE	17 (81%)	9 (82%)
MALE	4 (19%)	2 (18%)
RACE		
WHITE	20 (95%)	9 (82%)
BLACK	1 (5%)	1 (9%)
HISPANIC	0 (0%)	1 (9%)
AGE (YR)		
N	21	11
MEAN	74.1	72.6
MEDIAN	81	79
RANGE		
AGE DISTRIBUTION		
25 - 44	1 (5%)	1 (9%)
45 - 64	1 (5%)	1 (9%)
65 - 84	16 (76%)	6 (55%)
85 +	3 (14%)	3 (27%)
WEIGHT (KGS)		
MEAN	74.57	68.03

Medical History

Although study #071 was originally conceived to study patients with uncomplicated UTI, there were more patients with complicated UTI in both the applicant's and the medical officer's evaluable pools. Tables 071.7 and 071.8 present the relevant medical conditions present in evaluable patients

Table-071.7
Relevant Medical Conditions
Occurring in the Applicant's Evaluable Patients

Condition*	Number (%) of Patients	
	Cefepime	Ceftazidime
Patients with		
Complicated UTI	N = 11	N = 5
Specific Urinary Tract Conditions		
*Upper UTI	3 (27)	0
*Obstruction	1 (9)	0
*Urinary Tract Catheter (All Types)	7 (64)	4 (80)
*Urinary Tract Surgery	2 (18)	1 (14)
*Urinary Tract Cancer	1 (9)	1 (20)
Patients with		
Uncomplicated UTI	N = 8	N = 5

a More than one condition may occur in a single patient.

* Condition used to classify UTI as complicated.

Table-071.8
Relevant Medical Conditions
Occurring in the Medical Officer's Evaluable Patients

Condition*	Number (%) of Patients	
	Cefepime	Ceftazidime
Complicated UTI	N = 12	N = 5
Upper UTI Only	1 (9)	0
Catheter Assoc.	2 (17)	0
Male > 40 years	6 (50)	4 (80)
Urinary Tract Cancer	1 (8)	0
Post-Urinary Tract Surgery	1 (8)	1 (20)
Uncomplicated UTI	N = 9	N = 6

*A single complicating condition was identified for each patient.

Concomitant Medications:

According to the applicant, all 19 (100%) of the evaluable patients in the cefepime group received concomitant medication. Nine (90%) of the 10 evaluable patients in the ceftazidime group received concomitant medication. The difference in the proportion of patients who received concomitant medication was not significant. Table-071.9 summarizes the concomitant medication exposure.

Table-071.9
Concomitant Medication Exposure
(According to the Applicant)

Medication Class	Number* (%) of Patients	
	Cefepime	Ceftazidime
N	19	10
At least one concomitant medication	19 (100)	9 (90)
Cardiovascular drugs	13 (68)	8 (80)
Central nervous system drugs	12 (63)	8 (80)
Electrolyte, caloric, and water balance	11 (58)	5 (50)
Gastrointestinal drugs	8 (42)	5 (50)
Hormones and synthetic substitutes	5 (26)	3 (30)
Blood formation and coagulation	4 (21)	5 (50)
Autonomic drugs	3 (16)	0
Eyes, ears, nose, and throat preps	2 (11)	1 (10)
Smooth muscle relaxants	3 (16)	1 (10)
Antihistamines	0	2 (20)
Unclassified therapeutic agents ^b	2 (11)	0
Skin and mucous membrane preps	1 (5)	0

a Patient may have had more than one medication concomitantly.

b Carbidopa-levodopa and allopurinol.

Study Drug Administration:

Both cefepime and ceftazidime were administered at 250 mg BID. A minimum of seven doses in 96 hours was one of the criteria for evaluability; however, patients who were classified as treatment failures before receiving seven doses did not have to meet the minimum dose criterion to be evaluable. In the cefepime group, the number of doses received ranged from four to 21; duration of dosing ranged from three to 11 days (one evaluable treatment failure received 4 doses of cefepime in 72 hours). In the ceftazidime group, number of doses received ranged from seven to 16; duration of dosing ranged from four to nine days. There was no statistical difference between the two treatment groups in duration of dosing ($p=0.905$). Table 071.12 summarizes the dosing data for patients evaluable for efficacy.

Table 071.12
Study Therapy for UTI
Evaluable Patients

Parameter	Number (%) of Patients Applicant	M.O.
<u>Cefepime</u>	N = 19	N=21
Duration of dosing (days)		
3	1 (5)	1 (5)
4	4 (21)	5 (24)
5	6 (32)	6 (29)
6	2 (11)	3 (14)
7	4 (21)	4 (19)
10	1 (5)	1 (5)
11	1 (5)	1 (5)
Mean		5.71
<u>Ceftazidime</u>	N = 10	N = 11
Duration of dosing (days)		
4	1 (10)	1 (9)
5	6 (60)	6 (55)
6	2 (20)	2 (18)
9	1 (10)	1 (9)
11	0	1 (9)
Mean		6.00

EFFICACY EVALUATION**Clinical Efficacy**

According to the applicant, overall, a satisfactory response to therapy was seen in 18/19 patients (95%) in the cefepime treatment group and in 10/10 patients (100%) in the ceftazidime treatment group. Table-071.13 presents the applicant's assessment of the clinical response for the overall UTI population and for the sub-groups of complicated and uncomplicated UTI patients.

Table-071.13
Clinical Efficacy According to the Applicant

Number of Diagnoses and Pathogens	----- Number of Patients -----					
	<u>Cefepime</u>			<u>Ceftazidime</u>		
	Sat.	Uns.	Total	Sat.	Uns.	Total
<u>COMPLICATED</u>						
Total Complicated	10	1	11	5	0	5
<u>UNCOMPLICATED</u>						
Total Uncomplicated	8	0	8	5	0	5
Total Patients	<u>18</u>	<u>1</u>	<u>19</u>	<u>10</u>	<u>0</u>	<u>10</u>
Percent	(95)	(5)		(100)		

NOTE: Sat.= Satisfactory; Uns.= Unsatisfactory.

According to the reviewer, overall, 17/21 patients (81%) in the cefepime treatment group and 11/11 patients (100%) in the ceftazidime treatment group were clinically cured at the 5-9 day post-therapy evaluation. An additional 2 patients (14%) in the cefepime treatment group had improved from baseline but were not completely cured by the 5-9 day post-therapy evaluation.

Table 071.14 presents the reviewer's assessment of the clinical efficacy of cefepime for the overall UTI population and the sub-groups of patients with complicated and uncomplicated UTI.

Table-071.14
Clinical Efficacy According to the Medical Officer

Parameter	CEFEPIME	CEFTAZID
NO. OF EVALUABLE PATIENTS	21	11
CURE	17 (81%)	11 (100%)
IMPROV	3 (14%)	0
FAILURE	1 (5%)	0
COMPLICATED UTI(Incl. Pyelo.)	12	5
CURE	9 (75%)	5 (100%)
IMPROV	2 (17%)	0
FAILURE	1 (8%)	0
UNCOMPLICATED UTI	9	6
CURE	8 (89%)	6 (100%)
IMPROV	1 (11%)	0

COMMENT: The difference in clinical efficacy noted between the treatment groups was not significant ($p > 0.05$). see Dr Lumpkin's Memorandum

COMMENT: Since there was only one patient in study #071 with pyelonephritis, the reviewer did not analyze pyelonephritis patient separately from other complicated UTI patients.

Bacteriologic Efficacy**Susceptibility of Pathogens:**

Forty-seven pathogens were isolated in pre-study cultures from the 48 patients. All of the 47 pathogens isolated (100%) were susceptible to cefepime. Forty-six (98%) were susceptible to ceftazidime and one (2%) was of intermediate sensitivity. Results of susceptibility tests for all organisms are presented in Table-071.15.

Table-071.15
Susceptibility of Pathogens Recovered from UTI Patients
(According to the Applicant)
Study #071

Infection Type/ Pathogen	----- Number of Pathogens* -----							
	<u>Cefepime Sensitivity</u>				<u>Ceftazidime Sensitivity</u>			
	Susc.	Inter.	Res.	Total	Susc.	Inter.	Res.	Total
UTI								
S. intermedius	1			1	1			1
Micrococcus sp.	1			1	1			1
P. aeruginosa	1			1	1			1
E. coli	26			26	26			26
C. freundii	1			1		1		1
K. pneumoniae	4			4	4			4
K. oxytoca	3			3	3			3
E. cloacae	1			1	1			1
E. aerogenes	2			2	2			2
P. mirabilis	3			3	3			3
M. morgani	3			3	3			3
Total	46			46	45	1		46
Percent	(100)				(98)	(2)		

* Pathogens from both treatment groups were to be tested for sensitivity to each study drug.

NOTE: Susc. = Susceptible; Inter. = Intermediate Susceptibility;
Res. = Resistant.

Bacteriologic Efficacy at the 5-9 Day Post-Therapy Evaluation:

According to the applicant, overall, 16/19 pathogens (84%) were eradicated in the cefepime treatment group, including 10/11 pathogens (91%) in patients with complicated UTI and 6/8 pathogens (75%) in patients with uncomplicated UTI. In the ceftazidime treatment group, 11/11 pathogens (100%) were eradicated, including 5/5 pathogens (100%) in patients with complicated UTI and 6/6 pathogens (100%) in patients with uncomplicated UTI. Table-16 presents the applicant's assessment of the bacteriologic response at the 5-9 day evaluation.

Table-071.16
Bacteriologic Efficacy at the 5-9 Day Post-Therapy Assessment
(According to the Applicant)
Study #071

Pathogen	----- Number of Pathogens -----					
	Cefepime			Ceftazidime		
	Erad.	Pers.	Total	Erad.	Pers.	Total
<u>COMPLICATED</u>						
E. coli	6	1	7	1		1
K. pneumoniae	2		2	1		1
E. cloacae	1		1			
E. aerogenes				1		1
P. mirabilis				1		1
M. morgani	1		1	1		1
Total Pathogens*	<u>10</u>	<u>1</u>	<u>11</u>	<u>5</u>		<u>5</u>
Percent	(91)	(9)		(100)		
<u>UNCOMPLICATED</u>						
E. coli	6		6	4		4
K. oxytoca		1	1	1		1
E. aerogenes		1	1			
P. mirabilis				1		1
Total Pathogens*	<u>6</u>	<u>2</u>	<u>8</u>	<u>6</u>		<u>6</u>
Percent	(75)	(25)		(100)		
ALL INFECTIONS	16	3	19	11		11
	(84%)			(100%)		

NOTE: Erad. = Eradicated; Pers. = Persisted.

* Based on 19 cefepime and 10 ceftazidime patients.

COMMENT: The 95% confidence interval (corrected for continuity) around the true difference in eradication rates is [-40%, +8%] which does not fulfill the currently accepted criteria for equivalence.

According to the reviewer, overall 15/21 pathogens (71%) were eradicated in the cefepime treatment group, including 8/12 pathogens (67%) in patients with complicated UTI and 7/9 pathogens (78%) in patients with uncomplicated UTI. In the ceftazidime treatment group, 12/12 pathogens (100%) were eradicated, including 5/5 pathogens in patients with complicated UTI and 7/7 pathogens (100%) in patients with uncomplicated UTI.

COMMENT: The 95% confidence interval (corrected for continuity) around the true difference in eradication rates is [-54%, -3%]. Since the confidence interval does not include 0, a statistical superiority for ceftazidime is suggested.

E. coli was the most frequently isolated pathogen; it was eradicated in 12/15 infections (80%) in the cefepime treatment group and in 6/6 infections (100%) in the ceftazidime treatment group. P. aeruginosa was not isolated from any patients

in this study.

Table-071.17 summarizes the reviewer's assessment of the bacteriologic response at the 5-9 day post-therapy assessment.

Table-071.17
Bacteriologic Efficacy at the 5-9 Day Post-Therapy Assessment
(According to the Medical Officer)

Parameter	CEFEPIME	CEFTAZID
COMPLICATED UTI	8/ 12 (67%)	5/ 5 (100%)
E. AEROGENES	0	1/ 1 (100%)
E. CLOACAE	1/ 1 (100%)	0
E. COLI	5/ 8 (63%)	1/ 1 (100%)
K. PNEUMONIAE	2/ 2 (100%)	1/ 1 (100%)
M. MORGANII	0/ 1 (0%)	1/ 1 (100%)
P. MIRABILIS	0	1/ 1 (100%)
UNCOMPLICATED UTI	7/ 9 (78%)	7/ 7 (100%)
E. AEROGENES	0/ 1 (0%)	0
E. COLI	7/ 7 (100%)	5/ 5 (100%)
K. OXYTOCA	0/ 1 (0%)	1/ 1 (100%)
P. MIRABILIS	0	1/ 1 (100%)
TOTAL INFECTIONS	15/ 21 (71%)	12/ 12 (100%)

Bacteriologic Efficacy at the 4-6 Week Post-Therapy Assessment:

No patients in either the cefepime or the ceftazidime treated group were evaluated 4 to 6 weeks after the completion of therapy.

Safety Evaluation

Deaths

No deaths occurred among the 32 patients who received cefepime.

One (6%) of the 16 patients who received ceftazidime died. The patient was a 70 y.o. white female with a long history of coronary artery disease. At the time of admission she had already suffered three myocardial infarctions. The patient was treated with ceftazidime for a UTI due to *C. freundii* which responded both clinically and bacteriologically to the study treatment. The patient died seven days after completing treatment.

Discontinuations

No patient in either the cefepime or ceftazidime treatment group discontinued therapy due to an adverse drug effect.

Clinical Adverse Drug Events

Two (6%) of the 32 patients in the cefepime group reported one ACE each. Both events were cases of diarrhea. One of these was associated with the presence of *C. difficile* and was of probable relationship to the study drug. The other case of diarrhea was of unknown relationship to cefepime. One (6%) of the 16 patients treated with ceftazidime reported one ACE (moniliasis), which was probably related to the study drug. All three ACE were of mild severity.

Local Reactions at the Infusion Site

All 32 patients (100%) who received cefepime and all 16 patients (100%) who received ceftazidime tolerated the drug well. All cefepime patients received study drug by IV administration. Fourteen ceftazidime patients received the study drug by IV administration; the other two patients received the drug by IV and IM administration. No patients were discontinued from either study drug because of intolerance at the infusion site.

Laboratory Test Abnormalities

No patients in either treatment group discontinued therapy due to abnormal laboratory test results.

There was no statistically significant differences between the treatment groups in the occurrence of laboratory test abnormalities in those patients with normal laboratory values at baseline (Table-071.18).

COMMENT: Although not statistically significant, a trend toward a greater percentage of patients experiencing decreases in calcium during or post-treatment was noted in the cefepime group.

Table-071.18
During- or Post-Treatment Laboratory Test Abnormalities
for Patients with a Normal Pretreatment Value
Study #071

Laboratory Test	----- Number (%) Patients -----					
	Cefepime			Ceftazidime		
	N ^a	Abnormal ^b	Cl. Rel. ^c	N ^a	Abnormal ^b	Cl. Rel. ^c
HEMATOLOGY						
Hematocrit	14	4 (29)	0	7	1 (14)	0
Platelet Count	21	0	0	14	1 (7)	0
WBC Count	23	2 (9)	0	14	1 (7)	0
Neutrophil Count	22	4 (18)	0	12	2 (17)	0
Eosinophil Count	19	4 (21)	0	10	5 (50)	0
COAGULATION						
Prothrombin	15	1 (7)	1 (7)	10	2 (20)	2 (20)
PTT	15	0	0	11	2 (18)	1 (9)
LIVER FUNCTION						
Alkaline phosphatase	17	3 (18)	0	11	2 (18)	0
AST (SGOT)	22	3 (14)	0	12	1 (8)	0
ALT (SGPT)	21	2 (10)	0	12	1 (8)	0
Total bilirubin	26	0	0	11	0	0
RENAL FUNCTION						
BUN	22	1 (5)	0	8	0	0
Creatinine	26	4 (15)	0	11	1 (9)	0
ELECTROLYTES						
Na ⁺	21			11		
Decrease		3 (14)	0		1 (9)	0
Increase		0	0		0	0
K ⁺	27			10		
Decrease		2 (7)	0		0	0
Increase		1 (4)	0		0	0
Ca ⁺⁺	16			8		
Decrease		5 (31)	0		1 (13)	0
Increase		0	0		0	0
PO ₄ [']	9			8		
Decrease		0	0		0	0
Increase		1 (11)	0		1 (13)	0

^a N indicates number of patients tested.

^b During- or post-treatment results outside the investigator's normal range limit in the direction of toxicity.

^c Cl. rel. (Clinically Relevant) patients are included in the 'Abnormal' column.

The small number of patients who had abnormal laboratory values at baseline makes conclusions difficult to reach. The outcome of patients with abnormal laboratory test results at baseline is presented in table-071.19.

Table-071.19
During- or Post-Treatment Laboratory Test Abnormalities
for Patients with an Abnormal Pretreatment Value
Study 411-071

Laboratory Test	Number (%) of Patients					
	Cefepime			Ceftazidime		
	N ^a	Worsened ^b	Cl. Rel. ^c	N ^a	Worsened ^b	Cl. Rel. ^c
HEMATOLOGY						
Hematocrit	10	2 (20)	0	7	2 (29)	0
Platelet Count	2	0	0	0	0	0
WBC Count	1	0	0	0	0	0
Neutrophil Count	1	0	0	0	0	0
Eosinophil Count	4	1 (25)	0	1	1 (100)	0
COAGULATION						
Prothrombin	6	3 (50)	3 (50)	2	0	0
PTT	5	0	0	1	0	0
LIVER FUNCTION						
Alkaline phosphatase	9	0	0	3	0	0
AST (SGOT)	4	0	0	2	0	0
ALT (SGPT)	3	0	0	2	1 (50)	0
Total bilirubin	0	0	0	3	0	0
RENAL FUNCTION						
BUN	8	1 (13)	1 (13)	5	2 (40)	1 (20)
Creatinine	3	1 (33)	0	2	0	0
ELECTROLYTES						
Na ⁺	8			2		
Decrease		0	0		0	0
Increase		0	0		0	0
K ⁺	2			3		
Decrease		0	0		0	0
Increase		0	0		0	0
Ca ⁺⁺	5			2		
Decrease		0	0		0	0
Increase		0	0		0	0
PO ₄ ⁻³	8			2		
Decrease		1 (13)	1 (13)		0	0
Increase		1 (13)	0		0	0

- a N indicates number of patients tested.
b During- or post-treatment as compared to pretreatment. Worsened indicates that the value changed to a worse class (Appendix G-22), not simply that the absolute value changed.
c Cl. Rel. (Clinically Relevant) includes those patients whose lab values became clinically relevant during- or post-treatment. These patients are included in the "Worsened" column.

Conclusions

Study #071 sought to evaluate the safety and efficacy of a low-dose (250 mg IV/IM every 12 hours) for the treatment of uncomplicated UTI.

The study did not fulfill its stated objective as the majority of patients enrolled had complicated UTI. Furthermore, in this mixed (complicated and uncomplicated UTI) population, cefepime did not appear to be as efficacious as ceftazidime at the dosage level studied.

Taking the bacteriologic outcome at 5 to 9 days post-therapy as the primary efficacy variable, the reviewer's analysis revealed that the overall eradication rate for cefepime was 15/21 (71%), in contrast the eradication rate for ceftazidime was 12/12 (100%). The 95% confidence interval around the true difference was [-54%, -3%] which implies a superiority for ceftazidime. The clinical response to treatment was also superior for ceftazidime.

Even using the applicant's analysis, the eradication rate at 5 to 9 days post-therapy for the patients treated with cefepime was 16/19 (84%) compared with 11/11 (100%) for the patients treated with ceftazidime. The 95% confidence interval around the true difference, using the applicant's results is [-40%, +8%] which although it includes 0, does not fulfill the currently accepted criteria for statistical equivalence.

Few clinical or laboratory adverse drug events occurred during this trial and most were of mild severity. Of note, was the one patient who developed diarrhea associated with infection with *C. difficile*. There were no significant differences between the treatment groups for safety related issues.

Caution must be used in interpreting the results of this trial since the number of patients involved is small. The small numbers have resulted in wide confidence intervals and, therefore, great uncertainty in predicting the true difference between the two treatment groups.

The sponsor has made no claim for efficacy for the dose (250 mg BID) studied in study #071 in their application. The results of this small study indicate that 250 mg every 12 hours may not be an effective dose for patients with complicated and uncomplicated UTI.

PROTOCOL: 411-083**Introduction:**

Study #083 provides safety and efficacy data for cefepime and ceftazidime in the treatment of patients with infections of the urinary tract (UTI) or accompanying usually related to the underlying infection caused by a broad range of pathogens.

Comment: Study #083 was considered pivotal by both the applicant and the medical officer.

Objectives:

- 1) To evaluate and compare the safety and therapeutic efficacy of cefepime, administered intramuscularly or by intravenous infusion at 500 mg q12h for up to 14 days, with the safety and efficacy of ceftazidime, administered intramuscularly or intravenously at 500 mg q12h for up to 14 days, in the treatment of acute urinary tract infections that were suspected to be complicated.
- 2) To determine the susceptibility of specific pathogens to cefepime.

Investigational Plan:**Design Overview:**

This study was designed as an open, randomized, comparative study. At each study center, patients were randomly assigned to receive one of the two treatments in a 2:1 (cefepime:ceftazidime) ratio.

Population Studied:

The protocol called for the enrollment of patients who had symptoms consistent with acute UTI that was suspected to be complicated (e.g., pyelocystitis, pyelonephritis, or pyelitis); or patients who had UTI and suspected A pathogen susceptible to both cefepime and ceftazidime had been recovered prior to the start of treatment.

This study excluded patients who had a history of impaired renal function (baseline serum creatinine level of ≥ 1.7 mg/dL or on renal dialysis); neurogenic bladder; surgical reconstruction of genitourinary system; continuous long-term indwelling urinary catheter placement; or patients with infections thought to require long-term antimicrobial treatment.

COMMENT: Although the protocol called for the exclusion of patients with neurogenic bladder, surgical reconstruction of the genitourinary system, or continuous long-term indwelling urinary catheter in actuality such patients were included in the evaluable population. The medical officer concurs with the inclusion of these patients as a part of the evaluable, complicated UTI population.

Drug Information and Dose Selection:

Cefepime was supplied by Bristol-Myers Squibb in vials containing 1 gram or 500 mg of a dry-powder blend of cefepime dihydrochloride and L-arginine. Ceftazidime was purchased and provided to investigators by Bristol-Myers Squibb in vials

containing 1 g or 500 mg of ceftazidime in a dry powder.

Investigators were to administer cefepime and ceftazidime in a dose of 500 mg B.I.D. by intramuscular injection or intravenous (IV) infusion for up to 14 days. Each patient must have received seven doses of study drug within 96 hours to be evaluable for efficacy.

Procedures and Observations

The procedures employed and the observations collected were consistent with those found in other UTI protocols and described in the preamble to this review.

RESULTS

The study was conducted at 17 centers in the United States.

Population Studied

Three hundred seventy one patients were enrolled in study #083. Of the 371 patients enrolled, 246 were randomized to receive cefepime and 125 were randomized to receive ceftazidime.

The randomization schedule was not followed correctly for two patients. Patient _____ was assigned to receive cefepime and was erroneously treated with ceftazidime. Patient _____ was assigned to receive ceftazidime and was treated with cefepime because the pharmacy accidentally opened the randomization for Patient _____ instead of for Patient _____. All patients were evaluated according to the drug they received.

Evaluability for the Safety Assessment:

All 371 patients enrolled received at least one dose of cefepime or ceftazidime and therefore were evaluable for the assessment of drug safety.

Evaluability for the Efficacy Assessment:

According to the applicant, 118/246 patients (48%) randomized to cefepime and 62/125 patients (50%) randomized to ceftazidime were evaluable for the efficacy assessment. According to the reviewer, 121/246 patients (49%) randomized to cefepime and 64/125 patients (51%) randomized to ceftazidime were evaluable for the efficacy assessment. Table-083.1 presents the total enrollment and the number of patients evaluable for efficacy at each study center.

Table-083.1
Enrollment and Evaluability for Efficacy

Center	Principal Investigator	Location	Enrol	Number of Patients					
				<u>Cefepime</u>		<u>Ceftazidime</u>			
				BMS	MO	Enrol	BMS	MO	
I-001	Zellner, S.	Fort Myers, FL	4	0	0	1	0	0	
I-003	Yangco, B.	Tampa, FL	3	0	0	2	0	0	
I-004	Sharifi, R.	Chicago, IL	76	30	31	38	14	15	
I-005	Geckler, R.	Baltimore, MD	44	17	19	24	12	13	
I-008	Epstein, H.	Gainesville, FL	20	9	9	10	7	7	
I-009	Jurgensen, P.	Savannah, GA	1	0	0	0	0	0	
I-014	Culkin, D.	Shreveport, LA	10	4	4	4	1	1	
I-024	Forlenza, S.	East Meadow, NY	1	0	0	0	0	0	
I-029	Sieger, B.	Orlando, FL	14	7	7	7	4	4	
I-030	Young, A.B.	Lexington, KY	5	1	1	3	0	0	
I-038	Pelletier, L.	Wichita, KS	1	0	0	1	0	0	
I-041	Lerner, C.	San Antonio, TX	1	0	0	2	0	0	
I-046	Smith, D.	Kansas City, MO	2	1	1	1	1	1	
I-047	Stein, D.	Minneapolis, MN	2	0	0	2	1	1	
I-049	Childs, S.	Alabaster, AL	45	43	41	23	20	20	
I-051	Mangi, R.	New Haven, CT	13	2	5	7	2	2	
I-053	Gainer, R.B.	Morgantown, WV	4	4	3	0	0	0	
TOTAL			246	118	121	125	62	64	
PERCENT				48%	49%		50%	51%	

COMMENT: None of the investigators who participated in study #083 are listed in the Division of Scientific Investigation's Restricted Investigator List.

Summary of Non-Evaluability:

The most common reason for which a patient was considered not-evaluable by both the applicant and the reviewer was the failure to isolate an appropriate pathogen at a pre-treatment culture. Table-083.2 presents the major reasons for which patients were considered not-evaluable.

Table-2
Reasons for Exclusion from the Efficacy Analysis
Study #083

Reason	Bristol-Myers-Squibb		Medical Officer	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
Total Excluded	128 (52)	63 (50)	125 (51)	61 (49)
Inappropriate Pre-Rx Asses.	17 (14)	6 (9)	15 (12)	6 (10)
No appropri. pathogen isol.	36 (29)	20 (31)	37 (30)	20 (33)
Resistant Organisms	9 (7)	3 (5)	9 (7)	3 (5)
No sensitivity testing	9 (7)	10 (16)	9 (7)	10 (16)
Other Antimicrobial given	15 (12)	5 (8)	10 (8)	5 (8)
No during therapy culture	12 (10)	4 (6)	12 (10)	2 (3)
Incomplete Rx	7 (6)	3 (5)	7 (6)	3 (5)
Inappropriate Post-Rx Asses.	23 (18)	12 (19)	26 (21)	12 (19)
Total Evaluable	118 (48)	62 (50)	121 (49)	64 (61)

Applicant and Reviewer Evaluability Differences:

Five (cefepime=5, ceftazidime=0) patients were considered not evaluable by the reviewer who were considered evaluable by the applicant. Three patients had post-therapy assessments outside the accepted range of +5 to +14 days after the completion of therapy. One patient had asymptomatic bacteriuria with only 1 pre-treatment culture documented. One patient was an uncomplicated cystitis patient with *S. epidermidis* as the documented pathogen. The medical officer does not consider *S. epidermidis* a valid cause of uncomplicated UTI.

Ten patients (cefepime=8, ceftazidime=2) were considered evaluable by the reviewer who were considered not evaluable by the applicant. Six patients (cefepime=4, ceftazidime=2) were considered not evaluable by the applicant because non-study antimicrobials were administered prior to the post-therapy culture. In all 6 cases, the non-study antimicrobials were administered for persistence or worsening of clinical signs and symptoms. These patients were, therefore, considered evaluable by the reviewer and were assigned the outcome of presumed persistence. Four patients (cefepime=4) who, according to the sponsor, had asymptomatic bacteriuria were considered evaluable by the reviewer either because two pre-treatment cultures were present or because signs and symptoms referable to the urinary tract were documented.

Demographic Characteristics:

Table-083.3 summarizes the demographic characteristics of the enrolled population. There were no significant differences in demographic variable between the two treatment groups.

Table-083.3
Demographic Characteristics of the Enrolled Population
(Table Prepared by Applicant)

Characteristic	Cefepime	Ceftazidime	p-value
N	246	125	
Sex: N (%)			0.680
Female	115 (47)	57 (46)	
Male	131 (53)	68 (54)	
Race: N (%)			0.649
Black	94 (38)	50 (40)	
White	144 (59)	73 (58)	
Hispanic	8 (3)	1 (1)	
Oriental	0	1 (1)	
Age Distribution: N (%)			
15 -- 17 yr	1 (<1)	0	
18 - 24 yr	20 (8)	10 (8)	
25 - 44 yr	46 (19)	28 (22)	
45 - 64 yr	61 (25)	26 (21)	
65 - 84 yr	106 (43)	57 (46)	
85 - 100 yr	12 (5)	4 (3)	
Age: (years)			0.880
Mean	57.9	57.3	
Median	64	63	
S.D.	20.1	19.8	
Minimum	15	21	
Maximum	100	95	

Tables-083.4 and -083.5 present the demographic characteristics of the applicant's and the reviewer's evaluable populations. In the applicant's evaluable population, there were no significant differences in demographic composition between the two treatment groups.

In the medical officer's evaluable population, there was no significant difference between the two treatment groups with respect to sex or race. However, there was a marked disparity between the two treatment groups with regard to mean age. The mean age of patients in the cefepime treatment group was 59, the mean age of patients in the ceftazidime treatment group was 47. Of interest the difference in mean age, between the two treatment groups seems to be largely due to a difference in the patients with uncomplicated UTI. Among patients with complicated UTI, the mean age in the cefepime treatment group was 58 years, the mean age of patients in the ceftazidime treatment group was 55 years, however, among patient with uncomplicated UTI, the mean age of patients in the cefepime treatment group was 66 years and the mean age of patients in the ceftazidime treatment group was 41 years. The difference in mean ages between the two population is statistically significant ($p < 0.01$, t-test).

Table-083.4
Demography of the Evaluable Population
(According to the Applicant)

Parameter	CEFEPIME	CEFTAZID
SEX		
FEMALE	56 (47%)	32 (52%)
MALE	62 (53%)	30 (48%)
RACE		
WHITE	80 (68%)	37 (60%)
BLACK	35 (30%)	24 (39%)
HISPANIC	3 (3%)	0 (0%)
ORIENTAL	0 (0%)	1 (2%)
AGE (YR)		
N	118	62
MEAN	58.5	53.6
MEDIAN	62	58
RANGE		
AGE DISTRIBUTION		
18 - 24	6 (5%)	7 (11%)
25 - 44	25 (21%)	16 (26%)
45 - 64	36 (31%)	15 (24%)
65 - 84	44 (37%)	23 (37%)
85 +	7 (6%)	1 (2%)

Table-083.5
Demography of the Evaluable Population
(According to the Reviewer)

Parameter	CEFEPIME	CEFTAZID
SEX		
FEMALE	59 (49%)	33 (51%)
MALE	62 (51%)	31 (49%)
RACE		
WHITE	81 (67%)	38 (59%)
BLACK	36 (30%)	25 (39%)
HISPANIC	4 (4%)	0 (0%)
ORIENTAL	0 (0%)	1 (2%)
AGE (YR)		
N	121	64
MEAN	59	47
RANGE		

Medical History:

Table-083.6 presents the applicant's assessment of the relevant medical conditions present in evaluable patients. The most commonly seen medical condition was obstructive uropathy in both the cefepime and ceftazidime treatment groups. There were no major differences between the treatment groups in terms of the presence of any relevant medical conditions.

Table-083.6
Relevant Medical Conditions in Evaluable Patients
(According to the Applicant)

Condition ^a	Number (%) ^b of Patients	
	Cefepime	Ceftazidime
Patients with Complicated UTI^c	N = 93	N = 50
Specific urinary tract conditions:		
•Upper UTI	25 (27)	17 (34)
•Obstruction	52 (56)	27 (54)
•Urinary tract catheter ^d (all types)	30 (32)	9 (18)
•Urinary tract surgery	32 (34)	15 (30)
•Urinary tract cancer	13 (14)	6 (12)
•UT anatomic abnormality	5 (5)	3 (6)
Lower UTI	3 (3)	0
Other conditions	19 (20)	13 (26)
Patients with Uncomplicated UTI^c	N = 25	N = 12

^aMore than one condition may occur in a single patient.

^bPercentages are based on the number of patients within each category.

^cBased on review by Bristol Myers-Squibb personnel.

^dMore than one catheter type may occur in a single patient.

*Condition used to classify a UTI as complicated.

Concomitant Medications:

According to the applicant, of the 118 evaluable patients who received cefepime, 106 (90%) received concomitant medication, including 3 (3%) who took allowed antimicrobial agents with no known activity against the genus of pathogen involved in the original infection (Patient received amantadine and nitrofurantoin, Patient received mycostatin, and Patient received quinine sulfate).

Of the 62 evaluable patients who received ceftazidime, 58 (94%) received concomitant medication, including 3 (5%) who took allowed antimicrobial agents with no known activity against the genus of pathogen involved in the original infection (Patient received metronidazole; Patients and both received mycostatin).

Study Drug Administration:

In the applicant's evaluable population, the duration of dosing for cefepime ranged from 4 to 16 days; eight patients received cefepime for longer than the 14 days anticipated by the protocol. The number of doses received ranged from 7 to 30. The Duration of dosing for ceftazidime ranged from 4 to 15 days; four patients received ceftazidime for longer than the 14 days anticipated by the protocol. The number of doses received ranged from 7 to 28. According to the applicant, there was no statistically significant difference ($p = 0.654$) in duration of dosing between the two treatment groups.

Among the reviewer's evaluable population, The duration of dosing for cefepime ranged from 2 to 16 days, the mean duration was 8.9 days; the mean duration of therapy for patients with complicated UTI was 9.2 days, the mean duration of therapy for patients with uncomplicated UTI was 7.4 days. The duration of dosing for ceftazidime ranged from 3 to 15 days; the mean duration of therapy was 8.9 days; the mean duration of therapy for patient with complicated UTI was 10.8 days; the mean duration of therapy for patients with uncomplicated UTI was 8.2 days. There was no significant difference in the duration of dosing between the two treatment groups.

Table-083.7 summarizes the duration of therapy for both the applicant's and the reviewer's evaluable population.

Table-0837
Study Therapy for UTI
Evaluable Patients

Parameter	Number (%) of Patients	
	BMS	M.O.
<u>Cefepime</u>	N = 118	N = 121
Duration of Dosing (Days)		
2	0	1 (1)
4	3 (3)	3 (2)
5	12 (10)	15 (12)
6	10 (8)	11 (9)
7	17 (14)	19 (16)
8	16 (14)	15 (12)
9	8 (7)	7 (6)
10	16 (14)	15 (12)
11 - 14	28 (24)	28 (23)
15 - 16	8 (7)	7 (6)
<u>Ceftazidime</u>	N = 62	N = 64
Duration of Dosing (Days)		
3	0	1 (2)
4	2 (3)	2 (3)
5	4 (6)	4 (6)
6	4 (6)	4 (6)
7	11 (18)	11 (17)
8	13 (21)	13 (20)
9	4 (6)	4 (6)
10	8 (13)	8 (13)
11 - 14	12 (19)	13 (20)
15	4 (6)	4 (6)

EFFICACY EVALUATION:**Clinical Efficacy:**

According to the applicant, overall, a satisfactory response to therapy was seen in 106/118 patients (90%) in the cefepime treatment group and in 55/62 patients (89%) in the ceftazidime treatment group. Table-083.8 presents the applicant's assessment of clinical response for the overall UTI population and for the sub-groups of complicated and uncomplicated UTI patients.

Table-083.8
Clinical Efficacy
(According to the Applicant)

Parameter	CEFEPIME	CEFTAZID
NO. OF EVALUABLE PATIENTS	118	62
SATIS	106 (90%)	55 (89%)
UNSAT	12 (10%)	7 (11%)
COMPLICATED UTI PATIENTS	93	50
SATIS	83 (89%)	43 (86%)
UNSAT	10 (11%)	7 (14%)
UNCOMPLICATED UTI PATIENTS	25	12
SATIS	23 (92%)	12 (100%)
UNSAT	2 (8%)	0

According to the reviewer, overall 84/121 patients (69%) in the cefepime treatment group and 44/64 patients (69%) in the ceftazidime treatment group were clinically cured at the 5-9 day post-therapy evaluation. An additional 18 patients (15%) in the cefepime treatment group and 11 patients (17%) in the ceftazidime treatment group had improved from baseline but were not completely cured by the 5-9 day post-therapy evaluation.

Table-083.9 presents the reviewer's assessment of the clinical efficacy of cefepime for the overall UTI population and for the sub-groups of patients with complicated UTI, pyelonephritis, and uncomplicated UTI.

COMMENT: A clinical response of undetermined was assigned by the medical reviewer to patients with asymptomatic bacteriuria at baseline.

Table-9
Clinical Efficacy
(According to the Reviewer)
Study #083

Parameter	CEFEPIME	CEFTAZID
NO. OF EVALUABLE PATIENTS	121	64
CURE	84 (69%)	44 (69%)
IMPROV	18 (15%)	11 (17%)
UNDET ¹	2 (2%)	0
FAILURE	17 (14%)	9 (14%)
PATIENTS WITH COMPLICATED UTI	75	36
CURE	55 (73%)	22 (61%)
IMPROV	11 (15%)	9 (25%)
FAILURE	9 (12%)	5 (14%)
PATIENTS WITH PYELONEPHRITIS	28	19
CURE	19 (68%)	13 (68%)
IMPROV	3 (11%)	2 (11%)
FAILURE	6 (21%)	4 (21%)
PATIENTS WITH UNCOMPLICATED UTI	18	9
CURE	10 (56%)	9 (100%)
IMPROV ¹	4 (22%)	0
UNDET	2 (11%)	0
FAILURE	2 (11%)	0

1- Clinical outcome in undetermined in patients with asymptomatic bacteriuria.

COMMENT: The clinical cure rate was similar for both treatment groups in all sub-groups except patients with uncomplicated UTI. In the uncomplicated UTI sub-group, the patients in the cefepime group were older (mean age = 66) compared with the ceftazidime treatment group (mean age = 41). The greater proportion of elderly people in the cefepime group may account for the lower cure rate seen with cefepime.

Bacteriologic Efficacy:**Susceptibility of Pathogens:**

According to the applicant, three hundred forty-nine pathogens were isolated in pre-treatment cultures from the 371 patients in the study. Of the 315 pathogens tested for susceptibility to cefepime, 303/315 (96%) were susceptible, 4/315 (1%) showed intermediate sensitivity, and 8/315 (3%) were resistant. Thirty-four pathogens were not tested for sensitivity to cefepime.

Of the 319 pathogens tested for susceptibility to ceftazidime, 300/319 (94%) were susceptible, 6/319 (2%) showed intermediate sensitivity, and 13/319 (4%) were resistant. Thirty pathogens were not tested. Results of susceptibility tests for all organisms are presented in Table-083.10.

Table-083.10
Susceptibility of Pathogens Recovered from UTI Patients
(Table Prepared by Applicant)

Infection Type/ Pathogen	Number of Pathogens ^a							
	Cefepime Sensitivity				Ceftazidime Sensitivity			
	Susc.	Inter.	Res.	Total	Susc.	Inter.	Res.	Total
<i>S. faecalis</i>	1	2	2	5	1		4	5
Enterococcus	1		3	4	1		3	4
Strep. (Group B)	2		1	3	2		1	3
<i>S. aureus</i>	2			2		2		2
<i>S. epidermidis</i>	3			3	1	1	1	3
<i>S. epidermidis</i> (MR)	1			1			1	1
<i>S. saprophyticus</i>	1			1			1	1
<i>S. hominis</i>	1		1	2	1	1		2
<i>S. simulans</i>	1			1	1			1
<i>S. warneri</i>	1			1	1			1
<i>P. aeruginosa</i>	23	1		24	24			24
<i>P. putida</i>	1			1	1			1
<i>E. coli</i>	167			167	169	1		170
<i>C. freundii</i>	8			8	8			8
<i>C. diversus</i>	3			3	3			3
<i>Shigella</i> sp.	1	1		2	2			2
<i>K. pneumoniae</i>	26			26	26			26
<i>K. ozaenae</i>	1			1	1			1
<i>K. oxytoca</i>	3			3	3			3
Enterobacter sp.	1			1	1			1
<i>E. cloacae</i>	6			6	6		1	7
<i>E. aerogenes</i>	6			6	5		1	6
<i>S. marcescens</i>	3			3	3			3
<i>Proteus</i> sp.	1			1	1			1
<i>P. mirabilis</i>	21			21	21			21
<i>M. morgani</i>	1			1	1			1
<i>P. rettgeri</i>	1			1	1			1
Acinetobacter sp.	1			1	1			1
<i>A. calcoaceticus</i>	1			1	1			1
<i>A. anitratus</i>			$\frac{1}{8}$	$\frac{1}{301}$		$\frac{1}{6}$		$\frac{1}{305}$
Total	289	4	8	301	286	6	13	305
Percent	(96)	(1)	(3)		(94)	(2)	(4)	

Bacteriologic Efficacy at the 5-9 Day Post-Therapy Evaluation:

According to the applicant, overall, 105/124 pathogens (85%) were eradicated in the cefepime treatment group, including 83/98 (85%) pathogens in patients with complicated UTI and 22/26 (85%) of pathogens in patients with uncomplicated UTI. In contrast, 50/62 pathogens (81%) were eradicated in the ceftazidime treatment group, including 39/50 (78%) pathogens in patients with complicated UTI and 11/12 (92%) of pathogens in patients with uncomplicated UTI.

The 95% confidence interval (with correction for continuity) around the true difference in overall eradication rate for the sponsor's data is [-5%, +16%] which fulfills the current regulatory definition of equivalence. The 95% confidence interval around the true difference in eradication rates of pathogens encountered in patients with complicated UTI is [-8% +22%], again the regulatory definition of equivalence is fulfilled.

Table 083.11 summarizes the bacteriological response at the +5 to+9 day assessment as determined by the applicant's analysis.

Table-083.11
Bacteriologic Efficacy at the 5 to 9 Day Post-Therapy Assessment
(According to the Sponsor)

PATIENTS WITH COMPLICATED UTI			
A. CALCOACETICUS	1/	1 (100%)	0
ACINETOBACTER SP.	0		1/ 1 (100%)
C. DIVERSUS	0		0/ 1 (0%)
C. FREUNDII	2/	2 (100%)	1/ 1 (100%)
E. AEROGENES		0	1/ 1 (100%)
E. CLOACAE	3/	3 (100%)	1/ 1 (100%)
E. COLI	51/	57 (89%)	21/ 30 (70%)
ENTEROBACTER SP.	1/	1 (100%)	0
K. OXYTOCA	1/	1 (100%)	1/ 1 (100%)
K. PNEUMONIAE	5/	7 (71%)	2/ 2 (100%)
P. AERUGINOSA	7/	11 (64%)	4/ 4 (100%)
P. MIRABILIS	7/	9 (78%)	4/ 4 (100%)
PROTEUS SP.	1/	1 (100%)	0
S. AUREUS	1/	2 (50%)	0
S. FAECALIS		0	1/ 1 (100%)
S. MARCESCENS	2/	2 (100%)	0
S. WARNERI		0	0/ 1 (0%)
SHIGELLA SP.		0	1/ 1 (100%)
STREP. (GROUP B)	1/	1 (100%)	1/ 1 (100%)
TOTAL COMPLICATED UTI	83/	98 (85%)	39/ 50 (78%)
PATIENTS WITH UNCOMPLICATED UTI			
E. COLI	17/	19 (89%)	7/ 8 (88%)
ENTEROCOCCUS		0	1/ 1 (100%)
K. PNEUMONIAE	0/	1 (0%)	1/ 1 (100%)
M. MORGANII	1/	1 (100%)	0
P. AERUGINOSA	0/	1 (0%)	1/ 1 (100%)
P. MIRABILIS	2/	2 (100%)	1/ 1 (100%)
P. RETTGERI	1/	1 (100%)	0
S. EPIDERMIDIS	1/	1 (100%)	0
TOTAL UNCOMPLICATED UTI	22/	26 (85%)	11/ 12 (92%)
TOTAL UTI	105/124	(85%)	50/ 62 (81%)

According to the medical officer, overall 105/128 pathogens (82% were eradicated in the cefepime treatment group, including 64/79 pathogens (81%) in patients with complicated UTI, 24/30 pathogens (80%) in patients with pyelonephritis, and 17/19 pathogens (89%) in patients with uncomplicated UTI. In the ceftazidime treatment group 49/64 pathogens (77%) were eradicated, including 27/36 pathogens (75%) in patients with complicated UTI, 14/19 pathogens (74%) in patients with pyelonephritis, and 8/9 pathogens (89%) in patients with uncomplicated UTI.

The 95% confidence interval (with correction for continuity) around the true overall difference in eradication rates is [-3%, +19%], which fulfills the current regulatory definition of equivalence. The 95% confidence interval (with correction for continuity) around the true difference in eradication rates for patients with complicated UTI is [-9%, +21%] which also fulfills the current regulatory definition of equivalence.

E. coli was the most commonly isolated pathogen; *E. coli* was eradicated in 70/82 infections (85%) in the cefepime treatment group and in 27/39 infections (69%) in the ceftazidime treatment group. *P. aeruginosa* was eradicated in 8/13 infections (62%) in the cefepime treatment group and in 5/5 infections (100%) in the ceftazidime treatment group.

COMMENT: The sponsor wishes to claim that cefepime is effective for infections due to *P. aeruginosa*, however, the eradication rate for this organism seems to be lower in the cefepime treatment group than in the ceftazidime treatment group.

Organisms persisting after cefepime treatment include *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *P. mirabilis* and *S. aureus*. Organisms persisting after ceftazidime treatment include *E. coli* and *K. pneumoniae*.

Table-083.12
Bacteriologic Efficacy at the 5-9 Day Assessment
(According to the Reviewer)

COMPLICATED UTI (Excluding Pyelonephritis)		
A. CALCOACETICUS	1/ 1 (100%)	0
ACINETOBACTER SP.	0	1/ 1 (100%)
C. DIVERSUS	0	0/ 1 (0%)
C. FREUNDII	1/ 1 (100%)	1/ 1 (100%)
E. AEROGENES	0	1/ 1 (100%)
E. CLOACAE	1/ 1 (100%)	1/ 1 (100%)
E. COLI	37/ 43 (86%)	8/ 14 (57%)
K. OXYTOCA	1/ 1 (100%)	1/ 1 (100%)
K. PNEUMONIAE	4/ 6 (67%)	2/ 3 (67%)
P. AERUGINOSA	8/ 12 (67%)	5/ 5 (100%)
P. MIRABILIS	6/ 8 (75%)	5/ 5 (100%)
P. RETTGERI	1/ 1 (100%)	0
PROTEUS SP.	1/ 1 (100%)	0
S. AUREUS	1/ 2 (50%)	0
S. FAECALIS	0	1/ 1 (100%)
S. MARCESCENS	1/ 1 (100%)	0
S. WARNERI	0	0/ 1 (0%)
STREP. (GROUP B)	1/ 1 (100%)	1/ 1 (100%)
TOTAL COMPLICATED UTI	64/ 79 (81%)	27/ 36 (75%)
PYELONEPHRITIS		
E. CLOACAE	1/ 1 (100%)	0
E. COLI	20/ 24 (83%)	13/ 18 (72%)
ENTEROBACTER SP.	1/ 1 (100%)	0
K. PNEUMONIAE	0/ 1 (0%)	0
P. AERUGINOSA	0/ 1 (0%)	0
P. MIRABILIS	1/ 1 (100%)	0
S. MARCESCENS	1/ 1 (100%)	0
SHIGELLA SP.	0	1/ 1 (100%)
TOTAL PYELONEPHRITIS	24/ 30 (80%)	14/ 19 (74%)
UNCOMPLICATED UTI		
E. COLI	13/ 15 (87%)	6/ 7 (86%)
ENTEROCOCCUS	0	1/ 1 (100%)
K. PNEUMONIAE	0	1/ 1 (100%)
M. MORGANII	1/ 1 (100%)	0
P. MIRABILIS	3/ 3 (100%)	0
TOTAL UNCOMPLICATED	17/ 19 (89%)	8/ 9 (89%)
TOTAL UTI	105/128 (82%)	49/ 64 (77%)

Bacteriologic Efficacy at the 4-6 Week Post-Therapy Assessment:

Comment: The protocol only requested 4-6 week follow-up on patients who were considered to have complicated UTI by the principal investigators.

According to the applicant, among patients with complicated UTI whose pathogen was eradicated at the first follow-up visit, 37 in the cefepime group and 13 in the ceftazidime group had a follow-up evaluation on Day 20-49 post-treatment. Five patients in the cefepime group and three patients in the ceftazidime group had evidence of a relapse. One relapse in the cefepime group was caused by

Klebsiella pneumoniae; the other four relapses in the cefepime group as well as the three relapses in the ceftazidime group were caused by *E. coli*. Four cefepime patients and one ceftazidime patient had reinfection with new pathogens. Table-083.13 summarizes the results of the follow-up assessments.

Table-083.13
Bacteriologic Efficacy at the 4-6 Week Post-Therapy Evaluation
in Patients with Complicated UTI
(According to the Applicant)

Parameters	Number (%) ^a of Patients	
	Cefepime	Ceftazidime
<u>Patients with Complicated UTI</u>	93	50
Total patients with 4-6 week (Day 21-42) follow-up culture	37	13
No follow-up culture	42	26
Persistence at Day 5-9 post-treatment	14	11
<u>Bacteriologic Response at 4-6 Weeks (Day 21-42)</u>		
Continued eradication	28 (76)	9 (69)
Eradication with relapse	5 (14)	3 (23)
Eradication with reinfection	4 (11)	1 (8)

^a Percentages based on all patients with 4-6 week follow-up.
NOTE: The actual window for the 4-6 week follow-up was post-treatment Days 20-49.

COMMENT: The medical officer included data from patients with both complicated and uncomplicated UTI in reported the results of the late (4-6 weeks) post-therapy assessment. reporting 7/26/94

According to the medical officer 54 patients in the cefepime treatment group (45%) and 25 patients in the ceftazidime treatment group (39%) had late post-therapy assessments. Of those patients assessed, 32 (59%) patients in the cefepime group and 16 patients (64%) in the ceftazidime treatment group had a bacteriologic response of continued eradication at 4 to 6 weeks post-therapy.

There were six relapses among the patients treated with cefepime. Organisms relapsing after cefepime therapy included *E. coli* (3), *K. pneumoniae* (1), *P. aeruginosa* (1) and *P. mirabilis* (1). None of these organisms were resistant to cefepime at the time of relapse. There were 3 relapses among the patients treated with ceftazidime. *E. coli* was the only organism which relapsed after treatment with ceftazidime.

There were 16 new infections which developed after cefepime treatment. The most common organisms causing a new infection were members of the *Enterococcus* spp. (10); *P. aeruginosa* (1); *P. maltophilia* (1); *E. coli* (2); *E. agglomerans* (1); and *Acinetobacter* spp. (1) were also seen. There were 6 new infections which developed after ceftazidime treatment. Organisms causing new infection after

ceftazidime treatment included *Acinetobacter* spp. (1), *E. cloacae* (2), *P. aeruginosa* (1), *Enterococcus* spp. (1), and *E. coli*(1).

The *Enterococci* were uniformly resistant to both study drugs, when tested, the other organisms causing relapse or reinfection were still susceptible to both cefepime and ceftazidime.

Table 083.14 summarizes the medical officer's assessments of the bacteriological response at the late post-therapy evaluation.

Table-083.14
Bacteriologic Results at the 4 to 6 week Post-Therapy Assessment
for Patients with Complicated and Uncomplicated UTI
(According to the Reviewer)

Parameters	Number (#)* of Patients	
	Cefepime	Ceftazidime
<u>M.O. Evaluable Patients</u>	121	64
Persistence at 5-9 Days	<u>-22</u>	<u>-17</u>
<u>Patients Eval. for 4-6 Week Asses.</u>	99	47
Not Assessed	<u>-45</u>	<u>-22</u>
<u>Patients Assessed at 4-6 Weeks</u>	<u>54</u>	<u>25</u>
Continued Eradication	32 (59)	16 (64)
Eradication with Relapse	6 (11)	3 (12)
Eradication with Reinfection	16 (30)	6 (24)

a Percentages based on all patients with 4-6 week follow-up.
NOTE: The actual window for the 4-6 week follow-up was post-treatment Days 20-49.

Safety Evaluation:**Deaths**

Nine deaths (cefepime = 6, ceftazidime = 3) occurred during the performance of protocol 411-083 in North America.

Cefepime Deaths

_____ - The patient was a 68 y.o. black male with complicated (BPH) UTI due to *P. mirabilis*. The patient was treated with cefepime for one day (7/22/89) after which the medication was discontinued due to inability to find I.V. access. The patient was started on TMP/SMX as an alternative. The patient's general condition deteriorated and he died on 8/1/89. The death was not thought to be related to the study drug.

_____ - The patient was a 61 y.o. black female with uncomplicated UTI due to *E. coli*. She was treated with cefepime from 2/1/89 - 2/7/89, she was reported to respond well to antibiotics and to return to baseline. The patient underwent gastrostomy tube placement and suffered a post-operative infection. On 3/1/89 the patient became acutely dyspneic, tachycardic and hypotensive and expired presumably due to pulmonary embolism.

_____ - The patient was a 77 y.o. white female with uncomplicated UTI due to *E. coli*. The patient was treated with cefepime from 2/9/89 - 2/14/89. The patient appeared to respond to therapy. On the day that the study drug was discontinued, the patient became clinically septic with fever and obtundation. The patient was started on clindamycin and gentamicin at that time. The patient appeared to respond but on 2/16/89 she became acutely short of breath and quickly arrested. The investigator thought the cause of death was an acute myocardial infarction or a pulmonary embolus.

Comment:

This patients was considered both a clinical and microbiological failure by the medical officer.

_____ - The patient was a 42 y.o. female with uncomplicated UTI due to *C. diversus*. The patient was treated with cefepime from 1/25/89 - 1/30/89. On 1/30/89 the patient was transferred to another hospital and cefepime was discontinued. While at the other hospital the patient became comatose. On 2/20/89 the patient expired. Autopsy revealed subarachnoid hemorrhage.

_____ - The patient was a 75 y.o. female with complicated (catheter associated) UTI due to *Enterococcus* spp. The patient was treated with cefepime from 5/15/89 - 5/17/89. The cefepime was discontinued when it was discovered that the *Enterococcus* was resistant. The patient died on 5/20/89. The investigator reports that the death was secondary to urosepsis.

_____ - The patient was an 81 y.o. white female with complicated UTI (stone, catheter associated) due to *Enterococcus* spp. The patient was treated with cefepime from 6/21/89 - 6/22/89. The cefepime was discontinued when it was discovered that the *Enterococcus* was resistant. The patient died on 6/25/89. The investigator reports that the death was secondary to acute myocardial infarction.

Ceftazidime Deaths

_____ - The patient is a 75 y.o. black female with complicated UTI (bladder outlet obstruction) due to *P. aeruginosa*. The patient was treated with

ceftazidime from 8/25/89 - 8/30/89. The patient appeared to respond to therapy and was discharged to home. On 9/5/89 the patient expired in another hospital. The cause of death was sepsis due to *C. freundii*, *P. aeruginosa* and Group-D Enterococci.

Comment:

This patients was considered not evaluable by the medical officer for the failure to perform appropriate assessments at specified times.

- The patient is a 81 y.o. white female with uncomplicated UTI due to *E. coli*. The patient was treated with ceftazidime from 9/9/89 - 9/19/89. The patient responded to therapy but experienced recrudescence of fever within 24 hours after discontinuation of ceftazidime. The patient was started on piperacillin and vancomycin. The patient responded to antibiotics. On 9/28/89 the patient expired while in the hospital. The cause of death was not known. The investigator did not believe that death was related to ceftazidime.

Comment:

This patient was considered both a clinical and a microbiological failure by the medical officer.

- The patient is a 94 y.o. white female with uncomplicated UTI due to *E. coli*. The patient was treated with ceftazidime from 12/26/89 - 12/30/89. On the day antibiotics were discontinued the patient developed fever and was started on ticarcillin-clavulanate. An abdominal X-ray showed perforated diverticula. On 1/4/90 the patient expired.

Discontinuations

Six patient (cefepime=4, ceftazidime=2) discontinued therapy during protocol 411083.

Cefepime Discontinuations

_____ - Cefepime was discontinued due to lack of treatment effect. The patient was started on mezlocillin and gentamicin.

Comment:

This patient received only two doses of cefepime prior to removal from the study. The medical officer, therefore, considered this patient to be not-evaluable.

Cefepime was discontinued due to a rash of moderate severity which was thought to be probably related to the drug.

Cefepime was discontinued due to fever while on therapy. The fever was viewed as an adverse drug reaction, rather than a sign of lack of therapeutic effect by the principal investigator. The patient was treated with ciprofloxacin with good result.

- Cefepime was discontinued due to a mild leg ache which was thought to be probably related to the drug. No treatment was given, the ADR resolved spontaneously.

Ceftazidime Discontinuations

- Ceftazidime was discontinued to a mild rash which was thought to be probably related to the drug. The patient was treated with benadryl.

- This 53 y.o white female was admitted to the hospital with nephrolithiasis and *Shigella* spp. UTI. The patient underwent epidural anesthesia prior to lithotripsy but experienced respiratory compromise after the administration of anesthesia, so general anesthesia was administered. The patient failed to awaken from anesthesia and had a seizure in the recovery room. The patient was discontinued from the study at this time.

Clinical Adverse Drug Events:

At least one clinical adverse drug event (CADE) occurred in 39/246 patients (16%) in the cefepime treatment group and in 19/125 patients (15%) in the ceftazidime treatment group. The proportion of patients reported CADEs was not significantly different between the two treatment groups. A total of 62 CADE were reported in the 40 patients in the cefepime group who reported CADE. A total of 28 CADE were reported among the 19 patients in the ceftazidime group who reported CADEs.

For both treatment groups, the gastrointestinal and nervous systems were most commonly affected. In the cefepime group, rash, headache, diarrhea and vomiting occurred in greater than 1% of the population exposed. In the ceftazidime group, rash, headache, nausea and vomiting occurred in greater than 1% of the population exposed.

The majority of CADE were of mild or moderate severity. In the cefepime group, 5 severe CADE were reported (headache(1), dyspnea(1), pseudomembranous colitis(2) and peripheral edema(1)). In the ceftazidime group, 2 severe CADE were reported (coma(1), exacerbation of COPD(1)).

Table 083.15 lists clinical adverse drug events by severity and organ system involved.

Table-083.15
Clinical Adverse Drug Events Listed By Severity
Study #083

Event	Cefepime N = 246					Ceftazidime N = 125				
	Mild	Mod.	Sev.	Total	Rate	Mild	Mod.	Sev.	Total	Rate
Body as a Whole	-	1	0	1	<1	-	-	-	-	-
Fever	-	1	-	1	<1	-	-	-	-	-
Skin/Skin Structures	3	3	-	6	2	2	1	-	3	2
Cyanosis, acral	-	1	-	1	<1	-	-	-	-	-
Hives	-	-	-	-	-	-	1	-	1	<1
Pruritus	1	-	-	1	<1	1	-	-	1	<1
Rash	1	3	-	5	2	2	-	-	2	2
Redness, Heel	1	-	-	1	<1	-	-	-	-	-
Warmth, Heel	1	-	-	1	<1	-	-	-	-	-
Neurological	10	1	1	12	5	4	0	1	5	4
Coma	-	-	-	-	-	-	-	1	1	<1
Confusion	-	-	-	-	-	1	-	-	1	<1
Disorientation	-	-	-	-	-	1	-	-	1	<1
Dizziness	2	-	-	2	<1	-	-	-	-	-
Headache	6	1	1	8	3	4	-	-	4	3
Insomnia	1	-	-	1	<1	-	-	-	-	-
Weakness	1	-	-	1	<1	-	-	-	-	-
Respiratory	0	2	1	3	1	-	1	1	2	2
COPD, Exac.	-	-	-	-	-	-	-	1	1	<1
Cough	-	-	1	1	<1	-	-	-	-	-
Dyspnea	-	1	1	2	<1	-	-	-	-	-
Failure, Resp	-	-	-	-	-	-	1	-	1	<1
Pleural Effusion	-	1	-	1	<1	-	-	-	-	-
Cardiovascular	1	1	2	4	2	-	-	-	-	-
Cardiac Arrest	-	1	1	2	<1	-	-	-	-	-
Hypertension	1	-	-	1	<1	-	-	-	-	-
Hypotension	-	-	1	1	<1	-	-	-	-	-
Gastrointestinal	14	2	2	18	7	10	0	0	10	8
Bloating Sensation	-	-	-	-	-	1	-	-	1	<1
Colitis, PMC	-	-	2	2	<1	-	-	-	-	-
Constipation	-	1	-	1	<1	1	-	-	1	<1
Diarrhea	2	2	-	4	2	1	-	-	1	<1
Ileus	1	-	-	1	<1	-	-	-	-	-
Indigestion	1	-	-	1	<1	-	-	-	-	-
Nausea	2	-	-	2	<1	3	-	-	3	2
Oral Thrush	1	-	-	1	<1	-	-	-	-	-
Pain, Abdominal	1	-	-	1	<1	-	-	-	-	-
Pain, Epigastric	2	-	-	2	<1	-	-	-	-	-
Spasm, Abdom	1	-	-	1	<1	-	-	-	-	-
Throat, Tightness	-	-	-	-	-	1	-	-	1	<1
Vomiting	5	-	-	5	2	5	-	-	5	4

Body system totals reflect number of patients who experienced an CADE within that body system. If an individual patient had adverse events of more than one severity, the most severe events is reported.

Individual patients may have adverse events in more than one body system.

Table-083.15 - Continued
Clinical Adverse Drug Events Listed By Severity
Study #083

Event	Cefepime N = 246					Ceftazidime N = 125				
	Mild	Mod.	Sev	Total	Rate	Mild	Mod	Sev	Total	Rate
Genitourinary	2	1	0	3	1	1	0	0	1	<1
Hematuria	1	-	-	1	<1	-	-	-	-	-
Retention	-	1	-	1	<1	-	-	-	-	-
Vaginitis	-	-	-	-	-	1	-	-	1	<1
Yeast Infection	1	-	-	1	<1	-	-	-	-	-
Musculoskeletal	4	0	1	5	2	2	0	0	2	2
Cramps, Extremes	3	-	-	3	1	-	-	-	-	-
Pain, Back	1	-	-	1	<1	2	-	-	2	<2
Pain, Chest	2	-	-	2	<1	-	-	-	-	-
Pain, Legs	1	-	-	1	<1	-	-	-	-	-
Pain, Neck	1	-	-	1	<1	-	-	-	-	-Swelling,
Legs	-	-	1	1	<1	-	-	-	-	-
Special Senses	-	-	-	-	-	-	-	-	-	-
Totals	23	9	7	39*	16%	14	3	2	19	15%

Body system totals reflect number of patients who experienced an CADE within that body system. If an individual patient had adverse events of more than one severity, the most severe events is reported.

Individual patients may have adverse events in more than one body system.

*The severity of ACE was not recorded for one cefepime patient.

Relationship of ACE to Study Drugs

According to the applicant, ten events in 10 (4%) of the 246 patients who received cefepime were considered probably related to the drug (2 cases each of rash and diarrhea, and 1 case each of fever, leg pain, pruritus, pseudomembranous enterocolitis, vomiting, and yeast infection in the urogenital system). Thirty-six ACE in 19 (8%) of the 246 patients were judged to be of unknown relationship to cefepime.

One ACE (rash) in one of the 125 patients who received ceftazidime was considered probably related to the drug. Fourteen ACE in 8 (6%) patients were considered of unknown relationship to ceftazidime.

Table-083.16 summarizes the number of patients who experienced an adverse events of probable or unknown relationship to the study drug.

Table-083.16
 Numbers of Patients with ACE Related to Study Drug
 (According to the Applicant)
 Study #083

Relationship To Study Drug	Number (%) of Patients		p-value
	Cefepime N = 246	Ceftazidime N=125	
Prob. rel.	10 (4)	1 (1)	
Unknown	17 (7)	8 (6)	
Total	27 (11)	9 (7)	0.400

* Patients with multiple ACE of different relationships to study drug are only included in the most related category.

Local Reactions at the Infusion Site:

Among the 246 patients exposed to cefepime, 9 (4%) reported infiltration, phlebitis or other local reactions at the infusion site. Of the 125 patients who were exposed to ceftazidime, 7 (6%) reported infiltration, phlebitis or other local reactions at the infusion site. There was no statistically significant difference in the incidence of reactions at the infusion site.

Laboratory Test Abnormalities:

No patient in either treatment group discontinued early due to abnormal laboratory test results.

According to the applicant, the only statistically significant difference between treatment groups in patients with normal pre-treatment test results was for partial thromboplastin time (PTT). The distribution of during- or post-treatment PTT results was more abnormal in the ceftazidime group ($P = 0.036$). The abnormal results included one cefepime patient and three ceftazidime patients who developed clinically relevant PTT results. The clinical significance of the statistical difference is unclear. Although not clinically significant, patients who began the study with abnormal hematologic parameters tended to worsen on cefepime therapy but not on ceftazidime therapy. This trend was noted by the medical officer but was not statistically significant.

Table-083.17 summarizes the results for five categories of laboratory tests: hematology, coagulation, liver function, renal function, and electrolytes. Since abnormal pretreatment values indicate pathophysiology that preceded study therapy, this table includes test results only from those patients with normal pretreatment values for whom at least one during- or post-treatment value was also obtained. The table indicates per test how many patients had a during- or post-treatment laboratory value that was considered abnormal in the direction of toxicity and how many of the abnormalities were considered clinically relevant.

Table-083.18 summarizes the changes noted during therapy of laboratory test results for those patients in which an abnormal laboratory test result was already present at baseline. In a majority of patients in this group, during- and post-treatment results either remained in the same class as the pretreatment value or improved by at least one class. There were no statistically significant differences between the treatment groups among those patients with abnormal laboratory values present at baseline.

Table-083.17
 During- or Post-Treatment Laboratory Test Abnormalities
 for Patients with a Normal Pretreatment Value
 Study 411-083
 (According to the Applicant)

Laboratory Test	Number (%) Patients					
	Cefepime			Ceftazidime		
	N	Abnormal ^a	Cl.Rel. ^b	N	Abnormal ^a	Cl.Rel. ^b
HEMATOLOGY						
Hematocrit	118	58 (49)	0	60	24 (40)	0
Platelet count	194	6 (3)	1 (1)	95	3 (2)	0
Leukocyte count	220	15 (7)	0	107	10 (9)	0
Neutrophil count	198	12 (6)	0	100	5 (5)	0
Eosinophil count	180	10 (6)	1 (1)	92	10 (11)	2 (2)
COAGULATION						
Prothrombin	157	15 (10)	1 (1)	71	11 (15)	1 (1)
PTT	181	7 (4)	1 (1)	86	8 (9)	3 (3)
LIVER FUNCTION						
Alkaline phosphatase	173	10 (6)	0	82	4 (5)	1 (1)
AST (SGOT)	159	27 (17)	2 (1)	82	14 (17)	1 (1)
ALT (SGPT)	173	24 (14)	0	82	10 (12)	0
Total bilirubin	192	2 (1)	0	87	2 (2)	0
RENAL FUNCTION						
BUN	181	14 (8)	0	85	12 (14)	0
Creatinine	187	10 (5)	0	83	5 (6)	2 (2)
ELECTROLYTES						
Na ⁺	168			78		
Decrease		21 (13)	0		9 (12)	0
Increase		8 (5)	0		4 (5)	1 (1)
K ⁺	179			91		
Decrease		15 (8)	0		10 (11)	0
Increase		15 (8)	2 (1)		5 (5)	1 (1)
Ca ⁺⁺	144			78		
Decrease		26 (18)	1 (1)		13 (17)	0
Increase		4 (3)	0		3 (4)	0
PO ₄ ⁻³	169			77		
Decrease		24 (14)	3 (2)		4 (5)	2 (3)
Increase		16 (10)	1 (1)		9 (12)	0

a During- or post-treatment results outside the investigator's normal range limit in the direction of toxicity.

b Patients with Cl.Rel. (clinically relevant) values are included in the "Abnormal" column.

NOTE: N = number of patients tested.

Table-083.18
During- or Post-Treatment Laboratory Test Abnormalities
for Patients with an Abnormal Pretreatment Value
Study 411-083
(According to the Applicant)

Laboratory Test	Number (%) Patients					
	Cefepime			Ceftazidime		
	N	Worsened ^a	Cl. Rel. ^b	N	Worsened ^a	Cl. Rel. ^b
HEMATOLOGY						
Hematocrit	114	17 (15)	2 (2)	53	5 (9)	0
Platelet count	7	1 (14)	0	4	0	0
Leukocyte count	12	3 (25)	1 (8)	6	0	0
Neutrophil count	10	0	0	3	0	0
Eosinophil count	10	2 (20)	0	1	0	0
COAGULATION						
Prothrombin	45	2 (4)	2 (4)	23	0	0
PTT	20	0	0	8	0	0
LIVER FUNCTION						
Alkaline phosphatase	35	1 (3)	0	12	0	0
AST (SGOT)	46	4 (9)	0	12	0	0
ALT (SGPT)	30	2 (7)	0	11	0	0
Total bilirubin	14	1 (7)	1 (7)	6	0	0
RENAL FUNCTION						
BUN	43	4 (9)	1 (2)	20	2 (10)	1 (5)
Creatinine	37	3 (8)	0	22	1 (5)	0
ELECTROLYTES						
Na ⁺	56			28		
Decrease		0	0		0	0
Increase		1 (2)	1 (2)		0	0
K ⁺	45			16		
Decrease		1 (2)	0		1 (6)	0
Increase		1 (2)	0		0	0
Ca ⁺⁺	57			16		
Decrease		6 (11)	1 (2)		1 (6)	1 (6)
Increase		0	0		0 (0)	0
PO ₄ ⁻³	36			16		
Decrease		4 (11)	2 (6)		0 (0)	0
Increase		0	0		0 (0)	0

a During- or post treatment as compared with pretreatment. Worsened indicates that the test value changed and was entered into a more abnormal class (Appendix G-22), not simply that the absolute value changed.

b Patients with Cl.Rel. (Clinically Relevant) values are included in the "Worsened" column.

CONCLUSIONS

This open, randomized, comparative clinical trial was designed to evaluate and compare the clinical and bacteriologic efficacy and the safety of cefepime and ceftazidime for the treatment of moderately severe urinary tract infections (UTI) suspected to be complicated. Cefepime administered parenterally at a dose of 0.5 g q12h was compared to ceftazidime administered at a dose of 0.5 g q12h. Patients enrolled in the study were randomly assigned to receive cefepime or ceftazidime in a 2:1 ratio, respectively. Cefepime was administered via the intravenous route to 200 patients; via the intramuscular route to 45 patients; and via both the intravenous and intramuscular route to 1 patient. Ceftazidime was administered via the intravenous route to 101 patients; via the intramuscular route to 22 patients and via the intravenous and intramuscular routes to 2 patients.

According to the medical officer, the overall bacteriologic eradication rate at the 5-9 days post-therapy evaluation was 105/128 (82%) in the cefepime treatment group and 49/64 (77%) in the ceftazidime treatment group. Among patients with complicated UTI (including patients with pyelonephritis), the bacteriologic eradication rate at the 5-9 days post-therapy assessment was 88/109 (81%) in the cefepime treatment group and 41/55 (75%) in the ceftazidime treatment group. Equivalence was demonstrated by the 95% confidence interval approach between cefepime and ceftazidime in the bacteriologic eradication rate at 5 to 9 days post-therapy in patients with complicated UTI (95% CI: [-9%, +21%]). The sub-groups of patients with uncomplicated UTI was too small for meaningful statistical analysis. Equivalence between the two treatment groups was also demonstrated for the applicant's evaluable population.

According to the medical officer, 54/121 patients (44%) in the cefepime treatment group were followed for 4-6 weeks post-therapy; among those assessed, 32/54 (59%) had continued eradication of their pathogen. For comparison 25/64 patients (39%) in the ceftazidime treatment group were followed for 4-6 weeks post-therapy; among those assessed, 16/25 (64%) had continued eradication of their pathogen.

The applicant claims that cefepime is effective for complicated UTI due to *Pseudomonas aeruginosa*, however, the eradication rate for infection caused by *P. aeruginosa* was only 8/12 (67%) (reviewer's analysis) in the cefepime group compared with 5/5 (100%) in the ceftazidime group.

With regard to the clinical cure rate, according to the medical officer, 84/121 patients (69%) in the cefepime treatment group and 44/64 patients (69%) in the ceftazidime treatment group were completely cured of their infections by the 5-9 days post-therapy assessment. There were no statistically significant differences noted in the clinical cure rate between the two treatment groups.

There was no significant difference in the rate of death or discontinuation between the two treatment groups. Clinical adverse drug events were generally mild and were similar in patients treated with cefepime and ceftazidime. A statistically greater number of patients in the ceftazidime group experienced elevations in their prothrombin time during or post-treatment, however, the clinical significance of this observation is unclear.

Thus, study #083 supports the applicant's claim for the safety and efficacy of cefepime in the treatment of patients with complicated and uncomplicated UTI at a dose of 500 mg IV/IM every 12 hours. The information presented in this study does not support the claim of efficacy for complicated UTI due to *Pseudomonas aeruginosa*.

PROTOCOL: 411-108:**Introduction**

Study #108 was designed to provide efficacy and safety data for cefepime and ceftazidime in treating patients with potentially complicated infections of the urinary tract (UTI), usually related to the underlying infection, caused by a broad range of pathogens.

Objectives

- 1) To evaluate the safety and efficacy of cefepime and ceftazidime when administered intravenously or intramuscularly at 500 mg Q12h in the treatment of complicated UTI. The safety and efficacy of cefepime and ceftazidime for the treatment of accompanying S/B were also evaluated, although this indication was not specifically defined as an objective in the Protocol.
- 2) To determine the susceptibility of specific pathogens to cefepime.

INVESTIGATIONAL PLAN**Design Overview**

This trial was a double-blinded, randomized (1:1 cefepime/ceftazidime), comparative clinical study at four centers in the United States. At each study center, patients were randomly assigned to receive one of the two treatments in a 1:1 (cefepime:ceftazidime) ratio.

Population Studied:

Inclusion and exclusion criteria common to all other UTI protocols submitted in this application were employed in study 411-108. Exceptions are noted below.

Male and female patients of any race with symptoms consistent with UTI suspected to be complicated were eligible for enrollment if they were at least 18 years of age, had a pathogen suspected to be susceptible to both cefepime and ceftazidime, and provided informed consent.

Patients were excluded if they had severely impaired renal or hepatic function or were on renal dialysis; had a disorder likely to influence the results of the study; had a history of neurogenic bladder disease, surgical reconstruction of the genitourinary system, or continuous long-term in-dwelling urinary catheter.

COMMENT: In practice, patients with neurogenic bladder, surgical reconstruction of the genitourinary system or continuous long-term in-dwelling urinary catheters were not excluded.

Study Drug Administration

Cefepime was supplied by Bristol-Myers Squibb in 500 mg or 1 g vials containing a dry-powder blend of cefepime dihydrochloride and L- arginine. Ceftazidime was purchased and provided to investigators by Bristol-Myers Squibb Company in 500 mg or 1 g vials containing ceftazidime in a dry powder.

Investigators were to administer cefepime and ceftazidime by intravenous infusion over a period of 30 minutes, with repeat dosing every 12 hours (500 mg BID) for

up to 14 days. Amendment 1 to the original Protocol allowed selected investigators the use of intramuscular administration of both study drugs.

Procedures and Observations:

The procedures employed and the observations collected were consistent with those found in other UTI protocols and described in the preamble to this review.

RESULTS

Patients were enrolled into study #108 from December 10, 1988 to May 24, 1991 at four centers in the United States.

Population Studied:

Eighty patients were enrolled into study #108. Of the eighty patients enrolled, 39 patients were randomized to the cefepime treatment group and 41 patients were randomized to the ceftazidime treatment group. There were no randomization variations in this study.

Evaluability for the Assessment of Safety:

All 80 enrolled patients received at least one dose of cefepime or ceftazidime and therefore were evaluable for the assessment of drug safety.

Evaluability for the Assessment of Efficacy:

According to the applicant, 29/39 patients (74%) randomized to cefepime and 18/41 patients (44%) randomized to ceftazidime were evaluable for the efficacy assessment. According to the reviewer, 29/39 patients (74%) randomized to cefepime and 19/41 patients (46%) randomized to ceftazidime were evaluable for the efficacy assessment. Table-108.1 presents the total enrollment and the number of patients evaluable for efficacy at each study center.

Table-108.1
Enrollment and Evaluability for Efficacy

Center	Principal Investigator	Location	Enrol	Number of Patients			Enrol	BMS	MO
				Cefepime		Ceftazidime			
I-001	Laurel Preheim	Omaha, NE	22	15	15	20	8	9	
I-003	Abdollah Iravani	Gainesville, FL	0	0	0	2	0	0	
I-004	Jacob Rajfer	Torrance, CA	6	3	3	8	1	1	
I-005	Stacy Childs	Alabaster, AL	11	11	11	11	9	9	
TOTAL			39	29	29	41	18	19	

Summary of Non-Evaluability:

For both the applicant and the reviewer, the major reason for non-evaluability was the failure to document an appropriate pathogen pre-treatment. Table 108.2 and Table 108.3 present the applicant and the reviewer's reasons for exclusion from the efficacy analysis.

Table-108.2
Reasons for Exclusion from the Efficacy Analysis
(According to the Applicant)

Infection Type/ Reason*	Number (#) ¹ of Infections	
	Cefepime	Ceftazidime
UTI (Number of Infections)	39	41
Total Excluded (Unevaluable)	10 (26)	23 (56)
No pre-Rx-culture	1 (3)	1 (2)
No pathogen isolated	2 (5)	9 (22)
Colony count < 10 ³ CFU/ml	1 (3)	2 (5)
No sensitivity testing done	0	2 (5)
Resistant organism	1 (3)	2 (5)
Inappropriate organism	1 (3)	0
Other antibiotic given post pre-culture	0	1 (2)
No during-Rx clinical assessment	2 (5)	1 (2)
Incomplete treatment	0	1 (2)
Other antibiotic given during study-Rx	1 (3)	1 (2)
Other antibiotic given pre post-clin.	1 (3)	2 (5)
Post-Rx visit out of window	0	1 (2)
Evaluable Infections	29 (74)	18 (44)

¹Numbers in parenthesis are percentage of total patients enrolled.

Table 108.3
Reasons for Exclusion from the Efficacy Analysis
(According to the Reviewer)

Reason*	Number (#) of Infections	
	Cefepime	Ceftazidime
Total Enrolled	39	41
Total Excluded	10	22
Pre-treatment culture out of range	0	1 (2)
No Pathogen Isolated	4 (10)	9 (22)
Resistant Organism Recovered	1 (3)	2 (5)
No sensitivity testing	0	1 (2)
No During Therapy Culture	0	0
Incomplete Treatment		
Due to ADR	0	0
Due to Death	0	0
Due to Protocol Error	1 (3)	1 (2)
Due to Patient Request	0	0
Other Antimicrobial Administered		
Oral Continuation of Treatment	0	2 (5)
Infection at Distant Site	1 (3)	1 (2)
Protocol Error	1 (3)	0
Resistant Organism	2 (5)	4 (10)
Post-treatment culture out of range	0	1 (3)
Evaluable UTI	29 (74)	19 (46)

*Numbers in parenthesis are percentage of total patients enrolled.

COMMENT: A significant difference exists in the overall rate of evaluability in both the applicant's and the medical officer's analysis. A larger proportion of patient in the cefepime treatment group were evaluable ($p=0.01$, Fisher's Exact Test) compared with the ceftazidime treatment group. The unexpectedly large number of patients in the ceftazidime treatment group in whom no pathogen was isolated accounts for the observed difference.

Applicant and Reviewer Evaluability Differences:

One patient in the ceftazidime group was considered not evaluable by the applicant because of the presence of a resistant organism. The patient was infected with three organisms of which two were sensitive and one was resistant. The medical officer considered the patient to be evaluable, however, only the response of the susceptible organisms was evaluated.

Demographic Characteristics:

According to the applicant, the majority of the patients in both treatment groups were males. Most patients were white in both treatment groups. The mean and median ages of patients in both treatment groups were similar; however, a slightly larger percentage of ceftazidime patients (54%) compared to cefepime patients (41%) were 65 years of age or older. Table-108.4 summarizes the demographic characteristics for all patients.

Table-108.4
Demographic Characteristics of the Enrolled Population
Study 411-108
(According to the Applicant)

Characteristic	Cefepime	Ceftazidime	p-value
N	39	41	
Sex: N (%)			1.000
Female	12 (31)	13 (32)	
Male	27 (69)	28 (68)	
Race: N (%)			0.525
Black	6 (15)	3 (7)	
White	27 (69)	32 (78)	
Hispanic	6 (15)	6 (15)	
Age Distribution: N (%)			
18-24 yrs	2 (5)	1 (2)	
25-44 yrs	5 (13)	6 (15)	
45-64 yrs	16 (41)	12 (29)	
65-84 yrs	15 (38)	22 (54)	
85-89 yrs	1 (3)	0	
Age: (yrs)			0.340
Mean	58.4	61.5	
Median	63	65	
S.D.	17.1	15.4	
Minimum	18	20	
Maximum	89	82	

The demographic characteristics of the enrolled population were similar to the demographic characteristics of the evaluable population, most patients in both groups were male and white. Again the ceftazidime group included slightly older individuals. Table-108.5 presents the demographic characteristics of the evaluable population according to the applicant.

Table-108.5
Demographic Characteristics of the Evaluable Population
Study 411-108
(According to the Applicant)

Characteristic	Cefepime	Ceftazidime	p-value
N	29	18	
Sex: N (%)			0.371
Female	9 (31)	8 (44)	
Male	20 (69)	10 (56)	
Race: N (%)			0.751
Black	6 (21)	2 (11)	
White	20 (69)	15 (83)	
Hispanic	3 (10)	1 (6)	
Age Distribution: N (%)			
20 yrs	1 (3)	0	
25-44 yrs	3 (10)	4 (22)	
45-64 yrs	14 (48)	3 (17)	
65-82 yrs	11 (38)	11 (61)	
Age: (yrs)			0.278
Mean	58.8	62.0	
Median	63	70	
S.D.	15.4	17.7	
Minimum	20	26	
Maximum	78	82	

COMMENT: Since the medical officer and the applicant differed on the evaluability of only one patient the baseline demographic characteristics of the medical officer's evaluable population are essentially the same as those presented above for the applicant's evaluable population.

Medical History:

According to the applicant, among evaluable patients who had complicated UTI there were significantly more ceftazidime patients (5/11) than cefepime patients (1/19) who had cancer of the urinary tract ($p=0.0091$); no adjustment was made for this difference during efficacy analysis because of the small number of patients. The two treatment groups were comparable for all other relevant medical conditions.

Table-108.6
 Relevant Medical Conditions - Evaluable Patients
 Study #108
 (According to the Applicant)

Condition ^a	Number (%) ^b of Patients	
	Cefepime	Ceftazidime
Patients with Complicated UTI^c	N = 19	N = 11
Specific Urinary Tract Conditions:		
*Upper UTI	4 (21)	4 (36)
*Obstruction	7 (37)	4 (36)
*Urinary tract catheter	5 (26)	4 (36)
*Cancer of urinary tract	1 (5)	5 (45)
*UT anatomic abnormality	5 (26)	1 (9)
*Urinary tract surgery	6 (32)	3 (27)
Other conditions ^a	7 (37)	6 (55)
Diabetes ^c	5 (26)	3 (27)
Patients with Uncomplicated UTI	N = 10	N = 7

a More than one condition may occur in a single patient.

b Percentages are based on number of patients within each category of infection (complicated or uncomplicated).

c Based on review by Bristol-Myers-Squibb Personnel.

According to the medical officer, relevant underlying medical disorders seemed to be equally distributed between the two groups. Table 108.7, following, summarizes the medical officer's assessment of relevant underlying medical disorders in evaluable patients

Table-108.7
 Relevant Medical Conditions - Evaluable Patients
 Study 411-108
 (According to the Medical Officer)

Condition ^a	Number (%) ^b of Patients	
	Cefepime	Ceftazidime
Evaluable Patients	N = 29	N = 19
Patients with Complicated UTI	N = 21	N = 12
Anatomic Abnormality	3 (14)	0
BPH	3 (14)	2 (17)
Catheter Associated	4 (19)	2 (17)
Male > 40 years	4 (19)	1 (8)
Urinary Tract Neoplasm	1 (5)	2 (17)
S/P Surgery	2 (10)	2 (17)
Stones	4 (19)	1 (8)
Obstruction	0	2 (17)
Uncomplicated UTI	N = 8	N = 7

a The medical officer identified one complicating condition for each patient.

b Percentages are based on number of patients within each category of infection.

Concomitant Medications:

According to the applicant, twenty-five (86%) of the 29 evaluable patients in the cefepime group received concomitant medication. Sixteen (89%) of the 18 evaluable patients in the ceftazidime group received concomitant medication. The difference in concomitant medication use between the two treatment groups was not statistically significant. Three patients in the cefepime treatment group and one patient in the ceftazidime treatment group received concomitant antimicrobial drugs, however, the drugs were not active against common UTI pathogens (e.g. metronidazole) and thus did not violate the evaluability criteria.

Study Drug Administration:

According to the applicant, both cefepime and ceftazidime were administered at 500 mg Q12h. In the cefepime group, the duration of dosing ranged from 6 to 15 days. In the ceftazidime group, the duration of dosing ranged from 7 to 15 days. For five patients in the cefepime group and three patients in the ceftazidime group, duration of dosing was 15 days, which was one day longer than specified in the Protocol. The difference between treatment groups in duration of dosing was not statistically significant ($p=0.407$). Table-108.8 summarizes the dosing data for patients evaluable for efficacy.

Table-108.8

Study Therapy for UTI Evaluable Patients
(According to the Applicant)
Study 411-108 (Blinded)

Parameter	Number (%) of Patients
<u>Cefepime</u>	N = 29
Duration of Dosing (days)	
6	3 (10)
7	3 (10)
8	5 (17)
9	1 (3)
10	2 (7)
11-15	15 (52)
<u>Ceftazidime</u>	N = 18
Duration of Dosing (days)	
7	1 (6)
8	4 (22)
10	4 (22)
11-15	9 (50)

According to the medical officer, in the cefepime group the duration of dosing ranged from 6 to 15 days, the mean duration of therapy was 6.43 days, the median duration of therapy was 10.5 days and the modal duration of therapy was 8 days. In the ceftazidime group the duration of therapy ranged from 7 to 15 days, the mean duration of therapy was 6.89 days, the median duration of therapy was 10.5 days, the modal duration of therapy was 14 days. Table-108.9 summarizes the study drug administration.

Table-108.9

Study Therapy for UTI Evaluable Patients
(According to the Medical Officer)
Study 411-108 (Blinded)

Parameter	Number (%) of Patients
<u>Cefepime</u>	N = 29
Duration of Dosing (days)	
6	3 (10)
7	2 (7)
8	5 (18)
9	1 (4)
10	3 (11)
11	3 (11)
12	1 (4)
13	3 (11)
14	3 (11)
15	5 (18)
<u>Ceftazidime</u>	N = 19
Duration of Dosing (days)	
7	2 (11)
8	4 (21)
10	4 (21)
13	1 (5)
14	5 (26)
15	3 (16)

EFFICACY EVALUATION**Clinical Efficacy**

According to the applicant, overall, a satisfactory response to therapy was seen in 26/29 patients (90%) in the cefepime treatment groups and in 15/18 patients (83%) in the ceftazidime treatment group. Table-108.10 presents the applicant's assessment of the clinical response for the overall UTI population and for the sub-groups of complicated and uncomplicated UTI patients.

Table-108.10

Clinical Efficacy
(According to the Applicant)
Study #108

Parameter	CEFEPIME	CEFTAZID
NO. OF EVALUABLE PATIENTS	29	18
SATIS	26 (90%)	15 (83%)
UNSAT	3 (10%)	3 (17%)
COMPLICATED UTI PATIENTS	19	11
SATIS	18 (95%)	9 (82%)
UNSAT	1 (5%)	2 (18%)
UNCOMPLICATED UTI PATIENTS	10	7
SATIS	8 (80%)	6 (86%)
UNSAT	2 (20%)	1 (14%)

According to the reviewer, overall, 17/29 patients (59%) in the cefepime treatment group and 13/19 patients (68%) in the ceftazidime treatment group were clinically cured at the 5-9 day post-therapy evaluation. An additional 8 patients (28%) in the cefepime treatment group and 2 patients (11%) in the ceftazidime treatment group had improved from baseline but were not completely cured by the 5-9 day post-therapy evaluation.

Table-108.11 presents the reviewer's assessment of the clinical efficacy of cefepime for the overall UTI population and for the sub-groups of patients with complicated UTI, pyelonephritis, and uncomplicated UTI.

Table-108.11
Clinical Efficacy
 (According to the Reviewer)
 Study #108

Parameter	CEFEPIME	CEFTAZID
NO. OF EVALUABLE PATIENTS	29	19
CURE	17 (59%)	13 (68%)
IMPROV	8 (28%)	2 (11%)
UNDET	0	1 (5%)
FAILURE	4 (14%)	3 (16%)
COMPLICATED UTI	14	9
CURE	9 (64%)	5 (56%)
IMPROV	5 (36%)	1 (11%)
UNDET	0	1 (11%)
FAIL	0	2 (22%)
PYELONEPHRITIS	7	4
CURE	2 (29%)	2 (50%)
IMPROV	3 (43%)	1 (25%)
FAIL	2 (29%)	1 (25%)
UNCOMPLICATED UTI	8	6
CURE	6 (75%)	6 (100%)
FAIL	2 (25%)	0

see p.65

9
+4
13
+6
19

one patient in "wrong" group
FA 7/26/94

COMMENT: The pyelonephritis sub-group of the cefepime treatment group is comprised of 71% males, in contrast the pyelonephritis sub group of the ceftazidime treatment group is composed of 50% males. The higher proportion of males in the cefepime treatment group may account for the lower clinical cure rate seen in this group.

Bacteriologic Efficacy**Susceptibility of Pathogens:**

According to the applicant, seventy-seven pathogens were isolated in pretreatment cultures from the 80 patients in the study. Of the 73 pathogens tested for susceptibility to cefepime, 64 (88%) were susceptible, 4 (5%) were of intermediate susceptibility, and 5 (7%) were resistant. Four pathogens were not tested for susceptibility to cefepime.

As expected, the pathogens isolated most frequently included *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. All isolates of these pathogens, except one cefepime-resistant isolate of *K. pneumoniae*, were susceptible or of intermediate susceptibility in vitro to both cefepime and ceftazidime.

Of the 73 pathogens tested for susceptibility to ceftazidime, 67 (92%) were susceptible, 1 (1%) was of intermediate susceptibility, and 5 (7%) were resistant. Four pathogens were not tested for susceptibility to ceftazidime. Results of susceptibility tests for all organisms are presented in Table-108.11

Table-108.11
Susceptibility of Pathogens Recovered from UTI Patients
Study #108
(Table Prepared by the Applicant)

Infection Type/ Pathogen	----- Number of Pathogens* -----					-----				
	<u>Cefepime Susceptibility</u>					<u>Ceftazidime Susceptibility</u>				
	Susc.	Inter.	Res.	Not Done	Total	Susc.	Inter.	Res.	Not Done	Total
UTI										
<i>S. faecalis</i>		1	2		3			3		3
Enterococcus			1		1			1		1
<i>S. epidermidis</i>	1				1	1				1
<i>P. aeruginosa</i>	8	3			11	11				11
<i>E. coli</i>	34			1	35	34			1	35
<i>C. freundii</i>	1				1	1				1
<i>C. amalonaticus</i>	1				1	1				1
<i>K. pneumoniae</i>	8		1		9	8	1			9
<i>K. oxytoca</i>	2				2	2				2
<i>E. aerogenes</i>	2				2	2				2
<i>P. mirabilis</i>	1				1	1				1
<i>M. morgani</i>	1				1	1				1
<i>P. stuartii</i>	1				1	1				1
<i>E. agglomerans</i>	1				1	1				1
<i>A. anitratus</i>			1		1			1		1
Diphtheroids	1				1	1				1
Fungus				1	1					1
Total	62	4	5	2	73	65	1	5	2	73
Percent	(87)	(6)	(7)			(92)	(1)	(7)		

COMMENT: 3/11 isolates of *P. aeruginosa* were of intermediate susceptibility to cefepime, however, all isolates of *P. aeruginosa* were fully susceptible to ceftazidime.

Bacteriologic Efficacy at the 5-9 Day Post-Therapy Evaluation:

According to the applicant, overall, 26/30 pathogens (87%) were eradicated in the cefepime treatment group, including 17/20 pathogens (85%) in patients with complicated UTI and 9/10 pathogens (90%) in patients with uncomplicated UTI. In contrast, 13/18 pathogens (72%) were eradicated in the ceftazidime treatment group, including 8/11 pathogens (73%) in patients with complicated UTI and 5/7 (71%) of pathogens in patients with uncomplicated UTI.

COMMENT: The medical officer did not perform a confidence interval analysis on the eradication results because of the small numbers of patients involved in this study.

Table-108.12 presents the applicant's assessment of the bacteriological response at the 5-9 day post-treatment assessment.

Table-108.12

Bacteriologic Efficacy at the 5-9 Day Post-Therapy Assessment
(According to the Applicant)
Study #108

Number of Infections	----- Number of Pathogens -----					
	Cefepime			Ceftazidime		
	Erad.	Pers.	Total	Erad.	Pers.	Total
COMPLICATED						
S. epidermidis	1		1			
P. aeruginosa	4		4	3		3
E. coli	6	3	9	3	3	6
K. pneumoniae	3		3	1		1
K. oxytoca	1		1	1		1
E. aerogenes	2		2			
Total Pathogens*	17	3	20	8	3	11
Percent	(85)	(15)		(73)	(27)	
UNCOMPLICATED						
P. aeruginosa				1		1
E. coli	8	1	9	3	2	5
K. pneumoniae	1		1	1		1
Total Pathogens*	9	1	10	5	2	7
Percent	(90)	(10)		(71)	(29)	
Total Pathogens	26	4	30	13	5	18
Percent	(87)	(13)		(72)	(28)	

NOTE: Erad. = Eradicated; Pers. = Persisted.

According to the reviewer, overall, 25/30 pathogens (83%) were eradicated in the cefepime treatment group, including 12/15 pathogens (80%) in patients with complicated UTI, 6/7 pathogens (86%) in patients with pyelonephritis, and 7/8 pathogens (88%) in patients with uncomplicated UTI. In contrast, 15/19 pathogens (79%) were eradicated in the ceftazidime treatment group, including 7/9 pathogens (77%) in patients with complicated UTI, 3/4 pathogens (75%) in patients with pyelonephritis, and 5/6 pathogens (83%) in patients with uncomplicated UTI.

E. coli was the most frequently isolated pathogen; it was eradicated in 14/18 (78%) of patients in the cefepime treatment group and in 7/11 (64%) of patients in the ceftazidime treatment group. The difference in eradication rates is not significant ($\chi^2=0.68$).

COMMENT: There are no major differences in demographic variables between the two treatment groups in the sub-group of patients with *E. coli* infection to account for the difference in eradication rates seen.

P. aeruginosa was eradicated in 3/4 patients (75%) in the cefepime treatment group and in 4/4 patients (100%) in the ceftazidime treatment group.

COMMENT: The numbers of patients infected with *P. aeruginosa* is too small to draw valid conclusions regarding the efficacy of cefepime in treating infections due to this organism.

Table-108.13 presents the reviewer's assessment of the bacteriologic response at the 5 to 9 day post-therapy evaluation.

Table-108.13

Bacteriologic Efficacy at the 5-9 Day Assessment
(According to the Reviewer)
Study #108

Parameter	CEFEPIME	CEFTAZID
COMPLICATED UTI		
E. COLI	7/ 9 (78%)	1/ 3 (33%)
K. OXYTOCA	1/ 1 (100%)	0
K. PNEUMONIAE	2/ 2 (100%)	2/ 2 (100%)
P. AERUGINOSA	2/ 3 (67%)	4/ 4 (100%)
TOTAL COMPLICATED UTI	12/ 15 (80%)	7/ 9 (77%)
PYELONEPHRITIS		
E. AEROGENES	2/ 2 (100%)	0
E. COLI	1/ 2 (50%)	2/ 3 (67%)
K. OXYTOCA	0	1/ 1 (100%)
K. PNEUMONIAE	1/ 1 (100%)	0
P. AERUGINOSA	1/ 1 (100%)	0
S. EPIDERMIDIS	1/ 1 (100%)	0
TOTAL PYELONEPHRITIS	6/ 7 (86%)	3/ 4 (75%)
UNCOMPLICATED UTI		
E. COLI	6/ 7 (86%)	4/ 5 (80%)
K. PNEUMONIAE	1/ 1 (100%)	1/ 1 (100%)
TOTAL UNCOMPLICATED	7/ 8 (88%)	5/ 6 (83%)
TOTAL UTI	25/ 30 (83%)	15/ 19 (79%)

Bacteriologic Response at the 4-6 Week Post-Therapy Assessment:

According to the applicant, among evaluable patients with complicated UTI who had eradication at the first follow-up, 11 in the cefepime group and 7 in the ceftazidime group had a follow-up evaluation on Day 26-44 (4-6 weeks) post-treatment. Four patients in the cefepime group and two patients in the ceftazidime group had evidence of a relapse. One relapse in the cefepime group was caused by *P. aeruginosa*; the other three relapses in the cefepime group were caused by *E. coli*. One relapse in the ceftazidime group was caused by *K. pneumoniae*, and the other relapse was caused by *K. oxytoca*. One cefepime patient, in addition to their relapse, also had a reinfection with a new pathogen, *E. aerogenes*. Table 108.19 summarizes the results of the follow-up assessments.

Among patients who had complicated UTI and who returned for the evaluation at post-treatment Day 26-44, the bacteriologic response continued to be eradicated for 64% in the cefepime group and 71% in the ceftazidime group.

Table-108.14
Bacteriologic Efficacy at the 4-6 Week Post-Therapy Assessment
Evaluable Patients with Complicated UTI
(According to the Applicant)
Study #108

Parameters	Number (%) ^a of Patients	
	Cefepime	Ceftazidime
<u>BMS Eval Complicated UTI</u>	19	11
Persistence at 5-9 Days	<u>-3</u>	<u>-3</u>
<u>Patients Eval. for 4-6 Week Asses.</u>	16	8
Not Assessed	<u>-5</u>	<u>-1</u>
<u>Patients Assessed at 4-6 Weeks</u>	<u>11</u>	<u>7</u>
Continued Eradication	7 (64)	5 (71)
Eradication with Relapse	3 (27)	2 (29)
Eradication with Relapse and Reinfection	1 (9)	0

a Percentages based on all patients with 4-6 week follow-up.
NOTE: The actual window for the 4-6 week follow-up was post-treatment Days 20-49.

According to the reviewer, overall 18 patients in the cefepime group and 16 patients in the ceftazidime group were evaluated at the late follow-up visit. In the cefepime group, 14/18 patients evaluated (78%) had a response of continued eradication 4-6 weeks post-therapy, 11/16 patients evaluated (69%) in the ceftazidime group had a response of continued eradication 4-6 weeks post-therapy.

Three relapses occurred in patients in the cefepime treatment group. The organisms relapsing were *P. aeruginosa* (1) and *E. coli* (2). There was one patient (6%) who had both relapse with *E. coli* and reinfection with *E. aerogenes*. There were 4 relapses (25%) in the ceftazidime group. The organisms causing relapse were *K. oxytoca* (1), *E. coli* (2), and *K. pneumoniae* (1).

There were no patients with reinfection alone in the cefepime group. There was one reinfection (6%) in the ceftazidime group; the reinfection was caused by *E. coli*.

COMMENT: All organisms causing either relapse or reinfection in both treatment groups were still susceptible to both drugs at the time they were recovered. (i.e. there was no evidence of the development of resistance during therapy).

Table-108.15 summarizes the reviewer's assessments of the bacteriologic response at the 4-6 weeks post-therapy evaluation.

Table-108.15

Bacteriologic Efficacy at the 4-6 Week Post-Therapy Assessment
in Patients with Both Complicated and Uncomplicated UTI
(According to the Reviewer)
Study #108

Parameters	Number (%) ^a of Patients	
	Cefepime	Ceftazidime
<u>MO Evaluable UTI Patients</u>	29	19
Persistence at 5-9 Days	-3	-3
<u>Patients Eval. for 4-6 Week Asses.</u>	26	16
Not Assessed	-8	-0
<u>Patients Assessed at 4-6 Weeks</u>	<u>18</u>	<u>16</u>
Continued Eradication	14 (78)	11 (69)
Eradication with Relapse	3 (17)	4 (25)
Eradication with Reinfection	0	1 (6)
Eradication with Relapse and Reinfection	1 (6)	0

^a Percentages based on all patients with 4-6 week follow-up.

NOTE: The actual window for the 4-6 week follow-up was post-treatment Days 20-49.

Safety Evaluation

Deaths

Cefepime Deaths:

Two deaths occurred among patients treated with cefepime.

- The patient was a 75 y.o. male with multiple medical problems who was treated for complicated UTI with cefepime. The patient received one dose of cefepime. The medication was discontinued after one dose because the urine culture grew *Candida*. The patient died almost one month later from complications of acute myocardial infarction.

- The patient was a 75 y.o. male who was treated with cefepime for complicated UTI. The patient received one dose of cefepime. The medication was discontinued after one dose because the urine culture grew yeast. The patient died over 2 months later from complications of bilateral pneumonia.

COMMENT:

The deaths which occurred in the cefepime group did not appear to be due to direct toxic effect of drug or treatment failure.

Ceftazidime Deaths

One death occurred among patients treated with ceftazidime.

The patient had a past medical history of atherosclerosis and prostatic carcinoma with metastasis to bone. The patient was treated for an *E. coli* UTI with ceftazidime. The patient relapsed 12 days post therapy. The patient expired 5 weeks after completion of therapy from complications of prostatic carcinoma.

COMMENT:

Although the patient experienced a microbiological relapse, the death does not appear to be related to the infection under treatment.

Discontinuations

No patient discontinued cefepime therapy due to adverse clinical events.

Two patients discontinued ceftazidime therapy due to adverse clinical events. Patient discontinued therapy after 4 days due to a rash. Patient discontinued therapy after experiencing dizziness and weakness after an injection.

Adverse Clinical Events

According to the sponsor, 12/39 patients (31%) in the cefepime group reported a total of 37 ACE (1 cefepime patient was lost to follow-up). Four events (headache, chest pain, diarrhea, and vomiting) affected at least two cefepime patients. In the cefepime group, 6 ACE in 3 (8%) of the 39 patients were considered probably related to treatment. These included one case each of arm pain, shoulder pain, thirst, paresthesia, genital pain, and pruritus. Fourteen ACE in seven (18%) patients were of unknown relationship. These included two

cases each of headache and vomiting and one case each of body pain, syncope, diarrhea, dyspepsia, eructation, ileus, nausea, anxiety, drowsiness, and insomnia. Seventeen ACE in nine (23%) patients were judged to be unrelated to cefepime treatment.

In the ceftazidime treatment group, 14/40 (35%) patients in the ceftazidime group experienced a total of 26 ACE (1 ceftazidime patient was lost to follow-up). Four events (diarrhea, abdominal pain, dizziness, and rash) affected 2 or more patients. In the ceftazidime group, two ACE in two patients (5%) were considered probably related to treatment. These included one case each of rash and vaginitis. Eight ACE in seven (17%) patients were of unknown relationship. These included two cases of diarrhea and one case each of asthenia, phlegm, dizziness, insomnia, paresthesia, and twitching. Sixteen ACE in eight (20%) patients were considered unrelated to ceftazidime treatment.

There was no statistically significant difference ($p=0.794$) in the incidence of ACE between the two treatment groups.

Table 108.16 summarizes the adverse clinical events occurring within each body system and the investigator's assessment of relatedness to drug therapy.

Table-108.16
Adverse Clinical Events, by Body System and Relationship to Study Drug
(According to the Applicant)
Study #108

Body System/ Primary Term	----- Cefepime ^a -----			----- Ceftazidime ^b -----			Total	
	N = 39			N = 41				
	Relationship			Relationship				
	Prob.	Unk.	Not	Total	Prob.	Unk.	Not	Total
Body as a Whole								
Asthenia					1			1
Headache		2	1	3				
Pain		1		1			1	1
Pain, arm(s)	1			1				
Pain, chest			1	1				
Pain, shoulder(s)	1			1				
Cardiovascular System								
Blood pressure disorder							1	1
Electrocardiogram abnormal			1	1				
Hypotension			1	1			1	1
Murmur							1	1
Pain chest			2	2			1	1
Supraventricular extrasystoles			1	1				
Syncope		1		1				
Vascular disorder							1	1
Digestive System								
Constipation							1	1
Diarrhea		1	2	3		2		2
Dyspepsia		1		1				
Eructation		1		1				
Hemorrhage			1	1				
Ileus		1		1				
Nausea		1		1				
Pain, abdomen							2	2
Phlegm						1		1
Thirst	1			1				
Vomiting		2	1	3			1	1
Nervous System								
Agitation							1	1
Anxiety		1		1				
Dizziness						1	1	2
Drowsiness		1		1				
Insomnia		1		1		1		1
Paresthesia	1			1		1		1
Somnolence			1	1				
Twitching						1		1
Respiratory System								
Dyspnea			1	1			1	1
Hiccup			1	1				
Hyperventilation			1	1				
Pain, throat			1	1				

Table-108.16 - Continued
Adverse Clinical Events, by Body System
and Relationship to Study Drug
(According to the Applicant)
Study #108

Body System/ Primary Term	----- Cefepime ^a -----				----- Ceftazidime ^b -----			
	N = 39				N = 41			
	<u>Relationship</u>				<u>Relationship</u>			
	Prob.	Unk.	Not	Total	Prob.	Unk.	Not	Total
Skin and Appendages								
Rash					1		1	2
Special Senses								
Eye hemorrhage			1	1				
Visual field defect							1	1
Urogenital System								
Pain, genital-area	1			1				
Pruritus	1			1				
Uremia							1	1
Vaginitis					1			1
TOTAL	<u>6</u>	<u>14</u>	<u>17</u>	<u>37</u>	<u>2</u>	<u>8</u>	<u>16</u>	<u>26</u>

NOTE: Prob. = Probably related to cefepime; Unk. = Unknown relationship; Not = Not related.

Most clinical adverse drug events reported were of mild or moderate severity.

Of the 37 ACE reported in the cefepime group, three (dyspnea, hypotension, and tachypnea) were judged severe. None of those judged severe was considered to be related to the drug administered.

Of the 26 ACE reported in the ceftazidime group, one (aortic aneurysm, not related to drug administered) was judged life-threatening, and one (insomnia, of unknown relationship to study drug) was judged severe.

Table 108.17 indicates numbers of patients with ACE by severity and treatment group.

Table-108.17
Severity of ACE, by Treatment Group
(According to the Applicant)

Severity	<u>Number (#) of Patients</u>		p-value
	Cefepime N = 39	Ceftazidime N = 41	
Mild	7 (18)	11 (27)	
Moderate	4 (10)	1 (2)	
Severe	1 (3)	1 (2)	
Life-threatening		1 (2)	0.869

Local reactions at the infusion site occurred in two patients (7%) treated with cefepime and in seven patients (23%) treated with ceftazidime. No patient

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discontinued therapy because of local reactions at the infusion site. The difference in the incidence of local reactions is not significant (chi-square=2.90, $p>0.05$). Eleven cefepime and 11 ceftazidime patients received medication by IM injection. Administration by IM injection was well tolerated in all patients.

Laboratory Test Abnormalities

No patients in either treatment group discontinued therapy due to abnormal laboratory test results.

For patients whose pretreatment test results were normal, there was a statistically significant difference between the two treatment groups in the distribution of abnormal during and post-treatment calcium levels ($p=0.015$) and eosinophil counts ($p=0.029$). For calcium, a greater proportion of patients treated with ceftazidime experienced a drop in calcium levels during or after treatment. For eosinophil count, a greater proportion of patients treated with cefepime experienced an increased eosinophil count during or after treatment. For the remaining laboratory tests, there were no significant differences in the distribution of during-treatment or post-treatment laboratory test results between the treatment groups.

Table 108.18
 During- or Post-Treatment Laboratory Test Abnormalities
 for Patients with a Normal Pretreatment Value
 (According to the Applicant)
 Study 411-108 (Blinded)

Laboratory Test	Number (%) Patients					
	Cefepime			Ceftazidime		
	N ^a	Abnormal ^b	Cl.Rel. ^c	N ^a	Abnormal ^b	Cl.Rel. ^c
HEMATOLOGY						
Hematocri	22	5 (23)	0	20	3 (15)	0
Platelet Count	34	0	0	32	1 (3)	0
WBC Count	32	1 (3)	0	32	2 (6)	0
Neutrophil Count	32	1 (3)	0	31	0	0
Eosinophil Count	32	7 (22)	0	32	3 (9)	2 (6)
COAGULATION						
Prothrombin	26	3 (12)	0	26	1 (4)	0
PTT	24	4 (17)	1 (4)	17	4 (24)	0
LIVER FUNCTION						
Alkaline Phosphatase	29	3 (10)	0	26	3 (12)	0
AST (SGOT)	29	7 (24)	1 (3)	28	5 (18)	1 (4)
ALT (SGPT)	32	6 (19)	0	31	5 (16)	0
Total bilirubin	26	0	0	28	1 (4)	0
RENAL FUNCTION						
BUN	25	1 (4)	0	28	0	0
Creatinine	28	1 (4)	0	29	0	0
ELECTROLYTES						
Na+	31			22		
Decrease		2 (6)	0		1 (5)	0
Increase		4 (13)	0		2 (9)	0
K+	27			28		
Decrease		3 (11)	0		2 (7)	0
Increase		1 (4)	0		1 (4)	0
Ca++	24			26		
Decrease		1 (4)	0		8 (31)	0
Increase		0	0		0	0
PO ₄ ⁻³	25			23		
Decrease		2 (8)	0		0	0
Increase		1 (4)	0		0	0

a N indicates number of patients tested.

b During- or post-treatment results outside the investigator's normal range limit in the direction of toxicity.

c Patients with Cl.Rel. (Clinically Relevant) values are included in the "Abnormal" column.

For patients in whom an abnormal laboratory test result was noted prior to treatment, there were no significant differences noted between the two treatment groups in the changes which occurred in those parameters during or after treatment. Table 108.19 summarizes the experience during and after treatment for those patients in whom an abnormal laboratory value was noted prior to treatment.

Table 108.19

During- or Post-Treatment Laboratory Test Abnormalities
for Patients with an Abnormal Pretreatment Value
Study 411-108 (Blinded)

Laboratory Test	Number (%) of Patients					
	Cefepime			Ceftazidime		
	N ^a	Worsened ^b	Cl.Rel. ^c	N ^a	Worsened ^b	Cl . R e l . ^c
HEMATOLOGY						
Hematocrit	13	2 (15)	0	13	2 (15)	0
Platelet Count	1	0	0	1	0	0
WBC Count	3	0	0	1	0	0
Neutrophil Count	2	0	0	1	0	0
Eosinophil Count	2	0	0			
COAGULATION						
Prothrombin	4	0	0	3	0	0
PTT	6	0	0	12	0	0
LIVER FUNCTION						
Alkaline phosphatase	3	1 (33)	1 (33)	5	0	0
AST (SGOT)	5	1 (20)	1 (20)	4	1 (25)	1 (25)
ALT (SGPT)	2	1 (50)	1 (50)	1	1 (100)	1 (100)
Total bilirubin	5	0	0	2	0	0
RENAL FUNCTION						
BUN	11	3 (27)	1 (9)	6	0	0
Creatinine	8	0	0	5	0	0
ELECTROLYTES						
Na ⁺	4			12		
Decrease		0	0		0	0
Increase		0	0		0	0
K ⁺	7			6		
Decrease		0	0		0	0
Increase		0	0		0	0
Ca ⁺⁺	5			3		
Decrease		0	0		0	0
Increase		0	0		0	0
PO ₄ ⁻³	5			4		
Decrease		0	0		0	0
Increase		0	0		0	0

a N indicates number of patients tested.

b During- or post-treatment as compared to pretreatment. Worsened indicates that the value changed to a worse class (Appendix G-22), not simply that the absolute value changed.

c Patients with Cl.Rel. (Clinically Relevant) values are included in the "Worsened" column.

Conclusions

Using the bacteriologic efficacy at the 5 to 9 day post-treatment evaluation as the primary test of efficacy, a response of eradication was noted for 25/30 pathogens (83%) that were treated with cefepime and in 15/19 pathogens (79%) treated with ceftazidime. The corrected 95% confidence interval around the true difference in the eradication rates is [-23, +31], the wide confidence interval resulting from the small number of patients enrolled in this study. The sub-groups of uncomplicated UTI, pyelonephritis and complicated UTI other than pyelonephritis achieved similar eradication rates to the overall population, but the small numbers of patients involved makes statistical analysis unfruitful.

If one examines the applicant's results at the 5 to 9 day post-treatment evaluation, a response of eradication was noted in 26/30 infections (86%) treated with cefepime and in 13/18 (72%) treated with ceftazidime. The corrected 95% confidence interval around the true difference in eradication rates is [-14, +43] which fulfills the criteria for equivalence by the confidence interval approach.

At the 4-6 week post-therapy visit, overall there were 3 relapses and one combined relapse and reinfection in the cefepime group; there were 4 relapses and one reinfection in the ceftazidime group.

With regard to clinical efficacy, at the 5 to 9 day visit, overall a complete clinical cure was achieved in 17/29 patients (59%) treated with cefepime and in 13/19 patients (68%) of patients treated with ceftazidime. According to the applicant 26/29 patients (90%) had a satisfactory clinical outcome after cefepime treatment and 15/18 patients (83%) had a satisfactory clinical outcome after ceftazidime treatment.

COMMENT: According to the applicant, a successful clinical outcome included those patients who were cured and those whose symptoms improved. According to the medical officer, only those patients who were completely cured of their infection were considered to be clinical successes.

Twelve of 39 patients (31%) in the cefepime group experienced one or more adverse clinical events. Fourteen of the 41 patients (34%) in the ceftazidime group experienced one or more adverse clinical events. There was no difference in the incidence of deaths, discontinuation or adverse clinical events between the two treatment groups. Eosinophilia was seen in more cefepime patients than ceftazidime patients and hypocalcemia was seen in more ceftazidime patients than cefepime patients.

Thus, study #108 supports the applicant's claim for the safety and efficacy of cefepime in the treatment of patients with complicated and uncomplicated UTI at a dose of 500 mg IV/IM every 12 hours.

PROTOCOL: 411-097**Introduction:**

Study #097 provides safety and efficacy data for cefepime in treating patients with _____ or with serious infections of the urinary tract (UTI), or skin or skin structures (SSTI) caused by a broad range of bacterial pathogens.

Objective:

To evaluate the safety and efficacy of cefepime versus ceftazidime in the treatment of patients with suspected S/B, with or without a documented site of infection, or with serious UTI, or SSTI.

Investigational Plan**Design Overview:**

This trial was a randomized (1:1, cefepime:ceftazidime), comparative clinical study at multiple centers in North America. At the majority of the centers the investigation was conducted in an open fashion, however, at three center (042, 055, 056) the investigation was conducted in a double-blind manner.

Population Studied:

Many of the same inclusion and exclusion criteria common to other UTI protocols submitted in this application were employed in study #097. Exceptions are noted below.

The protocol for study #97 allowed for the inclusion of patients with serious and/or complicated UTI, including infection occurring in the presence of known anatomic abnormalities of the genitourinary tract, stones, stents, nephrostomy tubes or indwelling catheters. Patients with renal failure were enrolled and an adjustment was made in the dose of study medication administered.

COMMENT: The protocol also allowed for the inclusion of patients with suspected bacteremia without a source of infection, patients with serious _____ and/or patients with serious SSTI.

Patients with a life-threatening infection (signs or symptoms of septic shock), patients with neutropenia (< 500 cells/mm³), or patients on "do not resuscitate" status were to be excluded from enrollment.

Study Drug Administration:

In the non-blinded centers, investigators were to administer cefepime or ceftazidime by intravenous infusion over a period of 30 minutes, with repeat dosing every 12 hours (2 g Q12h) for cefepime and every 8 hours (2 g Q8h) for ceftazidime for up to 28 days (Amendment 5 specified 28 days; original Protocol specified 14 days). Patient with renal failure had an adjusted dose of drug administered.

At the blinded centers, cefepime and ceftazidime were administered by intravenous infusion over a period of 30 minutes. The first dose was to be active drug. Patients could receive study drug for up to 28 days. For Center I-042, each patient assigned to cefepime was to receive two daily doses of 2 g administered

every 12 hours and four daily doses of placebo (sterile saline solution) administered at 4, 8, 16, and 20 hours after the initial daily dose of cefepime. Each patient assigned to receive ceftazidime was to receive three daily doses of 2 g administered every eight hours and three daily doses of placebo administered at 4, 12, and 20 hours after the initial daily dose of ceftazidime. For centers I-055 and I-056, each patient assigned to cefepime was to receive two daily doses of 2 g administered every 12 hours and two daily doses of placebo (sterile saline solution) administered at 8 and 16 hours after the initial daily dose of cefepime. Each patient assigned to receive ceftazidime was to receive three daily doses of 2 g administered every eight hours and one daily dose of placebo (sterile saline solution) administered 12 hours after the initial daily dose of ceftazidime. In cases of renal impairment, placebos and active drug were adjusted so that the blinded nature of the study was maintained.

Procedure: and Observations:

The procedures employed and the observations collected were consistent with those found in other UTI protocols and described in the preamble to this review.

Population Studied

A total of 59 principal investigators from 55 centers at 68 different location in the United States, Canada and Puerto Rico enrolled patients from October 12, 1988 through September 29, 1991. For all indications studied, a total of 1089 patients were enrolled, 543 were randomized to cefepime and 546 were randomized to ceftazidime.

Randomization Variations:

Thirty-five patients were randomized to one drug and received the other. All patients were evaluated according to the drug they actually received.

Enrollment for the Study of UTI:

Of the 1089 patients enrolled, 441 fulfilled the protocol definition of UTI. 215 were randomized to the cefepime treatment group and 226 were randomized to the ceftazidime treatment group. 68 UTI patients were treated at blinded centers (cefepime=35, ceftazidime=33).

Evaluability for the Assessment of Safety:

All 215 patients randomized to cefepime and 226 patients randomized to ceftazidime received at least one dose of study medication and thus were evaluable for the assessment of safety.

Evaluability for the Assessment of Efficacy:

Table-097.1 presents the enrollment, the applicant's assessment of evaluability, and the reviewer's assessment of evaluability at each of the study centers.

COMMENT: The reviewer considered a slightly smaller percentage of enrolled patients evaluable compared with the applicant in both treatment groups.

Table-097.1
Enrollment and Evaluability

No.	Location	Enrolled	Number of Patients (Percent)				
			Cefepime		Enrolled	Ceftazidime	
			BMS	M.O.			BMS
Open Centers							
I-001	Houston, TX	1	1	1	3	2	2
I-004	Lexington, KY	3	1	1	2	1	1
I-006	Oklahoma City, OK	2	0	0	0	0	0
I-007	New York, NY	0			1	1	1
I-008	Philadelphia, PA	3	0	0	6	1	1
I-010	Milwaukee, WI	4	1	1	6	3	3
I-012	Montreal, Canada	1	0	0	2	0	0
I-013	Pontiac, MI	3	0	0	1	0	0
I-014	Toledo, OH	2	0	0	3	0	0
I-015	Albuquerque, NM	10	2	2	9	4	4
I-016	Johnson City, TN	2	1	1	4	2	2
I-017	Toronto, Canada	5	0	0	4	0	0
I-019	Charleston, SC	1	0	0	0	-	-
I-020	Rancho Mirage, CA	2	1	1	0	-	-
I-025	Buffalo, NY	8	5	5	12	8	8
I-026	Philadelphia, PA	1	0	0	3	0	0
I-027	Houston, Tx						
	San Jose, Costa Rica	33	0	0	22	0	0
I-028	Wilmington, DE	16	4	4	17	9	8
I-029	Fort Myers, FL	8	4	4	15	5	5
I-030	Nova Scotia, Canada	2	0	0	1	1	1
I-032	Charlotte, NC	0	-	-	1	0	0
I-033	Sarasota, FL	7	2	2	10	2	2
I-037	Barberton, OH	2	2	2	1	0	0
I-038	Des Moines, IA	3	0	0	1	0	0
I-041	Columbia, MO	5	3	3	5	0	0
I-043	Buffalo, NY	6	1	1	5	0	0
I-044	Portland, OR	2	1	1	3	1	1
I-049	Hines, IL	1	1	1	4	0	0
I-052	Durham, NC	6	2	2	6	2	2
I-053	Kansas City, MO	7	4	5	12	4	4
I-058	Chicago, IL	10	6	7	8	3	2
I-063	Cumberland, MD	4	2	2	4	3	3
I-066	Richmond, VA	0	-	-	1	1	1
I-072	Cincinnati, OH	2	1	1	0	-	-
I-075	Bismarck, ND	1	0	0	0	-	-
I-076	Cleveland, OH	2	0	0	2	0	0
I-077	Portland, OR	1	1	1	5	0	0
I-078	Bradenton, FL	0	-	-	1	1	1
I-079	El Paso, TX	14	7	7	12	9	8
I-084	Vallejo, CA	0	-	-	1	0	0
Total		180	53	55	193	63	60

Table-1 - Continued
Enrollment and Evaluability

No.	Location	Enrolled	Number of Patients (Percent)				
			Cefepime		Enrolled	Ceftazidime	
			BMS	M.O.			BMS
Blinded Centers							
I-042	Detroit, MI	25	8	8	30	9	8
I-055	Fort Myers, FL	7	2	2	1	0	0
I-056	Albuquerque, NM	3	2	2	2	1	1
Total		35	12	12	33	10	9
Grand Total		215	65	67	226	73	69
Percent			30%	31%		32%	31%

COMMENT: None of the investigators involved in this protocol are listed in the Division of Scientific Investigation's Restricted Investigator List.

Summary of Non-Evaluability:

Tables -097.2 and -097.3 present the major reasons for which patients were considered not-evaluable for the assessment of efficacy.

Table-097.2
Reasons for Exclusion from the Efficacy Analysis
(According to the Applicant)
Study #097

Infection Type/ Reason*	Number (%) of Infections			
	Cefepime		Ceftazidime	
Total Enrolled	215		226	
Total Excluded (Unevaluable) UTI	150	(70)	153	(68)
Center #27	33	(22)	22	(14)
No pretreatment culture	4	(3)	4	(3)
Pretreatment culture/visit out of window	0		1	(1)
No pathogen isolated	31	(21)	39	(25)
Only one pretreatment culture (asymptomatic UTI)	1	(1)	0	
No pretreatment colony count OR <10 ⁵	12	(8)	22	(14)
Susceptibility testing not done	10	(7)	9	(6)
Resistant organism	6	(4)	8	(5)
Inappropriate organism	1	(1)	8	(5)
Other antibiotic after pretreatment culture	3	(2)	2	(1)
Incomplete treatment	8	(5)	7	(5)
Other antibiotic during or post-therapy	10	(7)	1	(1)
No during-therapy culture	8	(5)	5	(3)
No post-treatment clinical assessment	8	(5)	15	(10)
Post-treatment visit/cult out of window	15	(10)	19	(12)
Evaluable UTI Infections	65	(30)	73	(32)

COMMENT: During the course of routine data assurance procedures, the

principal investigator at center #027 was not able to document the results of pre-treatment cultures in patients enrolled at his center. Therefore, the applicant chose not to submit patients from center 027 in support of their claim of efficacy. The medical officer concurs with the applicants decision in this regard. All patients from center #27 received at least one dose of study medication and thus, will be included in the analysis of safety.

COMMENT: In the applicant's analysis, more patients in the cefepime group were excluded for receiving non-study antimicrobials, however more patients in the ceftazidime group were excluded for failure to have a post-therapy clinical assessment.

Table-097.3
Reasons for Exclusion from the Efficacy Analysis
(According to the Reviewer)
Study #097

Infection Type/ Reason*	Number (%) of Infections	
	Cefepime	Ceftazidime
Enrolled	N = 215	N = 226
Total Excluded	148 (69%)	157 (69%)
Study #027	33 (23%)	22 (14%)
Pre-treatment culture out of range	6 (4%)	7 (4%)
No Pathogen Isolated	35 (24%)	50 (34%)
Resistant Organism Recovered	9 (6%)	12 (8%)
No susceptibility testing	2 (1%)	3 (2%)
No During Therapy Culture	3 (2%)	5 (3%)
Incomplete Treatment		
Due to ADR	1 (1%)	3 (2%)
Due to Death	5 (3%)	3 (2%)
Due to Treatment Failure	2 (1%)	0
Due to Protocol Error	1 (1%)	1 (1%)
Due to Patient Request	2 (1%)	2 (1%)
Other Antimicrobial Administered		
Oral Continuation of Treatment	5 (3%)	7 (5%)
Infection at Distant Site	8 (5%)	5 (3%)
Protocol Error	4 (3%)	2 (1%)
Resistant Organism	1 (1%)	0 (0%)
Post-treatment culture out of range	31 (21%)	35 (24%)
Evaluable UTI	67 (31%)	69 (31%)

COMMENT: According to the reviewer, the most common reason in both treatment group for considering a patient to be not evaluable was the failure to isolate an appropriate pathogen pretreatment.

Applicant and Reviewer Evaluability Differences:

There were FOUR patients (cefepime=3, ceftazidime=1) who were considered evaluable by the reviewer and unevaluable by the applicant. Two of the patients were excluded by the applicant because other antimicrobials were administered prior to the post-therapy culture, however, these other antimicrobials were administered because of persistence or worsening of clinical condition. The medical officer considered these patients to be evaluable clinical and microbiological failures. One patient was made unevaluable by the applicant for "infection not documented", however, the medical officer felt that the patient fulfilled the protocol definitions of evaluability. One patient was made unevaluable by the applicant because of an "infection with resistant organism", on review, however, the patient had an infection with three organisms, 2 were susceptible to cefepime and 1 was resistant. The patient was considered evaluable by the medical officer; the outcome of the two susceptible pathogens were assessed; the outcome of the resistant pathogen was not assessed.

Six patients (cefepime=1, ceftazidime=5) were considered unevaluable by the reviewer and evaluable by the applicant. Three patients had asymptomatic bacteriuria with only one pre-treatment culture documented. One patient had their post-therapy culture performed on day +16 which is outside the reviewer's acceptable range (+5 to +14 days post-therapy). One patient was started on a non-study antimicrobial for a skin infection prior to the post-treatment culture.

Demographic Characteristics:

The majority of patients enrolled in the cefepime treatment group were white (63%) females (53%). In contrast, the majority of patients enrolled in the ceftazidime treatment group were white (65%) males (51%). The difference in the sex distribution was not significant. There were no significant differences in any other demographic variables. Table-097.4 summarizes the demographic characteristics of the enrolled population.

Table-097.4
Demographic Characteristics of the Enrolled Population
Study #097 (All Centers)

Parameter	CEFEPIME		CEFTAZID	
SEX				
FEMALE	115	(53%)	111	(49%)
MALE	100	(47%)	115	(51%)
RACE				
WHITE	135	(63%)	146	(65%)
BLACK	55	(26%)	59	(26%)
HISPANIC	22	(10%)	19	(8%)
ORIENTAL	3	(1%)	2	(1%)
AGE (YR)				
N	215		226	
MEAN	56.8		58.1	
MEDIAN	63		64	
RANGE				
AGE DISTRIBUTION				
18 - 24	21	(10%)	19	(8%)
25 - 44	47	(22%)	49	(22%)
45 - 64	46	(21%)	46	(20%)
65 - 84	90	(42%)	96	(42%)
85 +	11	(5%)	16	(7%)
WEIGHT (KGS)				
N	195		191	
MEAN	68.58		68.70	
MEDIAN	67.1		66.2	
RANGE				

The demographic characteristics of the applicant's evaluable population was similar to the enrolled population. Again, there were no significant differences between the treatment groups. Table-097.5 summarizes the demographic characteristics of the applicant's evaluable population.

Table-097.5
Demographic Characteristics of the Evaluable Population
(According to the Applicant)
Study #097 (All centers)

Parameter	CEFEPIME	CEFTAZID
SEX		
FEMALE	33 (51%)	36 (49%)
MALE	32 (49%)	37 (51%)
RACE		
WHITE	34 (52%)	43 (59%)
BLACK	20 (31%)	17 (23%)
HISPANIC	11 (17%)	12 (16%)
ORIENTAL	0 (0%)	1 (1%)
AGE (YR)		
N	65	73
MEAN	58.2	58.7
MEDIAN	64	63
RANGE		
AGE DISTRIBUTION		
18 - 24	5 (8%)	6 (8%)
25 - 44	15 (23%)	15 (21%)
45 - 64	13 (20%)	18 (25%)
65 - 84	27 (42%)	28 (38%)
85 +	5 (8%)	6 (8%)
WEIGHT (KGS)		
N	57	59
MEAN	72.85	71.71
MEDIAN	71.7	69.0
RANGE		

In the reviewer's evaluable population, the majority of patients in both treatment groups were female. There were no significant differences between the two treatment groups in any of the major demographic characteristics. Table-097.6 summarizes the demographic characteristics of the reviewer's evaluable population.

Table-097.6
Demographic Characteristics of the Evaluable Population
(According to the Reviewer)
Study #097 (All centers)

Parameter	CEFEPIME		CEFTAZID	
SEX				
FEMALE	35	(52%)	35	(51%)
MALE	32	(48%)	34	(49%)
RACE				
WHITE	35	(52%)	42	(61%)
BLACK	20	(30%)	15	(22%)
HISPANIC	12	(18%)	11	(16%)
ORIENTAL	0	(0%)	1	(1%)
AGE (YR)				
N-	67		69	
MEAN	57.4		59.3	
MEDIAN	63		63	
RANGE				
AGE DISTRIBUTION				
18 - 24	6	(9%)	5	(7%)
25 - 44	15	(22%)	14	(20%)
45 - 64	14	(21%)	19	(28%)
65 - 84	28	(42%)	25	(36%)
85 +	4	(6%)	6	(9%)
WEIGHT (KGS)				
N	59		55	
MEAN	73.75		72.14	
MEDIAN	71.7		70.3	
RANGE				

Medical History:

According to the applicant, the most commonly encountered medical condition, in both treatment groups, was the presence of a catheter within the genito-urinary system. Table-097.7 summarizes the relevant medical history for evaluable UTI patients.

Table-097.7
Relevant Medical History for Evaluable UTI Patients
(According to the Applicant)
Study #097

Condition ^a	Number (%) ^b of Patients	
	Cefepime N = 65	Ceftazidime N = 73
Complicated UTI	N = 56	N = 58
Specific urinary tract conditions:		
*Upper UTI -	28 (50)	29 (50)
*Obstruction	20 (36)	20 (34)
*Urinary tract catheter (all types)	30 (54)	34 (59)
*Urinary tract surgery	13 (23)	9 (16)
*Urinary tract cancer	4 (7)	5 (9)
*Anatomic abnormality of urinary tract	2 (4)	3 (5)
*Other conditions	22 (39)	21 (36)
Uncomplicated UTI	N = 9	N = 15

- a More than one condition or catheter type may occur in a single patient.
 b Percentage are based on number of patients within each category of infection.
 * Conditions used to classify UTI as complicated.

Concomitant Medications:

The sponsor did not provide detailed information regarding concomitant medication use in UTI patients alone, however, most patients involved in the study received at least one concomitant medication. Patients who received concomitant antimicrobials were either considered not evaluable or treatment failures if the antimicrobial was administered because of the persistence or worsening of symptoms.

Study Drug Administration:

Table-097.8 presents the duration of study drug administration for the applicant's and the reviewer's evaluable population. According to the applicant, cefepime was given at a dose of 2 g BID. The dose was adjusted for four patients because of renal impairment. The duration of dosing ranged from 3 to 26 days. The number of doses received ranged from 4 to 50. Ceftazidime was given at a dose of 2 g Q8h. Dosing was adjusted for 20 patients because of renal impairment. Duration of dosing ranged from 4 to 22 days. Number of doses ranged from 5 to 56. A higher proportion of ceftazidime than cefepime patients had dosage adjusted because of renal impairment. There was no statistically significant difference between the two treatment groups with respect to duration of dosing (p = 0.308).

According to the reviewer, cefepime was administered to 67 evaluable patients

from 3 to 26 days. The mean duration of dosing was 8.3 days, and the median duration of dosing was 9.5 days. Ceftazidime was administered to 69 evaluable patients. The range of days of ceftazidime administration was from 3 to 25 days. The mean duration of therapy was 9.6 days and the median duration of ceftazidime therapy was 9.5 days.

Table-097.8
Study Therapy for Evaluable UTI Patients
Study #097 (All centers)

Infection Type/ Duration of Dosing	<u>Applicant</u>		<u>Medical Officer</u>	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
UTI	N = 65	N = 73	N = 67	N = 69
3	2 (3%)	0	2 (3%)	1 (2%)
4	5 (8%)	2 (3%)	5 (7%)	2 (2%)
5	8 (12%)	9 (12%)	11 (16%)	8 (10%)
6	10 (15%)	7 (10%)	10 (15%)	7 (8%)
7	5 (8%)	9 (12%)	4 (6%)	8 (13%)
8	8 (12%)	8 (11%)	8 (12%)	8 (10%)
9	3 (5%)	7 (10%)	3 (4%)	5 (8%)
10	5 (11%)	11 (15%)	5 (7%)	9 (13%)
11	16 (25%)	16 (22%)	8 (12%)	9 (15%)
12	-	-	3 (4%)	-
13	-	-	1 (1%)	-
14	-	-	4 (6%)	4 (6%)
15	3 (5%)	4 (4%)	2 (3%)	1 (1%)
16	-	-	-	1 (1%)
18	-	-	-	3 (4%)
22	-	-	-	1 (1%)
25	-	-	-	2 (3%)
26	-	-	1 (1%)	-

EFFICACY EVALUATION**Clinical Efficacy**

According to the applicant, overall, a satisfactory response to therapy was seen in 58/65 patients (89%) in the cefepime treatment group and in 58/73 patients (79%) in the ceftazidime treatment group. Table-097.9 presents the applicant's assessment of the clinical response for the overall UTI population and for the sub-groups of complicated and uncomplicated UTI patients.

Table-097.9
Clinical Efficacy
(According to the Applicant)
Study #097

Number of Diagnoses and Pathogens -	----- Number of Patients -----					
	<u>Cefepime</u>			<u>Ceftazidime</u>		
	Sat.	Un.	Total	Sat.	Un.	Total
COMPLICATED	49 (88)	7 (13)	56	45 (78)	13 (22)	58
UNCOMPLICATED	9 (100)	0	9	13 (87)	2 (13)	15
TOTAL	58 (89)	7 (11)	65	58 (79)	15 (21)	73

According to the applicant, overall in the centers in which the investigation was performed in a blinded manner, a satisfactory response to therapy was seen in 11/12 patients (92%) in the cefepime treatment group and in 7/10 patients (70%) in the ceftazidime treatment group. Table-097.10 presents the applicant's assessment of the clinical response for the overall UTI population studied at blinded centers and for the sub-groups of complicated and uncomplicated UTI patients.

Table-097.10
Clinical Efficacy
(According to the Applicant)
Study #097 - Blinded Centers

Number of Diagnoses and Pathogens	----- Number of Patients -----					
	<u>Cefepime</u>			<u>Ceftazidime</u>		
	Sat.	Un.	Total	Sat.	Un.	Total
COMPLICATED	7 (88)	1 (13)	8	7 (70)	3 (30)	10
UNCOMPLICATED	4 (100)	0	4	0	0	0
TOTAL	11 (92)	1 (8)	12	7 (70)	3 (30)	10

According to the reviewer, overall, 57/67 patients (85%) in the cefepime treatment group and 58/69 patients (75%) in the ceftazidime treatment group were clinically cured at the 5-9 day post-therapy evaluation. An additional 1 patient (1%) in the cefepime treatment group and 4 patients (6%) in the ceftazidime treatment group had improved from baseline but were not completely cured by the 5-9 day post-therapy evaluation.

Table-097.11 presents the reviewer's assessment of the clinical efficacy of cefepime for the overall UTI population and the sub-groups of patients with complicated and uncomplicated UTI.

Table-097.11
Clinical Efficacy
(According to the Reviewer)
Study #97 - All Centers

Parameter	CEFEPIME	CEFTAZID
NO. OF EVALUABLE PATIENTS	67	69
CURE	57 (85%)	52 (75%)
IMPROV	1 (1%)	4 (6%)
FAILURE	9 (13%)	13 (19%)
COMPLICATED UTI	36	35
CURE	28 (78%)	25 (71%)
IMPROV	1 (3%)	2 (6%)
FAILURE	7 (19%)	8 (23%)
PYELONEPHRITIS	22	23
CURE	20 (91%)	19 (83%)
IMPROV	0	2 (9%)
FAILURE	2 (9%)	2 (9%)
UNCOMPLICATED UTI	9	11
CURE	9 (100%)	8 (73%)
FAILURE	0	3 (27%)

According to the reviewer, overall at the centers in which the investigation was conducted in a blinded manner, 11/12 patients (92%) in the cefepime treatment group and 7/9 patients (78%) in the ceftazidime treatment groups were clinically cured at the 5-9 day post-therapy evaluation.

Table-097.12 presents the reviewer's assessment of the clinical efficacy of cefepime for the overall UTI population that was studied at the blinded centers and the sub-groups of patients with complicated and uncomplicated UTI.

Table-097.12
Clinical Efficacy
According to the Reviewer
Study #97 - Blinded Centers

Parameter	CEFEPIME	CEFTAZID
EVALUABLE PATIENTS	12	9
CURE	11 (92%)	7 (78%)
FAILURE	1 (8%)	2 (22%)

Bacteriologic EfficacySusceptibility of Pathogens:

According to the applicant, among patients with UTI, the most frequently isolated species were *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *P. aeruginosa*. Almost all isolates of these commonly encountered species were susceptible in vitro to both study drugs. In contrast, most species of *Enterococci* were regularly resistant to both cephalosporins.

Table 097.13
Susceptibility of UTI Pathogens to Study Drugs
Study 411-097-OPEN
(Data from Applicant)

Infection Type/ Susceptibility Pathogen	----- Number of Pathogens* -----							
	<u>Cefepime Susceptibility</u>				<u>Ceftazidime</u>			
	Susc.	Inter.	Res.	Total	Susc.	Inter.	Res.	Total
UTI								
Strep. sp.	1			1	1			1
<i>S. faecalis</i>	2	1	3	6	1		4	5
Strep. (alpha hemo.)	1			1	1			1
<i>S. viridans</i>	1			1	1			1
Strep. (Group D)	1			1	1			1
Enterococcus			7	7			7	7
Strep. (Group B)	2			2	2			2
Staph. sp.		1		1			1	1
<i>S. aureus</i>	6	1		7	5	1	1	7
Staph., coagulase (-)			1	1			1	1
<i>Pseudomonas</i> sp.	1			1	1			1
<i>P. aeruginosa</i>	27	2	2	31	29	1	1	31
<i>E. coli</i>	160	2	1	163	162		1	163
<i>C. freundii</i>	1			1	1			1
<i>C. diversus</i>	5			5	4			4
<i>C. amalonaticus</i>	1			1	1			1
<i>Salmonella</i> sp.	1			1	1			1
<i>Salmonella</i> (Group D)	1			1	1			1
<i>Klebsiella</i> sp.	5			5	5			5
<i>K. pneumoniae</i>	30			30	29			29
<i>K. oxytoca</i>	6			6	6			6
<i>Enterobacter</i> sp.	2			2	1		1	2
<i>E. cloacae</i>	6			6	5		1	6
<i>E. aerogenes</i>	5			5	4		1	5
<i>H. alvei</i>	1			1	1			1
<i>S. marcescens</i>	2			2	2			2
<i>P. mirabilis</i>	24			24	24			24
<i>M. morganii</i>	3			3	3			3
<i>P. rettgeri</i>	3			3	3			3
<i>P. stuartii</i>	2			2	2			2
<i>P. penneri</i>	1			1	1			1
<i>E. agglomerans</i>	1			1	1			1
<i>Acinetobacter</i> sp.	1			1				1
<i>Candida</i> sp.			1	1			1	1
Coliforms	2			2	2			2
Total UTI	305	7	15	327	301	2	20	323
Percent	(93)	(2)	(5)		(93)	(<1)	(6)	

COMMENT: Resistance to both drugs was presents in most species of enterococci tested. Small numbers of *E. coli* and *P. aeruginosa* were resistant to both drugs. Of note, *Enterobacter* spp. seemed to be more resistant to ceftazidime than to cefepime. The overall difference in resistance rates is not significant (P=0.45).

Bacteriologic Efficacy at the 5-9 Day Post-Therapy Evaluation:

According to the applicant, overall, 63/71 pathogens (89%) were eradicated in the cefepime treatment group, including 55/61 pathogens (90%) in patients with complicated UTI and 8/10 pathogens (80%) in patients with uncomplicated UTI. In the ceftazidime treatment group, 72/81 pathogens (89%) were eradicated, including 57/64 pathogens (89%) in patients with complicated UTI and 15/17 pathogens (88%) in patients with uncomplicated UTI. At the blinded centers, 12/13 pathogens (92%) were eradicated in the cefepime treatment group and 10/11 pathogens (91%) were eradicated in the ceftazidime treatment group. Table-097.14 presents the applicant's assessment of the bacteriologic response at the 5-9 day evaluation.

Table-097.14
Bacteriologic Efficacy at the 5-9 Day Post-Therapy Assessment
(According to the Applicant)

Parameter	CEFEPIME	CEFTAZID
COMPLICATED UTI		
C. AMALONATICUS	0	1/ 1 (100%)
C. DIVERSUS	2/ 2 (100%)	0
E. AGGLOMERANS	1/ 1 (100%)	0
E. CLOACAE	0	1/ 1 (100%)
E. COLI	33/ 34 (97%)	32/ 34 (94%)
ENTEROBACTER SP.	0	1/ 1 (100%)
H. ALVEI	0	1/ 1 (100%)
K. ORNITHINOLYTICA	0	1/ 1 (100%)
K. OXYTOCA	0/ 1 (0%)	2/ 2 (100%)
K. PNEUMONIAE	8/ 8 (100%)	6/ 7 (86%)
KLEBSIELLA SP.	1/ 1 (100%)	2/ 2 (100%)
P. AERUGINOSA	3/ 5 (60%)	5/ 8 (63%)
P. MIRABILIS	3/ 5 (60%)	4/ 4 (100%)
S. AUREUS	2/ 2 (100%)	0/ 1 (0%)
S. MARCESCENS	0	1/ 1 (100%)
S. VIRIDANS	1/ 1 (100%)	0
STREP. (GROUP B)	1/ 1 (100%)	0
COMPLICATED PATHOGENS	55/ 61 (90%)	57/ 64 (89%)
UNCOMPLICATED UTI		
C. DIVERSUS	1/ 1 (100%)	1/ 1 (100%)
E. CLOACAE	1/ 1 (100%)	0
E. COLI	4/ 6 (67%)	8/ 9 (89%)
K. PNEUMONIAE	0	2/ 2 (100%)
KLEBSIELLA SP.	1/ 1 (100%)	0
P. AERUGINOSA	0	1/ 2 (50%)
P. MIRABILIS	1/ 1 (100%)	1/ 1 (100%)
PSEUDOMONAS SP.	0	1/ 1 (100%)
STREP. (GROUP B)	0	1/ 1 (100%)
UNCOMPLICATED PATHOGENS	8/ 10 (80%)	15/ 17 (88%)
TOTAL PATHOGENS	63/ 71 (89%)	72/ 81 (89%)
BLINDED CENTERS	12/ 13 (92%)	10/ 11 (91%)

COMMENT: The 95% confidence interval around the true difference in eradication rates for the applicant's data is [-11%, +11%] which fulfills the criteria for equivalence by the 95% confidence interval approach.

According to the reviewer, overall 61/76 pathogens (80%) were eradicated in the cefepime treatment group, including 31/42 pathogens (74%) in patients with complicated UTI; 22/25 pathogens (88%) in patients with pyelonephritis; and 8/9 pathogens (89%) in patients with uncomplicated UTI. In the ceftazidime treatment group, 63/75 pathogens (84%) were eradicated, including 33/39 pathogens (85%) in patients with complicated UTI; 19/23 pathogens (83%) in patients with pyelonephritis; and 11/13 pathogens (85%) in patients with uncomplicated UTI.

According to the reviewer, overall at the centers in which the investigations was

conducted in a blinded manner, 10/14 pathogens (71%) were eradicated in the cefepime treatment group and 7/10 pathogens (70%) were eradicated in the ceftazidime treatment group.

E. coli was the most commonly encountered pathogen; it was eradicated in 37/40 infections (93%) in the cefepime treatment group and in 38/42 infections (90%) in the ceftazidime treatment group. *Pseudomonas aeruginosa* was eradicated in 2/6 infections (33%) in the cefepime treatment group and in 3/7 infections (43%) in the ceftazidime treatment group.

Table-097.15
 Bacteriologic Efficacy at the 5-9 Day Assessment
 All Centers
 (According to the Medical Officer)
 Study #097

Parameter	CEFEPIME	CEFTAZID
COMPLICATED UTI		
C. AMALONATICUS	0	1/ 1 (100%)
C. DIVERSUS	0/ 1 (0%)	0
E. AGGLOMERANS	0/ 1 (0%)	0
E. CLOACAE	1/ 1 (100%)	1/ 1 (100%)
E. COLI	18/ 19 (95%)	15/ 15 (100%)
ENTEROBACTER SP.	0	1/ 1 (100%)
H. ALVEI	0	1/ 1 (100%)
K. ORNITHINOLYTICA	0	1/ 1 (100%)
K. OXYTOCĀ	0/ 2 (0%)	1/ 1 (100%)
K. PNEUMONIAE	4/ 5 (80%)	5/ 6 (83%)
KLEBSIELLA SP.	1/ 1 (100%)	1/ 2 (50%)
P. AERUGINOSA	2/ 5 (40%)	2/ 5 (40%)
P. MIRABILIS	3/ 5 (60%)	3/ 4 (75%)
PSEUDOMONAS SP.	0	1/ 1 (100%)
S. AUREUS	1/ 1 (100%)	0
S. VIRIDANS	1/ 1 (100%)	0
COMPLICATED PATHOGENS	31/ 42 (74%)	33/ 39 (85%)
PYELONEPHRITIS		
C. DIVERSUS	1/ 1 (100%)	0
E. COLI	13/ 14 (93%)	17/ 20 (89%)
K. OXYTOCA	0	1/ 1 (100%)
K. PNEUMONIAE	3/ 3 (100%)	0
P. AERUGINOSA	0/ 1 (0%)	0
P. MIRABILIS	1/ 1 (100%)	0
S. AUREUS	3/ 3 (100%)	0/ 1 (0%)
S. FAECALIS	0/ 1 (0%)	0
S. MARCESCENS	0	1/ 1 (100%)
STREP. (GROUP B)	1/ 1 (100%)	0
PYELONEPHRITIS PATHOGENS	22/ 25 (88%)	19/ 23 (83%)
UNCOMPLICATED UTI		
C. DIVERSUS	1/ 1 (100%)	1/ 1 (100%)
E. COLI	6/ 7 (86%)	6/ 7 (86%)
K. PNEUMONIAE	0	3/ 3 (100%)
KLEBSIELLA SP.	1/ 1 (100%)	0
P. AERUGINOSA	0	1/ 2 (50%)
UNCOMPLICATED PATHOGENS	8/ 9 (89%)	11/ 13 (85%)
TOTAL PATHOGENS	61/ 76 (80%)	63/ 75 (84%)
BLINDED CENTERS	10/ 14 (71%)	7/ 10 (70%)

COMMENT: The 95% confidence interval around the true difference in eradication rates (with correction for continuity) is [-17%, +10%] which does not fulfill the criteria for statistical equivalence.

COMMENT: The majority of patients who had persistence of infection were in the complicated UTI sub-group. A demographic analysis of this sub-group shows that both the cefepime and the ceftazidime treatment groups were largely male (cefepime=67%, ceftazidime=83%) which could explain the lower eradication rate seen in this sub-group.

Bacteriologic Efficacy at the 4-6 Weeks Post-Therapy Assessment:

The applicant only evaluated the findings at the 4-6 week assessment for patients with complicated UTI. The results of the 4-6 week post-therapy assessment for the applicant's evaluable population is presented in Table-097.16. There are no significant differences between the treatment groups.

Table-097.16
Bacteriologic Efficacy at the 4-6 Week Post-Therapy Assessment
In Patients with Complicated UTI
(According to the Applicant)
Study #097

Parameter	Number (%)* of Patients	
	Cefepime	Ceftazidime
Number of Patients with Complicated UTI:		
Persistence at Day 5-9	56	58
No follow-up culture	6	7
4-6 week follow-up	37	40
	13	11
Bacteriologic Response at 4-6 Weeks:		
Continued eradication	8 (62)	7 (64)
Eradication with relapse	1 (8)	3 (27)
Eradication with reinfection	2 (15)	1 (9)
Eradication with relapse and reinfection	2 (15)	0

* Percentages are based on all patients with follow-up culture at 4-6 weeks.

The medical officer evaluated the response of all patients assessed at 4 to 6 weeks post-therapy; the information is presented graphically in table-097.17.

In the cefepime treatment group there were 3 patients who experienced a relapse of their original pathogen. Organisms relapsing after treatment with cefepime included *P. aeruginosa* and *P. mirabilis*. In the ceftazidime treatment group there were 7 patients who experienced a relapse with their original pathogen. Organisms relapsing after treatment with ceftazidime included *P. aeruginosa*, *P. mirabilis* and *S. marcescens*. None of the organisms had developed resistance to the study drug during therapy.

There were five reinfections with new organisms among patients in the cefepime treatment group and five reinfections among patients in the ceftazidime treatment group. Reinfections were caused by *Enterococcus* species in all instances except for one cefepime patient who had a reinfection with *C. freundii*.

Table-097.17
 Bacteriologic Efficacy at the 4-6 Week Post-Therapy Assessment
 (According to the Reviewer)
 Study #097

Parameter	Number (%)* of Patients	
	Cefepime	Ceftazidime
Number of Patients:	67	69
Persistence at Day 5-9	12	12
No follow-up culture	38	42
4-6 week follow-up	17 (25)	15 (22)
Bacteriologic Response at 4-6 Weeks:		
Continued eradication	8 (47)	3 (20)
Eradication with relapse	3 (18)	7 (47)
Eradication with reinfection	5 (29)	5 (33)
Eradication with relapse and reinfection	1 (6)	0

* Percentages are based on all patients with follow-up culture at 4-6 weeks.

COMMENT: There is no significant difference between the treatment groups in bacteriologic efficacy at 4 to 6 weeks post-therapy, however, there appears to be a trend to greater numbers of cefepime patients with sustained eradication of pathogens.

Safety Evaluation

COMMENT: According to the applicant, center 027 was not included in the efficacy analysis because of irregularities in the way the pre-treatment cultures were performed. The medical officer agreed with the applicant's decision to exclude the data from center #027 from the efficacy analysis. However, since patients at this center received the study drugs, they will be included in the analysis of drug safety.

Deaths

Thirty-one patients with urinary tract infection died while participating in study 411-097. Seventeen died during or after cefepime treatment; the death rate for cefepime patients was 7.9 deaths per 100 patients exposed. Fourteen patients died during or after ceftazidime treatment; the death rate for patients treated with ceftazidime was 6.1 deaths per 100 patients exposed. The difference in death rates between the two study arms was not statistically significant.

Cefepime Deaths

- The patient was a 72 y.o. female with catheter associated UTI due to *E. coli*. The patient was treated from 9/9 to 9/22/89 with cefepime. The treatment was successful both clinically and bacteriologically. The patient expired on 10/9/89 from respiratory failure. The death was not thought to be related to the urinary tract infection or the study drug therapy.

- The patient was an 82 y.o. female with non-resectable lung cancer. She was treated with cefepime for urosepsis due to *P. mirabilis*. After 2 days of therapy the patient died of respiratory failure. The death was attributed to complications of her underlying carcinoma.

- The patient was a 67 y.o. male with quadriplegia. The patient was treated with cefepime for an uncomplicated UTI due to *P. aeruginosa* and *P. mirabilis*. The patient developed pneumonia while on therapy and died after four days of treatment.

- The patient was a 72 y.o. male with multiple medical problems. The patient was treated with cefepime for an enterococcal UTI. The patient died two months after the completion of treatment from respiratory arrest.

- The patient was a 54 y.o. female with cervical cancer. The patient was treated with cefepime for a complicated UTI due to *Staphylococcus spp.* with cefepime. The patient worsened on therapy. After three days antimicrobial therapy was changed to imipenem/cilastatin. The patient continued to deteriorate, however, and eventually died of sepsis.

- The patient is an 85 y.o. female with history of NIDDM and CVA. The patient was treated for a catheter associated UTI due to *E. coli* with cefepime. Nine days after treatment the patient died of thrombo-embolic phenomena. The death was not felt to be related to the underlying infection or the study drug therapy.

The patient was a 62 y.o. male who was admitted in an unresponsive state secondary to a brain stem infarct. The patient developed UTI due to *E. coli* which was treated with cefepime. On the first day of therapy, the patient died of complications of his intracerebral infarct.

- The patient is a 78 y.o. female who was admitted for treatment of pneumonia. The pneumonia resolved on treatment with penicillin, keflin and gentamicin but the patient developed a UTI due to *S. marcescens*. The patient was treated with cefepime from 11/25 to 12/6/89. On 12/7/89 the patient died of cardiac arrest.

- The patient was an 85 y.o. female admitted for treatment of a fractured right hip. The patient developed a post-operative wound infection and also a urinary tract infection due to *E. coli*. The patient received cefepime from 2/7/90 to 2/20/90 but did not respond to therapy. The patient died of septic shock.

- The patient was an 83 y.o. female with an acute myocardial infarction who developed a post-operative (post-CABG) UTI with *P. mirabilis*. The patient was treated with cefepime but developed a reinfection with *P. aeruginosa* after therapy. The patient died secondary to aortic rupture 3 weeks after the completion of cefepime treatment.

- The patient was a 76 y.o. female with steroid dependent rheumatoid arthritis and thoracic cord compression. The patient was treated with cefepime for a complicated UTI due to *P. aeruginosa*. The patient died approximately 2 weeks after the completion of therapy. It was the opinion of the investigator that the patient died due to her underlying disease.

- The patient was an 86 y.o. female who was admitted for treatment of a Mallory-Weiss tear of the esophagus. The patient developed a UTI due to *K. pneumoniae* which was treated with cefepime for 9 days. The patient developed a CVA while on therapy and died of complication of the CVA.

- The patient is a 68 y.o. male with lymphoma who was treated with cefepime for a UTI due to *K. oxytoca* and *K. pneumoniae*. The patient appeared to respond to therapy but developed pneumonia and died of complications of pneumonia.

- The patient was an 81 y.o. female with LRTI and bacteremia due to *S. pneumoniae* and a UTI due to Group B Streptococcus. The patient was treated with cefepime from 3/1/90 to 3/6/90. The patient's condition worsened on therapy; she developed ARDS and became ventilator dependent. The antimicrobials were changed to vancomycin and ceftazidime but the patient died on 3/21/90.

- The patient was a 66 y.o. male who was admitted for weakness and pelvic pain. The patient had a history of adenocarcinoma of the colon and rectum with metastasis to the lungs, liver, bones and brain. The patient developed an *E. coli* UTI and was treated with cefepime from 5/10/90 to 5/15/90. The patient had a good response to treatment but died on 5/19/90 due to complication of his metastatic disease.

- The patient is a 72 y.o. female who was admitted for treatment of urosepsis with *K. pneumoniae* and *E. coli*. The patient was treated with cefepime from 12/7/90 to 12/20/90. While hospitalized, the patient was diagnosed with large cell liver carcinoma. The patient was taken off the study drugs and placed on "DNR" status. The patient expired on 1/3/91.

- The patient was a 62 y.o. female who was treated for urosepsis and pyelonephritis due to *E. coli* with cefepime. Seven hours after enrollment the patient became bradycardic and developed cardiac arrest. The patient's death was thought to be due to overwhelming Gram negative sepsis.

COMMENT: No deaths were directly attributable to the administration of

cefepime. Four patients had death due to worsening or progression of their infection.

Ceftazidime Deaths

- The patient was a 71 y.o. female with severe rheumatoid arthritis which was treated with immunosuppressive therapy. The patient was enrolled for treatment of pyelonephritis due to *E. coli*. The patient was treated with ceftazidime for two days. The patient expired during therapy from complication of *P. carinii* pneumopathy.

- The patient was 97 y.o. female with pneumonia and UTI due to *P. aeruginosa*. The patient was treated with ceftazidime from 2/22/89 to 3/3/89. The patient was believed to have initially responded to treatment but the patient respiratory status deteriorated. The patient died on 3/4/89. The investigator felt that both the patient's underlying health status and the acute infection contributed to the death.

- The patient was a 68 y.o. male who was admitted for treatment of a syncopal episode. The patient developed a catheter associated UTI due to *P. aeruginosa*. The patient was treated with ceftazidime from 9/5/89 to 9/14/89. The patient became comatose and eventually died of cardiac arrest on 10/25/89, over 1 month after completing the study treatment.

- The patient was a 97 y.o. male with prostatic carcinoma with metastasis to bone. The patient was enrolled for treatment of a complicated UTI due to *P. aeruginosa*. The patient was treated with ceftazidime from 10/1/89 to 10/11/89. Three days after the completion of therapy the patient developed respiratory distress. The patient was placed on "DNR" status and died on 10/21/89.

- The patient was a 79 y.o. male with a history of multiple medical problems including coronary artery disease, Paget's Disease and multiple CVA. The patient was admitted in congestive heart failure due to papillary muscle dysfunction. The patient was treated with ceftazidime from 2/19/90 to 3/3/90 for a complicated UTI due to *E. aerogenes*, *P. aeruginosa* and Group D Enterococcus. The patient died on 3/3/90 due to multi-organ system failure.

- The patient was a 56 y.o. male with multiple cranial nerve palsies; he had respiratory failure which made mechanical ventilation necessary. The patient was enrolled for a UTI due to *S. marcescens*. The patient was treated with ceftazidime from 7/26/89 to 8/7/89. The patient was reported to respond both clinically and bacteriologically. During the hospitalization, the patient developed a tracheo-esophageal fistula which resulted in massive aspiration and death on 8/23/89.

- The patient was an 83 y.o. male who was admitted for the treatment of bronchopneumonia. The patient was treated with multiple antimicrobials with good response. The patient developed a UTI due to *S. marcescens* and was treated with ceftazidime from 10/10/89 to 10/21/89. The patient was reported to respond to treatment both clinically and bacteriologically. On 10/20/89 the patient suffered a brain stem infarct and died on 10/25/89.

The patient was a 77 y.o. male with steroid dependent COPD who presented with an acute exacerbation of COPD. The patient required intubation and mechanical ventilation. During the hospitalization, the patient was diagnosed with an abdominal aortic aneurysm which was resected. Post-operatively, the patient developed a UTI due to *E. coli* and was treated with ceftazidime from 5/25/89 to 6/3/89. The patient recovered from his UTI but not from his underlying

illness.. The patient requested withdrawal of life support and died on 8/3/89.

- The patient was an 86 y.o. female who was admitted for the treatment of urosepsis due to *E. coli*. The patient was treated with ceftazidime from 7/19/90 to 8/1/90. The patient responded both clinically and bacteriologically. On 8/16/90 the patient died from a cardiac arrhythmia.

- The patient was a 64 y.o. female with multiple myeloma. The patient was admitted for treatment of a septic ankle. Blood, urine and synovial fluid all yielded *E. coli*. The patient was treated with ceftazidime from 10/6 to 10/27. The patient responded both clinically and bacteriologically. During the hospitalization the patient's mental status deteriorated and she died on 10/31. No explanation was found for the deterioration of the patient's condition.

- The patient was an 84 y.o. female who was admitted for the treatment of a hip fracture with a total hip replacement. After surgery the patient developed pneumonia and UTI due to *P. aeruginosa*. The patient was treated with ceftazidime from 3/29 to 4/7. The patient improved clinically. The patient died suddenly and unexpectedly on 4/7. The cause of death was not known.

- The patient was a 38 year old Black female with a history of intravenous drug abuse and HIV infection. The patient presented with generalized weakness, anorexia, dysphagia and right flank pain. The patient was treated for two days with ceftazidime for a non-hemolytic *Streptococcal* UTI. The patient died on March 3, 1990 from cryptococcal meningitis.

- The patient was a 94 y.o. female who was admitted with urosepsis and pneumonia due to *E. coli*, *K. pneumoniae* and *C. amalonaticus*. The patient was treated with ceftazidime from 5/24 to 6/6. The patient was reported to respond to therapy both clinically and bacteriologically. Three days after the completion of therapy, the patient developed congestive heart failure. The patient was placed on "DNR" status and expired on 6/9.

- The patient was a 54 y.o. male with alcoholic cirrhosis and portal hypertension. The patient was admitted for treatment of pyelonephritis due to *K. ornitholytica*. The patient was treated with ceftazidime from 8/9/91 to 8/26/91. The patient died of a gastrointestinal hemorrhage.

COMMENT: No patients died as a direct result of ceftazidime toxicity. No patients were thought, by the investigator involved, to have died from progression of their infectious process. Of interest, a majority of the patients who died had infections with *P. aeruginosa*.

DISCONTINUATIONS

Study drug was discontinued from six patients in the cefepime treatment group and from three patients in the ceftazidime treatment group for adverse drug effects. The most common reason for discontinuation of cefepime was the occurrence of a rash.

Cefepime Discontinuations

- Discontinued after 10 days of therapy for whole body rash.
- Discontinued after 5 days of therapy due to fever and rash.
- Discontinued after 5 days due to generalized macular rash.
- Discontinued after 7 days due to rash.

- Discontinued after 2 days due to generalized pruritus and rash.
- After one dose of cefepime, the patient developed hypotension during a surgical procedure. The physician elected to start broad-spectrum antimicrobial coverage post-operatively.

Ceftazidime Discontinuations

- Discontinued after 8 days because of leukopenia (WBC=1.8).
- Discontinued after 2 days due to rash.
- The patient is a 32 year old woman with pyelonephritis who discontinued therapy due to nausea and vomiting.

Clinical Adverse Drug Events

According to the medical officer, clinical adverse drug events (CADE) were reported in 74/215 (34%) of patients in the cefepime treatment group and in 78/225 patients (35%) in the ceftazidime treatment group. There was no statistically significant difference in the rate of occurrence of CADE.

Most CADE were of mild of moderate severity. The most commonly affected organ systems were the gastrointestinal and nervous systems. The most commonly reported CADE in the cefepime treatment group was headache while the most commonly reported CADE in the ceftazidime treatment group was diarrhea.

Table-097.18 lists CADE by severity and body system involved.

Table-097.18
Clinical Adverse Events
(According to the Reviewer)
Study #097

System/ Effect	Cefepime					Ceftazidime				
	Mild	Mod	Sev	NC	Tot	Mild	Mod	Sev	NC	Tot
Body as Whole¹	6	-	2	1	4	1	1	-	1	3
Allergic Rxn.	1	-	-	-	1	-	-	-	-	-
Anemia	1	-	-	-	1	-	-	-	-	-
Cold/Chills	1	-	2	-	3	1	-	-	-	1
Diaphoresis	2	-	-	-	2	-	-	-	-	-
Fatigue	-	-	-	-	-	-	-	-	1	1
Fever	2	-	-	1	3	-	1	-	-	1
Myalgia	1	-	-	-	1	-	-	-	-	-
Sweats	1	-	-	-	1	-	-	-	-	-
Cardiovascular	7	8	3	3	21	7	-	4	-	11
Angina	-	-	1	-	1	-	-	-	-	-
Arrhythmia	5	7	1	-	13	1	-	-	-	1
Cong Heart Fail	-	-	-	-	-	-	1	1	-	2
Edema, Extr	3	-	-	-	3	1	1	-	-	2
Edema, General	1	-	-	-	1	2	-	-	-	2
Edema, Pul	-	2	1	-	3	-	-	2	-	2
Embolus	-	-	1	-	1	-	-	-	-	-
Flushing	-	1	-	-	1	-	-	-	-	-
Hypertension	-	-	-	-	-	2	-	-	-	2
Hypotension	1	-	3	-	4	1	-	-	-	1
Gastrointestinal	23	9	-	3	35	27	13	-	3	43
Anorexia	-	1	-	-	1	-	-	-	-	-
Bleeding, GI	-	-	-	-	-	-	-	1	-	1
Candidiasis, Oral	-	1	-	-	1	1	2	-	-	3
Colitis, Pseud.	-	-	-	1	1	-	-	-	-	-
Constipation	9	1	1	1	12	6	-	-	2	8
Diarrhea	4	2	-	1	7	9	4	-	1	14
Emesis	9	2	-	-	11	6	2	-	-	8
Hematemesis	1	-	-	-	1	-	-	-	-	-
Hematochezia	-	1	-	-	1	-	1	-	-	1
Incontinence	-	-	-	-	0	-	1	-	-	1
Indigestion	2	2	-	-	4	3	-	-	-	3
Ischemia, Bowel	-	-	-	-	-	-	1	-	-	1
Melena	-	-	-	-	-	2	-	-	-	2
Nausea	7	1	-	1	9	6	1	-	-	7
Pain, Abd	2	1	1	-	4	2	-	-	-	2
Pain, Rectal	-	-	-	-	-	1	-	-	-	1
Pain, Teeth	-	-	-	-	-	-	-	-	1	1
Pain, Throat	-	-	-	-	-	1	2	-	1	3
Ulcers, Mouth	-	-	-	-	-	1	1	-	-	2
Genito-Urinary	4	2	-	2	8	6	4	-	-	10
Candida, Vag	-	-	-	-	-	1	1	-	-	2
Edema, Scrotal	-	-	-	-	-	-	2	-	-	2
Hematuria	1	-	-	-	1	-	-	-	-	-
Herpetic Lesions	-	-	-	-	-	-	-	-	1	1
Hypokalemia	1	-	-	-	1	-	-	-	-	-
Inflammation, groin	2	-	-	1	3	-	-	-	-	-
Incontinence	-	-	-	-	-	-	1	-	-	1
Kidney Fail.	-	-	-	1	1	-	-	-	-	-
Vaginitis	-	1	-	-	1	2	-	-	-	2
Pruritus, Vagin.	-	1	-	-	1	3	-	-	-	3
Musculo-skeletal	8	2	1	1	12	6	5	-	3	14
Pain, Back	1	-	-	1	2	-	-	-	-	-
Pain, Chest	5	1	1	-	7	2	2	-	2	6
Pain, Extr	1	-	-	-	1	2	3	1	2	8
Pain, Face	-	-	-	-	-	-	-	-	1	1
Pain, Neck	2	-	-	-	2	1	-	-	-	1
Pain	-	1	-	-	1	-	-	-	-	-

Table 19 - Continued
Adverse Clinical Events
 (According to the Medical Officer)
 Study 411-097-OPEN

System/ Effect	Cefepime					Ceftazidime				
	Mild	Mod	Sev	NC	Tot	Mild	Mod	Sev	NC	Tot
Neurological	16	9	4	2	31	17	14	-	3	34
Agitation	-	1	1	-	2	-	2	-	-	2
Anxiety	-	1	-	-	1	2	3	-	-	5
Coma/Stupor	-	-	1	-	1	-	-	1	-	1
Confusion	2	1	2	-	5	-	2	-	-	2
Depression	-	-	-	-	-	1	2	-	-	3
Dizziness	1	-	-	-	3	-	1	-	1	2
Headache	9	6	-	3	18	7	-	-	1	8
Insomnia	1	2	-	-	3	5	1	-	-	6
Lethargy	-	-	1	-	1	-	-	-	-	-
Paresthesia	3	-	-	-	3	1	-	-	-	1
Seizure	-	-	1	-	1	-	2	1	-	3
Syncope	-	-	-	-	-	1	-	-	-	1
Tremor	1	-	-	-	1	-	-	-	-	-
Respiratory	5	2	-	1	8	5	3	2	2	12
Air Leak	-	-	-	-	-	-	1	1	-	2
Asthma	1	-	-	-	1	-	-	-	1	1
Congest, Sinus	-	-	-	-	-	1	-	-	-	1
Cough	1	-	-	-	1	1	2	-	-	3
Distress, Resp	1	2	-	1	4	2	-	1	2	5
Effusion, Pleur	-	-	-	-	-	-	1	-	-	1
Epistaxis	1	-	-	-	1	1	-	-	-	1
Hiccups	-	-	-	-	-	-	1	-	-	1
Tachypnea	1	-	-	-	1	-	-	-	-	-
Rales	1	-	-	-	1	2	-	-	-	2
Special Senses	-	-	-	-	-	2	1	-	-	3
Blurred Vision	-	-	-	-	-	1	1	-	-	2
Redness, Eye	-	-	-	-	-	1	-	-	-	1
Skin	8	4	-	1	13	16	6	-	-	22
Blisters	-	-	-	-	-	1	-	-	-	1
Cracked lips	-	-	-	-	-	-	1	-	-	1
Hives	2	-	-	-	2	1	1	-	-	2
Peeling, Extr	-	-	-	-	-	1	-	-	-	1
Pruritus	4	2	-	-	6	1	2	-	-	3
Rash	2	1	-	1	4	11	4	-	-	15
Redness, Extr	-	-	-	-	-	1	1	-	-	2
Zoster, Exacer	-	-	-	-	-	1	-	-	-	1
Total Open Centers	20	10	9	15	54	29	17	7	11	64
Total Blinded Cens.	8	7	2	3	20	6	8	0	0	14
Total All Centers	28	17	11	18	74	35	25	7	11	78
Percent	38%	23%	15%	24%		45%	32%	9%	14%	

¹Organ system totals represent number of patients experiencing an adverse event in that organ system and are not column totals. When one patient experiences more than one adverse event in a given organ system, the most severe event is reflected in the organ system total.

²Totals are number of patients who experienced an adverse event of the indicated severity and are not column totals. When one patient experiences more than one adverse event the most severe event is reflected.

Local Reactions at the Infusion Site

Reactions at the infusion site occurred in 16/215 patients (7%) exposed to cefepime and in 10/225 patients (4%) exposed to ceftazidime. The difference in the incidence of local reactions at the infusion site between the two groups is not significant ($X^2=1.78$, $p>0.05$).

Laboratory Test Abnormalities

The data in this application was not organized in such a way that the laboratory adverse drug events that occurred in the UTI patients could be separated from the laboratory adverse drug events that occurred in patients studied for other possible indications under protocol 097. Laboratory adverse events occurring in patients with UTI will not be presented from study #097, however, they will be included in the final integrated summary of UTI safety at the end of this review.

Conclusions

Study #097 was a multi-center, North-American study which sought to evaluate the safety and efficacy of a high-dose (2 grams Q12h) of cefepime in comparison to a high-dose of ceftazidime (2 grams Q8h) for the treatment of patients with septicemia or severe localized infections. In all patients the study drug was administered intravenously.

Patients with both complicated and uncomplicated UTI were studied. In the overall population, most patients were white females, however, in the sub-population of complicated UTI patients, most patients in both treatment groups were males.

Considering the bacteriologic response at 5 to 9 days post-therapy as the primary determinant of efficacy in UTI, according to the medical officer, the eradication rate in the cefepime treatment group was 61/76 (80%). In contrast, the overall eradication rate among patients in the ceftazidime treatment group was 63/75 (82%). Among patients with complicated UTI (including pyelonephritis), the eradication rate in the cefepime treatment group was 53/67 (79%), the eradication rate in the ceftazidime treatment group was 52/62 (84%). The 95% confidence interval around the true difference in eradication rates in patients with complicated UTI was [-20%, +10%], therefore, equivalence was not demonstrated between the two treatment groups.

With regard to patients with uncomplicated UTI, the bacteriologic eradication rate at 5-9 days post-therapy in the cefepime treatment group was 8/9 (89%) and 11/13 (85%) in the ceftazidime treatment group. The number of patients enrolled makes confidence interval analysis superfluous.

With regard to the outcome at the blinded centers, the microbiologic response for all patients in the cefepime treatment group was 10/14 (71%). The microbiologic response for patients in the ceftazidime treatment group was 7/10 (70%). Although the two bacteriologic outcomes appear similar, again the number of patients involved is too small for useful confidence interval analysis.

If the applicant's analysis of the data is used, then equivalence is demonstrated by the 95% confidence interval approach. (95% C.I.: [-11, +11]).

The major difference between the applicant's evaluable data pool and the reviewer's evaluable data pool was the inclusion by the reviewer of several patients who were placed on alternative antimicrobial drugs prior to their post-therapy culture for the persistence or worsening of presenting symptoms. These patients were assigned the outcome of both clinical and bacteriologic failure. In all cases, patients received at least 3 days of study drug therapy before they were declared a failure by the medical officer.

Good eradication rates for *E. coli* were reported for both cefepime and ceftazidime, however, in study #097 both drugs performed poorly in treating infections caused by *P. aeruginosa*.

With regard to the clinical outcome, in the cefepime treatment group 57/67 patients (85%) were clinically cured by 5-9 days post-therapy. In the ceftazidime treatment group, 52/69 patients (75%) were clinically cured by the end of therapy.

Many patients died in both treatment groups in study #097. In the opinion of the medical officer this reflects the serious underlying pathology present in the patients recruited into this study. There were no significant differences in the rate of deaths, discontinuations of therapy or clinical adverse events between the two treatment groups. Laboratory adverse events were not examined because data for UTI patients was not supplied by the applicant.

EUROPEAN COMPARATIVE STUDIES**PROTOCOL: 411-083 (EUROPEAN CENTERS)****Introduction**

The objectives and investigational plan of study 411-083 conducted at the European centers are the same as those used for the North American Centers. Briefly, to review, study #411-083 is an open, randomized comparative study conducted at nine centers in Europe. The protocol called for the enrollment of patients with acute UTI that was suspected to be complicated. At each centers, patients were randomly assigned to receive either cefepime or ceftazidime in a 2:1 (cefepime:ceftazidime) ratio. Patients randomized to cefepime received 500 mg every 12 hours for up to 14 days. Patients randomized to ceftazidime received 500 mg every 8 hours for up to 14 days. The readers is referred to that portion of the review which discusses 411-083 - North American centers for further details(pp.34).

Population Studied**Enrollment and Evaluability"**

Table-083E.1 lists the enrollment at each of the nine centers involved in the study. All patients enrolled received at least one dose of cefepime or ceftazidime and therefore were evaluable for the assessment of safety.

Table-083E.1 also lists the applicant's and the medical officer's assessment of the number of patients evaluable for the efficacy assessment at each study center.

Table - 083E.1
Enrollment and Evaluability
Study #083 - European Centers

Center	Principal Investigator	Location	Enrol	Number of Patients				
				<u>Cefepime</u>		<u>Ceftazidime</u>		
				BMS	MO	Enrol	BMS	MO
I-018	H. Van Landuyt	Brugge, Belgium	4	1	1	2	1	1
I-021	A. Bertrand	Montpellier, France	1	0	0	1	0	0
I-025	J. Jourdan	Nimes, France	5	2	2		3	2
I-028	K. Naber	Straubin, Germany	16	10	10	14	5	6
I-031	D. Peyramond	Lyon, France	0	0	0	1	0	0
I-034	J. Estavpuer	Besancon, France	1	0	0	1	1	1
I-036	N. Brion	Aubervilliers, Frn.	18	5	5	7	2	4
I-044	P. Dellamonica	Nice, France	13	2	2	6	3	3
I-052	J. Kosmidis	Athens, Greece	1	1	1	1	1	1
TOTAL			59	21	21	36	16	18
Percent				36%	36%		44%	50%

Summary of Non-Evaluability:

Table-083E.2 presents the major reasons that patients were considered not evaluable by the sponsor for the efficacy assessment. Some patients may have more than one reason for which they were excluded by the applicant.

Table - 083E.2
Reasons for Exclusion from the Efficacy Analysis
(According to the Applicant)
Study #083 - European Centers

Reason*	Number (%) of Unevaluable Infections	
	Cefepime N=59	Ceftazidime N=36
NUMBER EXCLUDED:	N = 38	N = 20
<u>Pre-treatment :</u>		
Pre-treatment culture out of window	13 (34)	1 (5)
Pre-treatment colony count < 100,000	3 (8)	2 (10)
Asymptomatic UTI	4 (11)	0
No pathogen isolated	3 (8)	1 (5)
Resistant organism	1 (3)	3 (15)
No sensitivity testing done	1 (3)	2 (10)
Pre-treatment visit out of window	2 (5)	0
Other antibiotic given after pre-culture	1 (3)	0
Problem with diagnosis	0	1 (5)
<u>During-treatment :</u>		
Incomplete treatment	4 (11)	0
No during-therapy culture	3 (8)	1 (5)
Improper dosage	0	1 (5)
<u>Post-treatment :</u>		
Post-treatment visit out of window	9 (24)	8 (40)
Post-treatment culture out of window	7 (18)	6 (30)
No post-treatment culture	5 (13)	2 (10)
No 5-14 days urine culture obtained	2 (5)	4 (20)
Other antibiotic given before post-culture	4 (11)	0
No post-treatment clinical assessment	3 (8)	0
Other antibiotic given before post clinical	2 (5)	0
Patient lost to follow up	1 (3)	0
Total Evaluable	21 (39)	16 (44)

COMMENT: The most common reason that patients who were randomized to cefepime were excluded from the analysis of efficacy was a failure to perform the pre-treatment culture within the specified window period (34%), however, only 5% of patients randomized to ceftazidime were excluded for this reason. There is no information on the reason why this deficiency occurred more frequently in the cefepime group.

Table-083E.3 summarizes the reasons that patients were excluded from the assessment of efficacy by the medical officer. As was the case with the

applicant, the medical officer excluded the majority of patients from the cefepime group for the failure to properly perform the pre-treatment culture. In the ceftazidime group, the majority of patients were considered not evaluable for the failure to properly obtain the post-treatment culture.

Table - 083E.3
Reasons for Exclusion from the Efficacy Analysis
(According to the Reviewer)
Study #083 - European Centers

Reason*	Number (%) ¹ of Unevaluable Infections	
	Cefepime N=59	Ceftazidime N=36
TOTAL EXCLUDED:	N = 38	N = 18
No Pre-Treatment Assess. or Out of Window	12 (20)	1 (3)
No Pathogen or < 10 ⁵ CFU	6 (10)	2 (6)
Asymp. Bacteruria/Only 1 Culture	4 (7)	1 (3)
Resistant Organism	1 (2)	3 (8)
No During Therapy Culture or Out of Window	3 (5)	1 (3)
Other Anti-Microbial Administered	2 (3)	0
Incomplete Treatment		
Due to ADR	2 (3)	0
Due to Death	1 (2)	0
Due to Secondary Infection	1 (2)	0
Protocol Error ²	0	1 (3)
No Post-Treatment Asses. or Out of Window	6 (10)	9 (25)
TOTAL EVALUABLE:	21	18

- 1 The numbers in parenthesis are percent of total patient enrolled.
2 Includes: incorrect dose of drug administered.

Applicant and Reviewer Evaluability Differences:

The applicant and the medical officer agreed on the evaluability of all patients in the cefepime treatment group.

The applicant and the medical officer differed on the evaluability of four patients in the ceftazidime treatment group. Three patients were considered not-evaluable by the applicant and evaluable by the medical officer: one patient was excluded for "no post-treatment culture", however, an appropriate post-treatment culture was recorded; one patient was excluded for "problem with diagnosis", however, all the required information appeared to be recorded on the case report form; one patient was excluded for "post-treatment culture out of window", however, this patient developed a superinfection during treatment and therefore did not require a post-treatment evaluation. One patient was considered evaluable by the applicant and not-evaluable by the medical officer, this patient had asymptomatic bacteriuria with only 1 pre-treatment culture documented.

Demographic Characteristics:

Table - 083E.4 presents the demographic characteristics of the enrolled population.

Most patients in both treatment groups were white females. The age distribution was similar between the two treatment groups.

Table - 083E.4
Demographic Characteristics of the Enrolled Population
Study #083 - European Centers

Characteristic	Cefepime	Ceftazidime
N	59	36
Sex: N (%)		
Female -	34 (58)	17 (52)
Male	25 (42)	19 (53)
Race: N (%)		
White	57 (98)	36 (100)
Other	1 (2)	0
Not Recorded	1 (2)	0
Age Distribution: N (%)		
18 - 24 yr	2 (3)	1 (3)
25 - 44 yr	5 (8)	2 (6)
45 - 64 yr	7 (12)	5 (14)
65 - 84 yr	35 (59)	25 (69)
85 - 100 yr	10 (17)	3 (8)
Age: (years)		
Mean	69.4	69.8
Median	75	75
S.D.	17.8	15.4
Minimum	18	23
Maximum	90	94

Table-083E.5 presents the demographic characteristics of the applicant's and the medical officer's evaluable population.

Table - 083E.5
Demographic Characteristics of the Evaluable Population
Study #083 - European Centers

Characteristic	Number (%) of Patients			
	Medical Officer		Applicant	
	Cefepime N = 21	Ceftazidime N = 18	Cefepime N = 21	Ceftazidime N = 16
Sex				
Female -	10 (48)	10 (56)	10 (48)	10 (63)
Male	11 (52)	8 (44)	11 (52)	6 (38)
Race				
White	21(100)	18 (100)	21 (100)	16 (100)
Other	0	0	0	0
Age distribution (years)				
18-24	0	0	0	0
25-44	3 (14)	0	3 (14)	0
45-64	3 (14)	4 (22)	3 (14)	4 (25)
65-84	14 (67)	12 (67)	14 (67)	10 (63)
≥85	1 (7)	2 (11)	1 (5)	2 (13)
Age (years)				
Mean	64.3	71.0	64.3	70.3
Median	-	-	67	72
S.D.	-	-	16.2	12.7
Minimum	30	51	26	49
Maximum	85	87	85	90

COMMENT: There were no significant differences in demographic variable between the two treatment groups in either the applicant's or the reviewers evaluable populations

Medical History:

Table GR3E.6 presents the medical conditions relevant to the genitourinary tract in evaluable patients.

Table - 083E.6
Relevant Medical Conditions in Evaluable Patients
Study #083 - European Centers

Parameter	Number (%) of Patients	
	Cefepime N = 21	Ceftazidime N = 16
<u>Applicant's Analysis</u>		
	N = 21	N = 16
Complicated	13 (62)	8 (50)
Uncomplicated	7 (33)	7 (44)
Unable to determine	1 (5)	1 (6)
<u>Reviewer's Analysis</u>		
	N=21	N=18
Complicated	13 (67)	9 (50)
Anatomic Abnormality	3	0
BPH	2	2
Catheter Assoc.	2	0
Functional Abnormality	0	0
Neoplasm	4	5
Obstructive Uropathy	0	2
Stones	2	0
Pyelonephritis	1 (5)	1 (6)
Uncomplicated	7 (33)	8 (44)

COMMENT: According to both the applicant and the reviewer, most patients in both treatment groups had complicated UTI. According to the reviewer, the most frequently seen conditions complicating the UTI was the history or presence of a urinary tract neoplasm.

Concomitant Medications:

According to the applicant, twenty-two (96%) of the 23 patients evaluable for the primary efficacy analysis in the cefepime group received at least one concomitant drug and 8 (35%) received at least one concomitant non-drug therapy. Fifteen (94%) of the 16 patients evaluable for the primary efficacy analysis in the ceftazidime group received at least one concomitant drug and 4 (25%) received at least one concomitant non-drug therapy.

There was no statistically significant difference between the two treatment groups with regard to the use of concomitant therapy ($p=1.000$), and to the use of concomitant non-drug therapy ($p=0.726$).

Study Drug Administration:

All patients in the cefepime group received a dose of 500 mg Q12h. All patients in the ceftazidime group received a dose of 500 mg Q8h.

Table - 083E.7 presents the duration of study drug administration for the applicant's and the reviewer's evaluable population. Patients in the cefepime treatment group were treated for a slightly shorter period of time than patients in the ceftazidime group.

Table - 083E.7
Study Therapy for UTI Patients
Study #083 - European Centers

Parameter	Reviewer		Applicant	
	Cefepime 500mg Q12h N = 21	Ceftazidime 500mg Q8h N = 18	Cefepime 500mg Q12h N = 21	Ceftazidime 500mg Q8h N = 16
Duration of dosing* (Days)				
< 4	1 (5%)	0	0	0
4 < 7	14 (67%)	10 (56%)	9 (43%)	6 (38%)
7 < 10	4 (19%)	5 (28%)	10 (48%)	7 (44%)
10 < 15	2 (10%)	2 (11%)	2 (9%)	2 (13%)
≥ 15	0	1 (6%)	0	1 (6%)
Mean	7.2	7.8	6.9	7.5
Median	8.0	9.0	7.0	7.0

EFFICACY EVALUATION**Clinical Efficacy**

Table-083E.8 presents the clinical response to treatment for the applicant's evaluable population.

Table - 083E.8
Clinical Efficacy
(According to the Applicant)
Study #083 - European Centers

Classification	Number (%) of Infections			
	Cefepime		Ceftazidime	
	Sat.	Unsat.	Sat.	Unsat.
	N = 21		N = 16	
Complicated	13 (87)	2 (15)	7 (88)	1 (12)
Uncomplicated	6 (100)	0	8 (100)	0
Overall	19 (90)	2 (10)	15 (94)	1 (6)

Table-083E.9 presents the clinical efficacy as determined by the medical officer.

Table-083E.9
Clinical Efficacy
(According to the Reviewer)
Study #083 - European Centers

Parameter	CEFEPIME	CEFTAZID
NO. OF EVALUABLE PATIENTS	21	18
CURE	15 (71%)	12 (67%)
IMPROV	1 (5%)	3 (17%)
UNDET	0	1 (6%)
FAILURE	5 (24%)	2 (11%)
COMPLICATED UTI	13	9
CURE	7 (54%)	6 (67%)
IMPROV	1 (8%)	2 (22%)
FAILURE	5 (38%)	0
UNDET	0	1 (11%)
PYELONEPHRITIS	1	1
CURE	1 (100%)	0
FAILURE	0	1 (100%)
UNCOMPLICATED UTI	7	8
CURE	7 (100%)	6 (75%)
IMPROV	0	1 (13%)
FAILURE	0	1 (13%)

COMMENT: Overall, there were no significant differences noted between the

treatment groups in the proportion of patients who achieved a clinical cure. The numbers of patients involved in the sub-groups are too small to form statistically significant conclusions.

Bacteriologic Efficacy:

Susceptibility of Pathogens:

According to the applicant, one hundred and eight pathogens were isolated in pre-study culture from 91 of the 95 patients. Of these 108 pathogens, 4 were not tested for susceptibility to cefepime. Of the remaining 104 pathogens, 98 (94%) were susceptible to cefepime, 2 (2%) were of intermediate sensitivity and 4 (4%) were resistant. The 4 resistant pathogens were 3 *Streptococcus faecalis* and 1 *Streptococcus faecium*. Three of these 4 pathogens were also resistant to ceftazidime and one *Streptococcus faecalis* was found of intermediate sensitivity to ceftazidime. However, this pathogen was found of intermediate sensitivity to cefepime and resistant to ceftazidime by MIC method.

Susceptibility results are listed by organism in Table 083E.10.

Table 083E.10
Susceptibility to Cefepime of Initial Pathogen
All Patients
Study 411-083 Europe
(According to the Applicant)

Organism	NUMBER (%) OF TESTED ISOLATES *				
	Susceptible	Intermediate	Resistant	Not Done	Total
<i>C. freundii</i>	1 (100)				1
<i>E. aerogenes</i>	1 (100)				1
<i>E. agglomerans</i>	1 (100)				1
<i>E. cloacae</i>	7 (100)				7
<i>E. coli</i>	45 (100)			3	48
<i>K. oxytoca</i>	1 (100)				1
<i>K. pneumoniae</i>	6 (100)				6
<i>M. morgani</i>	1 (100)				1
<i>P. aeruginosa</i>	5 (100)				5
<i>P. mirabilis</i>	11 (92)	1 (8)		1	13
<i>P. stuartii</i>	2 (100)				2
<i>S. epidermidis</i>	5 (83)	1 (17)			6
<i>S. faecium</i>	0		1 (100)		1
<i>S. haemolyticus</i>	1 (100)				1
<i>S. marcescens</i>	3 (100)				3
<i>S. aureus</i>	4 (100)				4
<i>S. faecalis</i>	1 (25)		3 (75)		4
<i>S. hominis</i>	1 (100)				1
<i>S. liquefaciens</i>	1 (100)				1
<i>S. mitis</i>	1 (100)				1
Total	98 (94)	2 (2)	4 (4)	4	108

Bacteriologic Efficacy at the 5 to 9 Days Post-Therapy Evaluation:

Table 083E.11 summarizes the applicant's determination of the bacteriologic response at 5 to 9 days post-treatment. According to the application, overall 15/22 pathogens (68%) recovered from patients in the cefepime treatment group were eradicated; 18/18 pathogens (100%) recovered from patients in the ceftazidime treatment group were eradicated. According to the applicant, because of the low numbers of patients involved, there was insufficiency statistical power to draw any conclusions from this data.

Table - 083E.11
Bacteriologic Efficacy at the 5-9 Day Post-Therapy Evaluation
(According to the Applicant)
Study #083 - European Centers

Pathogen	Number (%) of Pathogen					
	Cefepime			Ceftazidime		
	Erad.	Pers.	Total	Erad.	Pers.	Total
S. mitis	0	0	0	1	0	1
S. epidermidis	1	1	2	0	0	0
S. hominis	0	1	1	0	0	0
P. aeruginosa	0	0	0	1	0	1
E. coli	8	3	11	9	0	9
C. freundii	0	0	0	1	0	1
K. pneumoniae	1	0	1	2	0	2
K. oxytoca	1	0	1	0	0	0
E. cloacae	0	1	1	2	0	2
E. aerogenes	0	0	0	1	0	1
S. marcescens	0	1	1	0	0	0
P. mirabilis	4	0	4	0	0	0
E. agglomerans	0	0	0	1	0	1
Total Pathogens *	15 (68)	7 (32)**	22	18 (100)	0	18

Note : Erad. = Eradicated; Pers. = Persisted.

* Based on 21 cefepime treated patients and 16 ceftazidime treated patients.

** All 7 asymptomatic relapses.

Table-083.12 summarizes the reviewer's determination of the bacteriologic efficacy at the 5 to 9 day post-therapy evaluation.

Table - 083.12
Bacteriologic Efficacy at the 5-9 Day Post-Therapy Evaluation
by Infecting Pathogen¹
(According to the Reviewer)
Study #083 - European Centers

Parameter	CEFEPIME	CEFTAZID
COMPLICATED UTI		
C. FREUNDII	0	1/ 1 (100%)
E. CLOACAE	0/ 1 (0%)	3/ 3 (100%)
E. COLI	3/ 5 (60%)	3/ 3 (100%)
K. OXYTOCA	1/ 1 (100%)	0
K. PNEUMONIAE	1/ 1 (100%)	1/ 1 (100%)
P. AERUGINOSA	0	1/ 2 (50%)
P. MIRABILIS	2/ 2 (100%)	0
S. AUREUS	0	1/ 1 (100%)
S. EPIDERMIDIS	1/ 2 (50%)	0
S. FAECALIS	0	1/ 1 (100%)
S. HOMINIS	0/ 1 (0%)	0
S. MARCESCENS	0/ 1 (0%)	0
TOTAL COMPLICATED	8/ 14 (57%)	11/ 12 (92%)
PYELONEPHRITIS		
K. PNEUMONIAE	0	0/ 1 (0%)
P. MIRABILIS	1/ 1 (100%)	0
TOTAL PYELONEPHRITIS	1/ 1 (100%)	0/ 1 (0%)
UNCOMPLICATED UTI		
E. AEROGENES	0	1/ 1 (100%)
E. AGGLOMERANS	0	1/ 1 (100%)
E. COLI	5/ 6 (83%)	5/ 5 (100%)
P. MIRABILIS	1/ 1 (100%)	0/ 1 (0%)
S. MITIS	0	1/ 1 (100%)
TOTAL UNCOMPLICATED	6/ 7 (86%)	8/ 9 (89%)
TOTAL UTI	15/ 22 (68%)	19/ 22 (86%)

1 Some patients have more than one pathogen.

Bacteriologic Efficacy at the 4-6 Week Post-Therapy Assessment:

The applicant did not formally present the results of the late post-therapy evaluation and, in fact, most patients were not evaluated in 4-6 week post-therapy window.

Table - 083E.13 presents the medical officer's assessment of the bacteriologic efficacy at the late post-therapy evaluation. The small number of patients assessed makes it difficult to draw conclusions regarding comparative efficacy.

Table - 083E.13
 Bacteriologic Efficacy at the 4-6 Weeks Post-Therapy Evaluation
 (According to the Reviewer)
 Study #083 - European Centers

Response	Number of Patients (Percent)	
	Cefepime	Ceftazidime
All UTI	N = 21	N = 18
Early Persistence	7	3
Continued Eradication	4 (57)	2 (33)
Erad / Relapse	0	0
Erad / Reinfection	2 (29)	3 (50)
Erad / Rel + Reinfest.	1 (14)	0
Not Assessed	7	10

There was one patient in the cefepime treatment group who relapsed after the completion of therapy. The patient had relapse of infection with *K. pneumoniae* which occurred 15 days after the completion of therapy. The organism was still susceptible to cefepime. This same patient also had a reinfection with two other organisms. There were no patients in the ceftazidime group who relapsed within 4 to 6 weeks post-therapy.

Six reinfections (cefepime=3, ceftazidime=3) with new organisms occurred after the completion of study drug therapy. Organisms causing reinfection in cefepime treated patients included *E. coli*, *K. oxytoca*, and *S. faecalis*. The *E. coli* was susceptible to cefepime, the *S. faecalis* was resistant and the *K. oxytoca* was not tested. All the reinfections in the ceftazidime treated patients were caused by *S. faecalis* which were resistant to ceftazidime.

Safety Evaluation

Deaths:

Five patients died (cefepime=2, ceftazidime=3) during the conduct of protocol 411-083 in the European centers.

Cefepime Deaths

- The patient was a 66 y.o white male with metastatic bronchogenic carcinoma. He was treated with cefepime for and uncomplicated UTI due to *K. pneumoniae* from July 21 - July 27, 1989. On August 1, 1989 the patient expired. The death was thought to be due to complications of his underlying lung carcinoma.

- The patient was an 88 y.o. white female with a UTI and sepsis due to *E. coli*. The patient was treated with cefepime from May 5 to May 7, 1989. On May 7, 1989 the patient expired due to uncontrolled sepsis.

Ceftazidime Deaths

- The patient was a 66 y.o white male with carcinoma of the prostate. The patient was treated with ceftazidime for a complicated UTI due to *E. coli* from February 16 to February 22, 1990. The patient expired on March 14, 1990. The cause of death was reported to as complications of carcinoma of the prostate.

- The patient was a 32 y.o white male with HIV infection and uncomplicated UTI due to *E. coli*. The patient was treated with ceftazidime from October 18 to October 23, 1989. The patient expired on November 8, 1989 from complication of HIV infection.

- The patient was a 75 y.o white male with benign prostatic hypertrophy. The patient was treated with ceftazidime from December 1 to December 5, 1989 for a complicated UTI due to *K. pneumoniae*. The patient did not appear to respond to therapy and, in fact, developed symptoms of "pneumopathy" while on therapy. The patient was taken off ceftazidime and placed on metronidazole and gentamicin, however, patient developed multi-organ system failure and expired December 16, 1989.

Discontinuations

Two patients discontinued therapy prematurely for treatment related reasons, both patients were treated with cefepime.

- Cefepime therapy was discontinued after 2 days because of the development of a generalized body rash.

- Cefepime therapy was discontinued after 5 days due to acute phlebitis.

Clinical Adverse Events

Five clinical adverse events were reported in five patients during the conduct of protocol 411-083 at the European centers. Four clinical adverse events were associated with cefepime therapy (4/59, 7%), one clinical adverse event was associated with ceftazidime therapy (1/36, 3%).

Cefepime Clinical Adverse Events

One patient developed a fungal infection while on therapy. The fungal infection was judged to be of moderate severity and was probably related to the study drug. One patient developed a generalized skin rash which was described as moderate in severity and probably related to the study drug. The patient was discontinued from cefepime therapy because of this rash (see cefepime discontinuations). Two patients experienced infiltration, phlebitis or other local reactions at the infusion site.

Ceftazidime Clinical Adverse Events

One patient developed vomiting which was described as of mild severity and probably related to therapy with the study drug. No patients experienced any reactions at the infusion site.

Laboratory Test Abnormalities

Comment: All requested laboratory tests were not performed for all patients enrolled, thus the number of patients tested (#abnormal/#tested) will vary for each laboratory parameter.

According to the applicant, among the patients in the cefepime group who had normal pre-treatment test results, 1 patient (2.7%) had post-treatment SGPT and 2 patients (5.7%) had during or post-treatment eosinophil counts that were judged to be abnormal in the direction of toxicity.

Among the patients in the ceftazidime group who had normal pre-treatment test results, 1 patient (4.2%) had during treatment SGOT and SGPT, 1 patient (3.2%) had post-treatment WBC and 1 patient (4.0%) had post-treatment potassium that were judged to be abnormal in the direction of toxicity.

Among the patients in the cefepime group who had abnormal pre-treatment results, 2 patients had liver function tests (SGOT and SGPT) and 1 patient had electrolytes (Calcium tests that worsened to clinically relevant levels).

Among the patient in the ceftazidime group who had abnormal pre-treatment results, 2 had hematology tests (platelet count and hematocrit), 1 had coagulation tests (prothrombin time) and 1 had electrolytes tests (calcium and sodium) that worsened to clinically relevant levels.

Conclusions

This open, randomized, comparative clinical trial was designed to evaluate and compare the clinical and bacteriologic efficacy and the safety of cefepime and ceftazidime for the treatment of moderately severe urinary tract infections (UTI) suspected to be complicated. Cefepime administered parenterally at a dose of 0.5 g q12h was compared to ceftazidime given 0.5 g q12h. Patients enrolled in the study were randomly assigned to receive cefepime or ceftazidime in a 2:1 ratio, respectively. The study was performed in 9 centers in western Europe.

The nine investigators involved in the study enrolled a total of 95 patients. 59 patients were randomized to cefepime and 36 patients were randomized to ceftazidime. The applicant considered 21/59 (36%) patients randomized to cefepime to be evaluable and 16/36 (44%) of patients randomized to ceftazidime to be evaluable. The medical reviewer considered 21/59 patients (36%) randomized to cefepime to be evaluable and 18/36 (50%) of patients randomized to ceftazidime to be evaluable.

Because of the small number of evaluable patients involved in this study it is

difficult to make any firm conclusions regarding the results, however, a marked disparity in eradication rates was noted for between the two treatment groups in both the applicant's evaluable population and the reviewer's evaluable population at the 5-9 day post-therapy assessment.

Overall, according to the applicant, the bacteriologic eradication rate at the 5-9 day post-therapy evaluation was 15/22 (68%) in the cefepime treatment group and 18/18 (100%) in the ceftazidime treatment group.

According to the medical officer, the overall bacteriologic eradication rate was 15/22 (68%) in the cefepime treatment group and 19/22 (86%) in the ceftazidime treatment group. Among patients with complicated UTI (including pyelonephritis) the eradication rate was 9/15 (60%) in the cefepime treatment group and 11/13 (85%) in the ceftazidime treatment group. Among patients with uncomplicated UTI, similar eradication rates were seen in both treatment groups: cefepime = 6/7 (86%) and ceftazidime = 8/9 (89%).

Thus the disparate eradication rates seems mainly due to the complicated UTI population. The discrepancy in eradication rates was not seen in the North American version of this study.

With regard to clinical efficacy, the applicant determined that 19/21 patients (90%) in the cefepime treatment group and 15/16 patients (94%) in the ceftazidime treatment group had a satisfactory clinical outcome. The medical officer determined that 15/21 patients (71%) in the cefepime treatment group and 12/18 patients (67%) in the ceftazidime treatment group were completely cured of their infection at the 5-9 day post-therapy assessment.

Both cefepime and ceftazidime appeared to be well tolerated in the population studied. There were no significant differences in the incidence of deaths, discontinuations, clinical, or laboratory adverse drug events.

Although the number of patients involved is small, because of the marked disparity in eradication rates between the cefepime and ceftazidime treatment groups at the 5 to 9 day post-therapy assessments, the medical officer does not consider this study supportive of the claim of efficacy for ceftazidime in patients with complicated UTI. This study is supportive, however, of the claim of efficacy in patients with uncomplicated UTI.

PROTOCOL: 411-111**Introduction**

Study #111 provides safety and efficacy data for cefepime when compared to ceftazidime in the treatment of patients with infections of the urinary tract, and skin and skin structure caused by a broad range of pathogens

Objectives:

To evaluate the safety and efficacy of cefepime versus ceftazidime in the treatment of patients with suspected with or without a documented site of infection or serious infections of the urinary tract, skin and skin structure.

Investigational Plan**Design Overview**

This trial was an open, randomized, comparative clinical study at multiple centers in Europe. Patients were randomized to cefepime or to ceftazidime in a 1:1 ratio.

Population Studied:

The inclusion and exclusion criteria were similar to those used in other UTI protocols submitted in support of this application and described in the preamble to this review.

Study Drug Administration

Cefepime was administered at a dose of 2 grams Q12h. Ceftazidime was administered at a dose of 2 gram Q8h. Both drugs were administered intravenously and infused over 30 minutes. The dose of both drugs could be modified for administration to patients with renal failure according to a pre-determined schema.

Procedures and Observations:

The procedures and observation described in protocol #111 were similar to those used in other UTI protocols submitted in support of this application and described in the preamble to this review.

Population Studied

Study #111 was conducted at six centers in Western Europe. Patients were enrolled in the study from March 1989 to March 1991. A total of 348 patients were enrolled. All patients were hospitalized and all patients were treated intravenously.

Evaluability for the Assessment of Safety:

There were 56 patients with UTI among the group randomized to cefepime and there were 73 patients with UTI among the group randomized to ceftazidime. All patients randomized received at least one dose of cefepime or ceftazidime and thus were evaluable for the assessment of safety.

Evaluability for the Assessment of Efficacy:

Table-111.1 lists the enrollment and evaluability at each study center as determined by the applicant and the reviewer.

Table-111.1
Enrollment and Evaluability
Study #111

Center	Principal Investigator	Location	Enrol	Number of Patients					
				Cefepime		Ceftazidime			
				BMS	MO	Enrol	BMS	MO	
I-003	I. Hoepelman	Utrecht, Holland	28	9	9	33	11	12	
I-004	F. Meunier	Brussels, Belgium	20	2	2	27	6	6	
I-005	J. Ksmidis	Athens, Greece	3	3	3	5	3	3	
I-006	T. Strand	Sankviken, Sweden	1	1	1	3	1	2	
I-008	S. Gillespie	London, England	3	0	0	3	0	0	
I-010	J. Riddell	Belfast, N. Ireland	1	0	0	2	0	0	
TOTAL			56	15	15	73	21	23	
PERCENT				27%	27%		29%	32%	

Summary of Nonevaluability

According to the applicant 41 patients in the cefepime group and 52 patients in the ceftazidime group were not evaluable. The major reason for non-evaluability in both treatment groups was the failure to isolate a pathogen pre-treatment. More patient in the cefepime group were considered not evaluable because of incomplete treatment compared with the ceftazidime group, the difference is not statistically significant. Table 111.2 summarizes the applicant's reasons for exclusion form the efficacy analysis.

Table-111.2
Reasons Patients Were Excluded
From the Primary Efficacy Sample
Study 411-111
(According to the Applicant)

Reason Unevaluable*	Number (%) of Unevaluable Patients	
	Cefepime	Ceftazidime
<u>Number Excluded:</u>	41	52
No pathogen isolated	10 (25)	14 (27)
Incomplete treatment	8 (20)	6 (12)
No post-Rx culture obtained	3 (8)	10 (20)
Patient lost to follow-up	6 (15)	6 (12)
Post-Rx culture out of window	5 (13)	6 (12)
Post-Rx visit out of window	4 (10)	5 (10)
No during-Rx culture	3 (8)	5 (10)
Other antibiotic given pre post-culture	5 (13)	2 (4)
No sensitivity testing done	1 (3)	5 (10)
No 5-14 day urine culture obtained	2 (5)	4 (8)
Pre-Rx colony count < 100,000	3 (8)	2 (4)
Resistant organism	2 (5)	2 (4)
Other antibiotic given during study-Rx	1 (3)	2 (4)
Other antibiotic given pre post-clinical assessment	2 (5)	1 (2)
No post-Rx clinical assessment	1 (3)	1 (2)
Other antibiotic given post pre-culture	0	2 (4)
Pre-Rx culture out of window	0	2 (4)
Pre-Rx culture after Rx started	1 (3)	1 (2)
Improper dosage	0	1 (2)
Inappropriate organism	1 (3)	0
Pre-Rx colony count not done	0	1 (2)
Unspecified diagnosis	1 (3)	0
1st post-Rx culture not in window	1 (3)	0
2nd post-Rx culture not in window	0	1 (2)

According to the medical officer, the most common reason that patients were considered not-evaluable in both treatment groups was the failure to isolate a pathogen pre-treatment. Table 111.3 summarizes the reasons that patients were excluded from the efficacy analysis by the medical officer.

Table 111.3
Reason for Exclusion from the Efficacy Analysis
Study 411-111
(According to the Medical Officer)

Reason*	Number (%) of Infections	
	Cefepime	Ceftazidime
Total Excluded	41	50
Pre-treatment culture out of range	2 (5)	1 (2)
No Pathogen Isolated	13 (32)	15 (30)
Resistant Organism Recovered	3 (7)	2 (4)
No sensitivity testing	0	2 (4)
No During Therapy Culture	0	3 (6)
Incomplete Treatment		
Due to Allergy	1 (3)	0
Due to Death	4 (10)	6 (12)
Due to Protocol Error	2 (5)	1 (2)
Other Antimicrobial Administered		
Oral Continuation of Treatment	1 (2)	3 (6)
Infection at Distant Site	3 (7)	1 (2)
Protocol Error	0	1 (2)
Resistant Organism	2 (5)	0
Post-treatment culture out of range	10 (24)	15 (30)
Evaluable UTI	15	23

Applicant and Reviewer Evaluability Differences

Three patients (cefepime=1, ceftazidime=2) were treated with non-study antimicrobials because of persistence or worsening of symptoms. These patients were considered not evaluable by the applicant but evaluable by the medical officer.

One patients (cefepime) was treated with norfloxacin (oral continuation of treatment) prior to the first post-therapy culture. This patient was considered not evaluable by the reviewer.

Randomization Variations:

The following randomization variations were reported by the applicant.

A total of 11 patients at center I-003 (patient numbers _____), 16 patients at center I-004 (patient numbers _____) and 5 patients at center I-008 were treated with study medication out of the sequence specified by the randomization schedule.

Patients _____ were assigned to the study but, before receiving treatment, were considered ineligible. These patient numbers were reallocated at a later date. Patient _____ was randomized to ceftazidime but was considered ineligible before treatment was administered. This patient's allocated drug was not reassigned.

No subject was enrolled under number I-004-034. According to the investigator, the randomization envelope for this patient number was misplaced.

Patient had been previously enrolled in the study under patient number
Patient had been previously randomized under patient number
The second entries of these patients were excluded from the analyses,
with the exception of the laboratory analyses.

Patient was randomized to ceftazidime but received cefepime; patient
was randomized to cefepime but was treated with ceftazidime.

Comment: No explanation was offered by the applicant for the observed
variations.

DEMOGRAPHIC CHARACTERISTICSEnrolled Population

The majority of patients randomized to cefepime were male (57%), however, the majority of patients randomized to ceftazidime were female (52%). The difference is not significant (chi-square=1.07, P.0.05). The racial and age distribution of the two treatment groups are similar. Table 111.4 summarizes the demographic characteristics of the enrolled population.

Table - 111.4
Demographic Characteristics of the Enrolled UTI Population
Study 411-111

Parameter	CEFEPIME	CEFTAZID
SEX		
FEMALE	24 (43%)	38 (52%)
MALE	32 (57%)	35 (48%)
RACE		
WHITE	54 (96%)	68 (93%)
BLACK	1 (2%)	2 (3%)
ORIENTAL	0 (0%)	1 (1%)
OTHER	1 (2%)	2 (3%)
AGE (YR)		
N	56	73
MEAN	63.1	63.8
MEDIAN	68	66
RANGE		
AGE DISTRIBUTION		
18 - 24	4 (7%)	1 (1%)
25 - 44	4 (7%)	4 (5%)
45 - 64	15 (27%)	28 (38%)
65 - 84	30 (54%)	36 (49%)
85 +	3 (5%)	4 (5%)

In the applicant's evaluable population, the majority of patients were female in both treatment groups. The racial and age distributions were similar in both treatment groups. Demographic characteristics of the applicant's evaluable population are presented in table 111.5.

Table 111.5
Demographic Characteristics of the Evaluable UTI Population
Study 411-111
(According to the Applicant)

Parameter	CEFEPIME	CEFTAZID
SEX		
FEMALE	8 (53%)	14 (67%)
MALE	7 (47%)	7 (33%)
RACE		
WHITE	15 (100%)	19 (90%)
BLACK	0 (0%)	1 (5%)
OTHER	0 (0%)	1 (5%)
AGE (YR)		
N	15	21
MEAN	62.7	58.6
MEDIAN	69	58
RANGE		
AGE DISTRIBUTION		
18 - 24	2 (13%)	1 (5%)
25 - 44	1 (7%)	1 (5%)
45 - 64	2 (13%)	10 (48%)
65 - 84	10 (67%)	9 (43%)

The medical officer's evaluable population has a similar demographic profile to the applicant's evaluable population. Demographic characteristics of the medical officer's evaluable population are presented in table 111.6.

Table 111.6
Demographic Characteristics of the Evaluable UTI Population
Study 411-111
(According to the Medical Officer)

Parameter	CEFEPIME	CEFTAZID
SEX		
FEMALE	9 (60%)	15 (65%)
MALE	6 (40%)	8 (35%)
RACE		
WHITE	15 (100%)	21 (91%)
BLACK	0 (0%)	1 (4%)
OTHER	0 (0%)	1 (4%)
AGE (YR)		
N	15	23
MEAN	64.4	59.3
MEDIAN	70	58
AGE DISTRIBUTION		
18 - 24	2 (13%)	1 (4%)
25 - 44	1 (7%)	1 (4%)
45 - 64	1 (7%)	11 (48%)
65 - 84	10 (67%)	10 (43%)
85 +	1 (7%)	0 (0%)

Medical History

The most common associated medical condition, in both treatment groups, was the presence of a catheter within the urinary system. There were no significant differences in the prevalence of urinary tract abnormalities between the two treatment groups. Table 111.7 summarizes the applicant's assessment of the frequency of associated medical conditions for the enrollees and evaluable population.

Table 111.7
Classification of Infection Types
Study 411-111

Parameter	Number (%) of Patients	
	Cefepime	Ceftazidime
Applicant's Assessment	N=15	N=21
Complicated	9 (60)	8 (38)
Uncomplicated	5 (33)	13 (62)
Unable to Determine	1 (7)	0
Medical Officer's Assessment*	N=15	N=23
Complicated	12 (80)	17 (74)
Pyelonephritis	4	6
BPH	1	1
Catheter	4	3
Male > 40 years	1	2
Urinary Tract Neoplasm	1	2
Post Urinary Tract Surgery	1	1
Nephrolithiasis	0	2
Uncomplicated	3 (20)	6 (26)

*Represents the one major reason the patient was considered a complicated UTI patient.

COMMENT: The medical officer considered a larger percentage of patients to have a complicated UTI than did the applicant.

Concomitant Drug Therapy

The applicant reported concomitant therapy for all indications studied under protocol 411-111. No data were available for concomitant medication use specifically in UTI patients. According to the applicant, forty-two (95%) of the 44 patients evaluable for the primary efficacy analysis in the cefepime group received at least one concomitant drug treatment. Forty-eight (94%) of the 51 evaluable patients in the ceftazidime group received at least one concomitant drug treatment.

There was no statistically significant difference between the two treatment groups with regard to the use of concomitant therapy ($p=0.469$), or to the use of concomitant non-drug therapy ($p=0.252$).

Study Drug Therapy

The applicant provided data for the duration of therapy for the evaluable

population for all indications. There was no breakdown of duration of therapy for UTI patients. The information that follow, therefore, represents the medical officer's analysis of individual patient profiles

The mean duration of therapy in the cefepime group was 9.40 days, the range was from 4 to 25 days. In the ceftazidime group, the mean duration of therapy was 10.17 days, the range was from 6 to 25 days. Table 111.8 details the duration of therapy.

Table 111.8
Duration of Study Therapy
Study 411-111
(According to the Medical Officer)

Days	Cefepime Patients (%) N=15	Ceftazidime Patients (%) M=23
4	2 (13)	0
6	0	2 (9)
7	4 (27)	3 (13)
8	2 (13)	4 (17)
9	1 (7)	1 (4)
10	3 (20)	4 (17)
11	1 (7)	3 (13)
12	0	4 (17)
14	1 (7)	1 (4)
25	1 (7)	1 (4)

EFFICACY ANALYSIS**Clinical Efficacy**

According to the applicant, overall, a satisfactory response to therapy was seen in 13/15 patients (87%) in the cefepime treatment group and in 18/21 patients (86%) in the ceftazidime treatment group. The difference in the clinical cure rates was not significant. Table 11.9 summarizes the applicant's determination of the clinical efficacy.

Table - 11.9
Clinical Efficacy
(According to the Applicant)
Study #111

Diagnosis/ Number of pathogens	Number (%) of Patients					
	Cefepime N=15			Ceftazidime N=21		
	Sat.	Unsat.	Total	Sat.	Unsat.	Total
Complicated	8 (89)	1 (11)	9	6 (75)	2 (25)	8
Uncomplicated	4 (80)	1 (20)	5	12 (92)	1 (8)	13
Undetermined ¹	1 (100)	0	1	--	--	--
Total	13 (87)	2 (13)	15	18 (86)	3 (14)	21

1- The applicant was not able to classify the UTI in one patient as complicated or uncomplicated.

According to the reviewer, overall, 11/15 patients (73%) in the cefepime treatment group and 17/23 patients (74%) in the ceftazidime treatment group were clinically cured at the 5-9 day post-therapy evaluation. There is no statistically significant difference in clinical cure rate between the two treatment groups. Table-111.10 summarizes the reviewer's assessment of the clinical response to therapy at the 5-9 day post-therapy evaluation.

Table - 111.10
Clinical Efficacy
(According to the Reviewer)
Study #111

Parameter	CEFEPIME	CEFTAZID
NO. OF EVALUABLE PATIENTS	15	23
CURE	11 (73%)	17 (74%)
FAILURE	4 (27%)	6 (26%)
COMPLICATED UTI	8	11
CURE	5 (63%)	7 (64%)
FAILURE	3 (38%)	4 (36%)
PYELONEPHRITIS	4	7
CURE	4 (100%)	7 (100%)
UNCOMPLICATED UTI	3	5
CURE	2 (67%)	3 (60%)
FAILURE	1 (33%)	2 (40%)

Bacteriologic Efficacy**Bacteriologic Efficacy at the 5-9 Days Post-Therapy Evaluation:**

According to the applicant, overall, 14/18 pathogens (78%) were eradicated in the cefepime treatment group, including 7/10 pathogens (70%) in patients with complicated UTI, and 7/8 pathogens (88%) in patients with uncomplicated UTI. In the ceftazidime treatment group, overall, 17/22 pathogens (77%) were eradicated including 11/15 pathogens (73%) in patients with complicated UTI, and 6/7 pathogens (86%) in patients with uncomplicated UTI. Table-111.14 presents the applicant's assessment of the bacteriologic efficacy at the 5-9 days post-therapy evaluation.

Table-111.14
Bacteriologic Efficacy at the 5-9 Days Post-Therapy Evaluation
 (According to the Applicant)
 Study #111

Parameter	CEFEPIME	CEFTAZIL
COMPLICATED UTI		
E. COLI	2/ 3 (67%)	8/ 9 (89%)
ENTEROBACTER SP.	1/ 1 (100%)	0
ENTEROCOCCUS	0/ 1 (0%)	0
H. ALVEI	1/ 1 (100%)	0
K. PNEUMONIAE	1/ 1 (100%)	2/ 2 (100%)
KLEBSIELLA SP.	1/ 1 (100%)	0
P. AERUGINOSA	0/ 1 (0%)	0/ 2 (0%)
P. MIRABILIS	0	1/ 2 (50%)
STREP. (GROUP B)	1/ 1 (100%)	0
TOTAL COMP	7/ 10 (70%)	11/ 15 (73%)
UNCOMPLICATED UTI		
C. FREUNDII	0	1/ 1 (100%)
E. CLOACAE	1/ 1 (100%)	0
E. COLI	4/ 5 (80%)	3/ 4 (75%)
P. AERUGINOSA	0	1/ 1 (100%)
P. VULGARIS	1/ 1 (100%)	0
S. LIQUIFACIENS	0	1/ 1 (100%)
STREP. (GROUP B)	1/ 1 (100%)	0
TOTAL UNCOMP	7/ 8 (88%)	6/ 7 (86%)
TOTAL UTI	14/ 18 (78%)	17/ 22 (77%)

According to the reviewer, overall, 13/18 pathogens (72%) were eradicated in the cefepime treatment group, including 7/10 pathogens (70%) in patients with complicated UTI, 2/3 pathogens (67%) in patients with pyelonephritis, and 4/5 pathogens (80%) in patients with uncomplicated UTI. In the ceftazidime treatment group, overall, 16/24 pathogens (67%) were eradicated, including 5/11 pathogens (45%) in patients with complicated UTI, 8/8 pathogens (100%) in patients with pyelonephritis, and 3/5 pathogens (60%) in patients with uncomplicated UTI. Table-111.12 presents the reviewer's assessment of the bacteriologic efficacy at the 5-9 days post-therapy evaluation.

Table - 111.12
Bacteriologic Efficacy at 5-9 Days Post-Therapy
(According to the Reviewer)
Study #111

Parameter	CEFEPIME	CEFTAZID
UNCOMPLICATED UTI		
E. CLOACAE	1/ 1 (100%)	0
E. COLI	1/ 2 (50%)	2/ 4 (50%)
S. LIQUIFACIENS	0	1/ 1 (100%)
TOTAL UNCOMP	2/ 3 (67%)	3/ 5 (60%)
PYELONEPHRITIS		
E. COLI	2/ 2 (100%)	7/ 7 (100%)
ENTEROBACTER SP.	1/ 1 (100%)	0
KLEBSIELLA SP.	1/ 1 (100%)	0
P. AERUGINOSA	0/ 1 (0%)	0
P. MIRABILIS	0	1/ 1 (100%)
TOTAL PYELONEPHRITIS	4/ 5 (80)	8/ 8 (100%)
COMPLICATED UTI		
C. FREUNDII	0	1/ 1 (100%)
E. COLI	3/ 4 (75%)	2/ 4 (50%)
ENTEROCOCCUS	0/ 1 (0%)	0
H. ALVEI	1/ 1 (100%)	0
K. PNEUMONIAE	1/ 1 (100%)	1/ 2 (50%)
P. AERUGINOSA	0	1/ 3 (33%)
P. MIRABILIS	0/ 1 (0%)	0/ 1 (0%)
STREP. (GROUP B)	2/ 2 (100%)	0
TOTAL COMPLICATED	7/ 10 (70%)	5/ 11 (45%)
TOTAL UTI	13/ 18 (72%)	16/ 24 (67%)

COMMENT: The results of 95% confidence interval analysis will not be reported for this study as the small number of patients involved leads to unusually wide confidence intervals.

COMMENT: The population descriptive data was examined for the complicated UTI group to determine if an explanation for the low eradication rate seen with ceftazidime could be found. There was a trend toward younger aged patients in the ceftazidime group (cefepime mean age = 73, ceftazidime mean age= 57). More patients in the cefepime group had the presence of a catheter as their only complicating factor (cefepime=5/9, ceftazidime=2/10).

Bacteriologic Efficacy at the 4-6 Weeks Post-Therapy Assessment:

COMMENT: The applicant did not report on the results of the late bacteriologic evaluation, therefore, all the following data is based on the medical officer's analysis.

Table-111.13 presents the reviewer's assessment of the bacteriologic efficacy at

the 4-6 weeks post-therapy assessment.

Table-111.13
Bacteriologic Efficacy at the 4-6 Weeks Post-Therapy Assessment
(According to the Reviewer)
Study #111

Parameters	Number (%) ^a of Patients	
	Cefepime	Ceftazidime
<u>M.O. Evaluable Patients</u>	15	23
Persistence at 5-9 Days	-5	-8
<u>Patients Eval. for 4-6 Week Asses.</u>	10	15
Not Assessed	-5	-11
<u>Patients Assessed at 4-6 Weeks</u>	5	4
Continued Eradication	3 (60)	1 (25)
Eradication with Relapse	1 (20)	3 (75)
Eradication with Reinfection	1 (20)	0 (0)

a Percentages based on all patients with 4-6 week follow-up.
NOTE: The actual window for the 4-6 week follow-up was post-treatment Days 20-49.

Analysis of Relapses

There were four relapses (cefepime=1, ceftazidime=3). In all instances the organism relapsing was *E. coli*. In 3/4 cases the organism was still susceptible to cefepime and ceftazidime at the time of relapse. The fourth organism was not tested for susceptibility.

Analysis of Reinfections

One symptomatic reinfection occurred in one cefepime treated patient. The organism causing reinfection was *S. faecalis*. The organism was not tested for susceptibility to the study drugs.

Safety Evaluation

Deaths

Seventeen deaths occurred in UTI patients enrolled in protocol 411-111. Seven deaths occurred in 56 UTI patients exposed to cefepime (Death Rate = 13%). Ten deaths occurred in 73 UTI patients exposed to ceftazidime (Death Rate = 14%). There was no statistical difference in the mortality rate between the two treatment groups.

Cefepime Deaths

- The patient was an 85 y.o. female with *E. coli* pyelonephritis. The patient expired 6 hours after the first dose of cefepime was administered. The cause of death was reported to be pulmonary embolus.

- The patient was a 19 y.o. female with inoperable ovarian cancer. The patient was treated with cefepime for a catheter associated *E. coli* UTI. The patient died 14-days after the completion of cefepime therapy. The cause of death was reported to be complication of ovarian cancer.

- The patient was a 55 y.o. male who was treated with cefepime for and uncomplicated *E. coli* UTI. The patient died 3 months after completing cefepime therapy. The cause of death was not known.

- The patient was a 68 y.o. male with metastatic small cell carcinoma of the lung. The patient was treated with cefepime for a catheter associated *E. coli* UTI. The patient died 4 days after the completion of therapy. The cause of death was reported as metastatic disease.

- The patient was an 80 y.o. male with carcinoma of the bladder. The patient was treated with cefepime for a suspected complicated UTI (however the culture grew *C. albicans*). The patient died while on therapy. The patient died during surgery to remove her bladder tumor.

- The patient was a 76 y.o. white female who was treated with cefepime for an uncomplicated *E. coli* UTI. The patient developed *Listeria* sepsis while on therapy and died of the complications of sepsis.

- The patient was a 67 y.o. male who was treated with cefepime for a catheter associated *E. coli* UTI. During therapy the patient developed sepsis due to *S. faecalis*. The source of the enterococcus was thought to be cholangitis. The patient died of complication of enterococcal sepsis.

Ceftazidime Deaths

- The patient was an 85 y.o. female with signs and symptoms of UTI. There was no growth on urine cultures however. The patient was treated empirically with ceftazidime. The patient steadily deteriorated and was found dead on the third day of therapy. The cause of death was unknown.

- The patient was a 67 y.o. female who was treated with ceftazidime for an uncomplicated UTI due to *E. coli*. The patient was reported to have improved clinically however, the patient suffered an acute cardiac arrest on the third day of therapy and died. Blood cultures at the time of death were negative.

- The patient was a 49 y.o. male with history of cerebral infarction. The patient was enrolled and treated with ceftazidime for a catheter

associated UTI due to *S. epidermidis*. The patient received one dose of ceftazidime prior to death. The patient died of intracerebral hemorrhage.

- The patient was a 58 y.o. female who was treated with ceftazidime for pyelonephritis due to *E. coli*. The patient responded well to therapy. The patient died 1 month after completing therapy. The cause of death was not known.

- The patient was a 44 y.o. female with a history of malignant melanoma with metastasis, who was treated for an uncomplicated UTI with ceftazidime. The patient died 2 months after the completion of treatment from complication of her malignancy.

- The patient was an 80 y.o. female who was treated with ceftazidime for an uncomplicated UTI due to *P. mirabilis*. The patient had clinical resolution of UTI symptoms while on therapy but developed pneumonia. The patient died 4 days after the completion of therapy. The causes of death were reported as pneumonia, congestive heart failure and pulmonary edema.

- The patient was a 70 y.o. male with history of carcinomatous peritonitis. The patient was treated with ceftazidime for an uncomplicated UTI due to *E. coli*. The patient had recurrence of UTI 7 days post-therapy. The patient died 14 days post-therapy. The cause of death was not determined.

- The patient was a 68 y.o. female with history of extensive cervical cancer. The patient was treated with ceftazidime for a catheter associated UTI due to *P. aeruginosa*. The patient died 2 days after the completion of treatment. The cause of death was reported as complications of cervical carcinoma.

- The patient was a 79 y.o. female who was treated with ceftazidime for a catheter associated UTI due to *E. coli*. While on therapy the patient developed sepsis with methicillin resistant *S. aureus*. The patient died of complications of *S. aureus* sepsis.

- The patient was a 78 y.o. male with rectal carcinoma. The patient was enrolled and treated with ceftazidime for signs and symptoms of UTI. The blood and urine cultures yielded *Bacteroides* spp. The study therapy was stopped after two days and anti-anaerobic therapy was started. The patient, however, died of sepsis.

Discontinuations

Two patients were removed from cefepime therapy due to the occurrence of an adverse clinical event. One patient was removed from therapy because of a rash, the other patient was removed from therapy due to a *C. albicans* superinfection.

No patients were removed from ceftazidime therapy due to the occurrence of an adverse clinical event.

Clinical Adverse Events

Three (5%) clinical adverse events occurred among the 56 UTI patients randomized to cefepime. Two patients developed rashes. One rash was of moderate severity and probably related to drug therapy. One rash was severe and was unrelated to drug therapy. One patient developed diarrhea. The diarrhea was of moderate severity and probably related to drug therapy.

Three (4%) clinical adverse events occurred among the 73 UTI patients randomized

to ceftazidime. All three patients developed candidiasis. Two episodes of candidiasis were of moderate severity and one was mild. In all instances the adverse event was thought to be probably related to drug therapy.

COMMENT: There is no statistical difference in the rate of occurrence of clinical adverse events between the two treatment groups.

Local Tolerance

Eight patients (14%) of the 56 randomized to cefepime experienced phlebitis or other reaction at the infusion site. Four patients (5%) of the 73 randomized to ceftazidime experienced phlebitis or other reaction at the infusion site. The difference in the rate of occurrence of local reactions at the infusion is not significant (Chi-square=2.9, P>0.05).

Laboratory Test Abnormalities

Protocol #111 was designed to study the safety and efficacy of cefepime for a variety of indication. The applicant did not organize their data in such a way that laboratory test abnormalities occurring in UTI patients could be separated from laboratory test abnormalities occurring in patients studied for claims of efficacy in other indications. Therefore, no data on laboratory test abnormalities will be included in this study report. However, any laboratory test abnormalities which occurred in UTI patients enrolled in study #111 will be included in the integrated summary of safety for UTI patients.

Conclusions

Protocol #411-111 was an open, randomized, comparative trial performed at six diverse geographic locations in Western Europe. The study compared high doses of both cefepime (2G Q12h) and ceftazidime (2G Q8h). The population studied were older individuals (the mean age in both groups was approximately 63 years) who in the majority of cases (95%) had at least one pre-existing medical problem.

The overall bacteriologic eradication rate at the 5-9 days post-therapy evaluation was similar between the two treatment groups. The similarity in eradication rates was seen in both the applicant's analysis and the medical officer's analysis. The similarity in eradication rates between the two treatment groups was also maintained within the sub-groups of uncomplicated UTI and patients with pyelonephritis. In patients with complicated UTI, according to the reviewer, there was a trend toward higher eradication rates in the cefepime treatment group compared with the ceftazidime treatment group. Because of the small number of patients involved, this trend did not reach statistical significance.

Again, because of the small numbers of patients involved in this study, no confidence interval analysis was performed.

There were no significant differences between the treatment groups in terms of the major safety related parameter (i.e. deaths, discontinuation, clinical adverse events, and local tolerance). Laboratory test abnormalities were not assessed.

Study #111 is supportive of the claim of safety and efficacy for cefepime in comparison to ceftazidime for the treatment of patients with complicated and uncomplicated UTI.

NORTH AMERICAN NON-COMPARATIVE STUDIES**PROTOCOL: 411-061****Introduction**

Study #061 provides safety and efficacy data for cefepime in treating patients with infections of the urinary tract (UTI), skin and skin structures (SSTI), usually related to the underlying infection, caused by a broad range of pathogens.

Investigational Plan**Design Overview**

Protocol #411-061 is an open, non-comparative, dose-ranging study conducted at multiple centers within the United States

Population Studied:

The inclusion and exclusion criteria common to all other UTI protocols submitted in this application were employed in study #061. Exceptions are noted below.

Patients with long-term indwelling catheters were to be excluded from this protocol.

Patient with neurogenic bladder or surgical reconstruction of the urinary tract were originally to be excluded, however, two amendments to the protocol were submitted which allowed entry of these patients.

Study Drug Administration

Cefepime was supplied by Bristol-Myers Squibb Company in vials containing 500 mg or 1 g of either a lyophilized mixture of cefepime and NaCl or a dry-powder blend of cefepime dihydrochloride and L-arginine (added by Amendment 2). Patients were to receive 1 g every 12 hours for up to 14 days for cefepime/arginine or 30 days for cefepime/NaCl (the original Protocol specified 10 days). Amendment 1 to the Replacement Protocol allowed investigators 004, 007, 011, 028, and 048 to administer other doses. Depending on the severity of their infections, patients could receive doses of 250 mg (for uncomplicated UTI only), 500 mg, 1 g, or 2 g every 12 hours, or 2 g every 8 hours, for up to 14 days. Only patients with very severe life-threatening infections were put on the 2 g TID regimen. (The lowest designated dose of 250 mg BID was not used in this study.)

Procedures and Observations:

The procedures employed and the observations collected were consistent with those found in other UTI protocols and described in the preamble to this review.

Population Studied

Patients were enrolled between June 11, 1987 and December 8, 1988. 594 patients were enrolled for all indications studied under protocol 411-061. All 594 patients enrolled in the study received at least one dose of cefepime: 553 were treated with cefepime/NaCl and 41 with cefepime/arginine. All but 11 patients were treated in the hospital. These 11 patients received IV administration twice

a day in the physician's office.

Evaluability for the Assessment of Safety:

Of the 595 patients enrolled, 115 were enrolled for the treatment of UTI. All UTI patients received at least one dose of cefepime and, therefore, were evaluable for the assessment of drug safety.

Evaluability for the Assessment of Efficacy:

Table-061.1 presents the number of patients enrolled at each study centers. The applicant's and the medical officer's assessment of the evaluability of enrolled patients are also presented.

Table-061.1
Enrollment and Evaluability
Study #061

Study Center	Principal Investigator*	Location	Number of Patients		
			Enrolled	BMS Eval	M.O. Eval
SINGLE INFECTION TYPE					
I-003	Stephen Farkas	Barberton, OH	23	20	3
I-004	R. Schwartz	Ft. Myers, FL	3	1	1
I-005	Harold Neu	New York, NY	1	1	1
I-006	Bienvenido Yangco	Tampa, FL	13	1	1
I-007	Jack LeFrock	Sarasota, FL	4	2	2
I-008	Stacy Childs	Alabaster, AL	1	1	1
I-011	Carlos Ramirez	San Juan, PR	8	2	1
I-012	Timothy Lane	Greensboro, NC	3	1	1
I-013	Robert McCabe	Martinez, CA	5	2	2
I-015	Sandra-Handwerger	New York, NY	1	0	0
I-016	Michael Gelfand	Memphis, TN	5	1	0
I-023	William Mogabgab	New Orleans, LA	1	0	0
I-025	Lionel Mandell	Hamilton, Ontario	2	1	1
I-030	Susan Forlenza	East Meadow, NY	7	1	1
I-031	Gary Wormser	Valhalla, NY	3	1	1
I-035	R. Brooks Gainer	Morgantown, WV	5	2	2
I-037	Paul Iannini	Danbury, CT	9	1	1
I-040	John Ryan				
	Richard Mangi	West Haven, CT	14	6	5
I-042	Nicolas Christou	Montreal, Quebec	3	0	0
I-043	Joseph G. Jemsek	Charlotte, NC	1	0	0
I-048	Stephen Green	Hampton, VA	4	1	0
		Newport News, VA			
TOTAL UTI			116	45	24
Percent Evaluable				39%	21%

COMMENT: None of the investigators involved in study 411-061 appear in the Division of Scientific Investigations' restricted investigators list. Dr. Michael Gelfand was placed on the "Assurances Accepted" list in 1981.

COMMENT: Three center (003, 006 and 040) enrolled the majority of patients in the study.

Summary of Non-Evaluability:

According to the applicant, 71 patients were considered not evaluable for the determination of efficacy. The most common reason for unevaluability was the failure to isolate a pathogen pre-treatment. Table 061.2 lists the major reason for unevaluability as determined by the applicant.

Table 061.2
Summary of Major Reason Unevaluable
(According to the Applicant)

Reason for Exclusion	Number (%) of Infections
Total Enrolled	116
Total Excluded (Unevaluable)	71 (61)
Pre-Rx Visit Out Of Window	5 (4)
No Pre-Rx Culture	1 (1)
No Pathogen Isolated	9 (8)
Pre-Rx Culture Out Of Window	3 (3)
Asymptomatic UTI, 1 Pre-Rx Culture	2 (2)
No Pre-Rx Colony Count	5 (4)
Pre-Rx Colony Count < 100,000	2 (2)
Sensitivity Testing Not Done	1 (1)
Resistant Organism	6 (5)
Incomplete Treatment	3 (3)
No During Therapy Culture	2 (2)
Other Antibiotic Given Pre Post-Culture	3 (3)
No Post-Therapy Assessment	9 (8)
Post-Therapy Assessment Out of Window	20 (17)
Total Evaluable	45 (39)

The medical officer considered 92 patients not-evaluable for the determination of efficacy. The most common reason for non-evaluability was the failure to perform a post-treatment culture or clinical assessment within an acceptable time period. Table 061.3 presents the major reason for unevaluability as determined by the medical officer.

Table 061.3
Major Reasons for Non-Evaluability
Study 411-061
(According to the Medical Officer)

Reason	Number of Patients (%) ¹
Total Enrolled	116
Total Excluded	92 (79)
Pre-treatment culture out of range	9 (8)
No Pathogen Isolated	11 (9)
Resistant Organism Recovered	7 (6)
Incomplete Treatment	
Due to ADR	1 (1)
Due to Death	2 (2)
Other Antimicrobial Administered	
Oral Continuation of Treatment	5 (4)
Infection at Distant Site	1 (1)
Post-treatment culture out of range	56 (48)
Total Evaluable	24 (21)

1 Percentages are based on total number of patients enrolled.

Applicant/Reviewer Evaluability Differences

Many more patients were considered not evaluable by the medical officer than by the sponsor. The difference stems from the fact that the applicant considered those patients in whom a post-therapy culture and assessment was performed on day 3 or more after therapy to be evaluable. The medical officer required that the post-therapy assessment be performed between 5 and 14 days after the conclusion of therapy.

Demographic Characteristics:

Most UTI patients (61%) enrolled in study 411-061 were female. 86% were white. The mean age was 63.9 years. Table 061.4 presents the demographic characteristics of the enrolled population.

Table-061.4
Demographic Characteristics of the Enrolled Population
Study #061

Parameter	CEFEPIME	
SEX		
FEMALE	71	(61%)
MALE	45	(39%)
RACE		
WHITE	100	(86%)
BLACK	15	(13%)
ORIENTAL	1	(1%)
AGE (YR)		
N	116	
MEAN	63.9	
MEDIAN	69	
RANGE		
AGE DISTRIBUTION		
18 - 24	6	(5%)
25 - 44	15	(13%)
45 - 64	29	(25%)
65 - 84	60	(52%)
85 +	6	(5%)

Both the applicant's evaluable population and the medical officer's evaluable population were similar in demographic composition to the enrolled population. There was a higher percentage of female in the applicant's evaluable population when compared with the medical officer's evaluable population. Tables 061.5 and 061.6 present the demographic characteristics of the applicant's and the reviewer's evaluable populations.

Table 061.5
Demographic Characteristics
Study 411-061
(According to the Applicant)

Parameter	CEFEPIME	
SEX		
FEMALE	32	(71%)
MALE	13	(29%)
RACE		
WHITE	41	(91%)
BLACK	4	(9%)
AGE (YR)		
N	45	
MEAN	63.2	
MEDIAN	70	
RANGE		
AGE DISTRIBUTION		
18 - 24	3	(7%)
25 - 44	7	(16%)
45 - 64	9	(20%)
65 - 84	24	(53%)
85 +	2	(4%)

Table 061.6
Demographic Characteristics
Study 411-061
(According to the Reviewer)

Parameter	CEFEPIME	
SEX		
FEMALE	14	(58%)
MALE	10	(42%)
RACE		
WHITE	22	(92%)
BLACK	2	(8%)
AGE (YR)		
N	24	
MEAN	61.3	
MEDIAN	66	
RANGE		
AGE DISTRIBUTION		
18 - 24	1	(4%)
25 - 44	5	(21%)
45 - 64	6	(25%)
65 - 84	11	(46%)
85 +	1	(4%)

Medical History:

Tables 061.7 and 061.8 lists the applicant's and the reviewer's assessment of medical conditions related to the genitourinary tract present in patients at the time of randomization.

COMMENT: The applicant attempted to identify all relevant medical conditions present in a given patient. In contrast, the reviewer attempted to identify the single most significant condition present.

Table 061.7
Relevant Medical Conditions for UTI
Evaluable Patients
Study 411-061
(According to the Applicant)

Condition*	Number (%) of Patients
COMPLICATED UTI	N = 24
Specific Urinary Tract Conditions:	
*Upper UTI	13 (54)
*Obstruction	5 (21)
Urinary Tract Catheter (All Types)	11 (46)
*Urethral Catheter	9
*Urinary Stent	1
Intermittent Catheter	1
Other Conditions	6 (25)
Diabetes	5 (21)
UNCOMPLICATED UTI	N = 21

a More than one condition may occur in a single patient.

* Condition used to classify UTI as complicated.

Table 061.8
 Relevant Medical Conditions for UTI
 Evaluable Patients
 Study 411-061
 (According to the Reviewer)

Condition ^a	Number (%) of Patients
COMPLICATED UTI	N = 11
Specific Urinary Tract Conditions:	
Anatomic Abnormalities	1 (9)
Catheter Associated	2 (18)
Functional Abnormalities	2 (48)
Male > 40 years	6 (55)
PYELONEPHRITIS	N = 9
UNCOMPLICATED UTI	N = 4

^aOnly one condition is listed for each patient.

Concomitant Medications:

According to the applicant, 97% of the evaluable patients took at least one concomitant medication during their participation in the study. In the applicant's evaluable population, no patients received systemic anti-microbial agents active against the pathogens in UTI. In the reviewer's evaluable population, patients who took systemic anti-microbial drugs for persistence or worsening of symptoms were considered evaluable but they were considered to be clinical and bacteriologic failures.

Study Drug Administration:

According to the applicant, cefepime/NaCl was given to 42 (93%) of the 45 evaluable UTI patients at a dose of 1 g BID and to 2 (4%) patients at a dose of 2 g BID. Duration of dosing ranged from 4 to 12 days. Cefepime/arginine was given to 1 (2%) of the 45 evaluable UTI patients at a dose of 2 g BID. Duration of dosing was 14 days. Table 061.9 summarizes the dosage and duration of study therapy for evaluable UTI.

Table 061.9
Study Therapy for UTI Evaluable Patients
Study 411-061
(According to the Applicant)

Parameter	Number (%) of Patients	
	1 g BID	2 g BID
Cefepime	N = 42	N = 3
Duration of Dosing (days)		
4	1 (2)	
5	14 (33)	
6	12 (29)	
7	3 (7)	
8	5 (12)	
9	2 (5)	
10	1 (2)	1 (33)
11-12	4 (10)	2 (67)

According to the medical officer, all 24 evaluable patients received cefepime/NaCl. 22 patients were treated with 1 g BID and 2 patients were treated with 2 g BID. The range of duration of therapy was from 4 to 12 days. The mean duration of dosing was 7.9 days. Table 061.10 summarizes the study therapy for evaluable UTI patients according to the medical officer.

Table 061.10
Study Therapy for UTI Evaluable Patients
Study 411-061
(According to the Reviewer)

Parameter	Number (%) of Patients	
	1 g BID	2 g BID
Cefepime	N = 22	N = 2
Duration of Dosing (days)		
4	1 (5)	
5	2 (10)	
6	6 (27)	
7	2 (10)	
8	4 (18)	
9	2 (10)	
10	2 (10)	1 (50)
11	2 (10)	1 (50)
12	1 (5)	

Efficacy Evaluation

Clinical Efficacy

Table 061.11 summarizes the applicant's determination of the clinical efficacy at the 5 to 9 day post-therapy evaluation. According to the applicant, overall, 41/45 patients (91%) had a satisfactory clinical outcome, including 21/24 patients (88%) with complicated UTI and 20/21 patients (95%) with uncomplicated UTI.

Table 061.11
Clinical Response for UTI
Study 411-061
(According to the Applicant)

Parameter	CEFEPIME
UTI/OVERALL	N = 45
SATIS	41 (91%)
UNSAT	4 (9%)
UTI/COMP	N = 24
SATIS	21 (88%)
UNSAT	3 (13%)
UTI/UNCOMP	N = 21
SATIS	20 (95%)
UNSAT	1 (5%)

According to the medical officer, overall, a clinical cure was achieved in 18/24 patients (75%). 1/24 patients (4%) was considered improved. 5/24 patients (21%) were considered clinical failures. The three subgroups had clinical cure rates that were similar to the UTI population as a whole (complicated UTI=73%, pyelonephritis=78%, uncomplicated UTI=75%). Table 061.12 summarizes the medical officer's determination of the clinical response.

Table 061.12
Clinical Response for UTI
Study 411-061
(According to the Medical Officer)

Parameter	CEFEPIME

NO. OF EVALUABLE PATIENTS	24
UTI/ALL PATIENTS	
CURE	18 (75%)
IMPROV	1 (4%)
FAILURE	5 (21%)

NO. OF EVALUABLE PATIENTS	11
UTI/COMP	
CURE	8 (73%)
FAILURE	3 (27%)

NO. OF EVALUABLE PATIENTS	9
UTI/PYELONEPHRITIS	
CURE	7 (78%)
FAILURE	2 (22%)

NO. OF EVALUABLE PATIENTS	4
UTI/UNCOMP	
CURE	3 (75%)
IMPROV	1 (25%)

Bacteriologic Efficacy**Susceptibility of Pathogens:**

According to the applicant, *E. coli* was the most common pathogen isolated from patients with UTI, accounting for 61 (57%) of the 107 isolates tested, followed by *K. pneumoniae* in 10 (9%). Only 7 of 107 isolates tested were resistant to cefepime, including such usually resistant pathogens as *Enterococcus*, methicillin-resistant staphylococci, and *Acinetobacter anitratus*.

Table 061.13
Susceptibility of Pathogens Isolated
Study 411-111
(According to the Applicant)

Pathogen	Number (%) of Pathogens			Total
	----- Type of Sensitivity -----			
	Susceptible	Intermediate	Resistant	
<i>S. viridans</i>	1 (100)			1
<i>Enterococcus</i>	1 (20)		4 (80)	5
<i>Strep. (Group B)</i>	2 (100)			2
<i>S. aureus</i>	1 (100)			1
<i>S. aureus (MR)</i>			1 (100)	1
<i>P. aeruginosa</i>	5 (71)	2 (29)		7
<i>Escherichia sp.</i>	1 (100)			1
<i>E. coli</i>	60 (98)		1 (2)	61
<i>C. freundii</i>	1 (100)			1
<i>K. pneumoniae</i>	10 (100)			10
<i>K. oxytoca</i>	1 (100)			1
<i>E. cloacae</i>	3 (100)			3
<i>E. aerogenes</i>	3 (100)			3
<i>S. marcescens</i>	1 (100)			1
<i>P. mirabilis</i>	5 (100)			5
<i>M. morgani</i>	2 (100)			2
<i>P. stuartii</i>	1 (100)			1
<i>A. anitratus</i>			1 (100)	1
Total	98 (92)	2 (2)	7 (7)	107

Bacteriologic Efficacy at the 5-9 Days Post-Therapy Evaluation:

According to the applicant, overall, 45/48 pathogens (92%) were eradicated by cefepime, including 24/25 pathogens (96%) in patients with complicated UTI, and 21/24 pathogens (88%) in patients with uncomplicated UTI. Table-061.14 summarizes the applicant's assessment of the bacteriologic response to cefepime at the 5-9 days post-therapy evaluation.

Table-061.14
Bacteriologic Efficacy at the 5-9 Days Post-Therapy Assessment
(According to the Applicant)
Study #061

Pathogen	----- Number of Pathogens -----					
	<u>Uncomplicated</u>			<u>Complicated</u>		
	Erad.	Pers.	Total	Erad.	Pers.	Total
<i>S. viridans</i>				1		1
Strep. (Group B)	2		2			
<i>S. aureus</i>	1		1			
<i>P. aeruginosa</i>	2		2	1	1	2
<i>E. coli</i>	12	1	13	15	1	16
<i>C. freundii</i>				1		1
Salmonella (Group D)				1		1
<i>K. pneumoniae</i>	2		2		1	1
<i>E. cloacae</i>	2		2			
<i>E. aerogenes</i>	1		1	1		1
<i>S. marcescens</i>	1		1			
<i>P. mirabilis</i>	1		1			
<i>M. morgani</i>				1		1
Total Pathogens*	24	1	25	21	3	24
Percent	(96)	(4)		(88)	(13)	

* Based on 45 patients.

According to the reviewer, overall, 20/24 pathogens (83%) were eradicated by cefepime treatment including 9/11 pathogens (82%) in patients with complicated UTI, 7/9 pathogens (78%) in patients with pyelonephritis, and 4/4 pathogens (100%) in patients with uncomplicated UTI. Table-061.15 presents the reviewer's assessment of the bacteriologic efficacy at 5-9 days post-therapy.

Table-061.15
Bacteriologic Efficacy at the 5-9 Days Post-Therapy Assessment
(According to the Reviewer)
Study #061

Parameter	CEFEPIME

UTI/ALL PATIENTS	
E. AEROGENES	2/ 2 (100%)
E. COLI	14/ 16 (88%)
K. PNEUMONIAE	2/ 3 (67%)
P. AERUGINOSA	1/ 1 (100%)
P. MIRABILIS	0/ 1 (0%)
S. ENTERITIDIS	1/ 1 (100%)
TOTAL/ALL PATIENTS	20/ 24 (83%)

UTI/COMP	
E. AEROGENES	2/ 2 (100%)
E. COLI	5/ 6 (83%)
K. PNEUMONIAE	1/ 2 (50%)
S. ENTERITIDIS	1/ 1 (100%)
TOTAL/COMP	9/ 11 (82%)

UTI/PYELONEPH	
E. COLI	6/ 7 (86%)
P. MIRABILIS	0/ 1 (0%)
P. AERUGINOSA	1/ 1 (100%)
TOTAL/PYELO	7/ 9 (78%)

UTI/UNCOMP	
E. COLI	3/ 3 (100%)
K. PNEUMONIAE	1/ 1 (100%)
TOTAL/UNCOMP	4/ 4 (100%)

E. coli was the most commonly isolated pathogen, it was eradicated in 14/16 infections (88%).

Persistence was noted in patients infected with E. coli, K. pneumoniae, and P. mirabilis. One patient was treated for an infection due to P. aeruginosa, the infection was eradicated.

Bacteriologic Efficacy at the 4-6 Weeks Post-Therapy Evaluation:

Although the protocol specified an evaluation at 4 to 6 week after the conclusion of therapy, in reality most patients were not assessed at this point. In fact, the sponsor did not comment on the results of this evaluation in their study report.

According to the medical officer, of the 24 evaluable patients, there were 3 early persistence which were not eligible for late assessment, 5 were assessed for bacteriologic outcome after the 5-9 day post-therapy assessment and 16 patient were not assessed further after the 5-9 day assessment.

Of the 5 patients assessed, 1 patient showed continued eradication at 4-6 weeks post therapy. Four patients had become reinfected with new pathogens after their initial post-therapy evaluation.

Organisms causing reinfection included Enterococci (2), *K. pneumoniae*(1), *K. oxytoca*(1), and *P. aeruginosa*(1). The Enterococci were resistant to cefepime, the two species of *Klebsiella* were sensitive to cefepime. The *Pseudomonas* was not tested.

Safety Evaluation

Deaths

Seven deaths occurred among UTI patients in study 411-061.

- The patient was a 63 y.o. male with carcinoma of the lung; he was ventilator dependent. The patient was treated for a UTI due to *P. aeruginosa* with cefepime from 10/8-10/15/87. On 10/22 the patient requested that ventilatory support be discontinued. On 10/27 the patient died of respiratory insufficiency.

- The patient was a 72 y.o. male with a history of hypertension, renal insufficiency, diabetes, and multiple CVAs. The patient was admitted for vomiting and altered mental status. A urine culture grew *E. coli* and the patient was treated for six days with cefepime with good clinical and bacteriological response. The patient expired one day after completing therapy. The cause of death was not known, however, the investigator did not believe the death was related to the patient's UTI or to cefepime therapy.

- The patient was an 85 y.o. female who was treated with cefepime from 9/1-9/7/88 for a UTI due to *K. pneumoniae*. The patient responded to therapy. On 9/8/88 the patient began to have chest pain. The patient was found to have suffered an acute myocardial infarction. The patient died the same day from cardiac arrest.

- The patient was a 73 y.o. male with a history of multiple CVAs. The patient presented to the emergency room hypotensive and unresponsive. The patient required intubation and mechanical ventilation. While in the hospital, the patient developed a metabolic acidosis, a gastrointestinal bleed and a UTI due to *E. coli*. The patient was treated with cefepime from 9/25-9/27/87. The patient continued to deteriorate clinically and died on 9/28/87. Blood cultures at the time of death were sterile. The investigator did not believe that the patient's death was related to sepsis.

- The patient was a 41 y.o. female with a history of breast cancer with metastasis to lung and bones. The patient was admitted with fever and symptoms of UTI. The patient treated with cefepime for 6 days. Cefepime therapy was discontinued when multiple urine cultures were sterile. The patient died 2 weeks after the last day of cefepime therapy. The patient's death was thought to be secondary to her malignancy.

- The patient was 73 y.o. female with squamous cell carcinoma of the lung. The patient was admitted for treatment of a hydropneumothorax. The patient developed an *E. coli* UTI while in the hospital. The patient was treated with cefepime from 3/24-3/30. The patient responded to treatment. The patient was discharged to hospice care where she died on 4/12.

- The patient was an 82 y.o. male who presented on 5/7 with progressive shortness of breath and chest pain. The patient was found to have a gastric ulcer. During the hospitalization, the patient developed atrial

fibrillation. On 5/21 the patient suffered a cerebellar CVA. On 5/23 the patient became febrile. A chest x-ray showed bilateral pneumonia, the urine culture grew Enterococci. Cefepime was started on 5/23. On 5/24 the patient vomited and aspirated gastric contents. Clindamycin was added to cefepime to cover for aspiration pneumonia. The patient was placed on DNR status. The patient died on 5/29. No autopsy was performed.

COMMENT: All deaths occurred in individuals with multiple, serious pre-existing medical problems. No deaths appeared to be due to a direct effect of cefepime therapy or to therapeutic failure.

DISCONTINUATIONS

Three patients discontinued cefepime therapy due to adverse events.

- The patient was treated with cefepime from 3/27-4/7. On 4/1 the patient was noted to have an absolute eosinophil count of 2400 cells/mm³. Cefepime was discontinued because of eosinophilia.

COMMENT: Patient was receiving aspirin and dilantin concurrently.

- The patient received one dose of cefepime on 2/10. On 2/11 the patient's serum creatinine had risen from 1.6 mg/dL on admission to 2.4 mg/dL. On 2/12 the creatinine had risen to 3.2 mg/dL. Cefepime was discontinued due to high serum creatinine. By 2/16 the creatinine had fallen to 1.7 mg/dL.

COMMENT: Patient also received an intravenous contrast agent during the same time period.

- Cefepime was discontinued after two days of therapy because of intolerance at the infusion site.

Clinical Adverse Events

Clinical adverse events were noted in 9/116 UTI patients (8%) exposed to cefepime. Most adverse events were felt to be unrelated to drug therapy. There were two events (monilia, vaginal; pseudomembranous colitis) thought to be probably related to drug therapy. One event (chest tightness) was of unknown relationship to drug therapy.

Most adverse events were of mild or moderate severity. One event, seizure, was considered severe.

Table 061.16 lists individual adverse clinical events by severity and relationship to study therapy.

Table 061.16
Clinical Adverse Events
(According to the Medical Officer)

Relationship/ Event	Number of Events			Total
	Mild	Moderate	Severe	
Probably Related				
Monilia, Vaginal	-	1	-	1
Colitis, Pseudomemb	-	1	-	1
Unknown Relationship				
Tightness, Chest	1	-	-	1
Not Related				
Hemoptysis	-	1	-	1
Nausea	1	1	-	2
Pain, Chest	-	1	-	1
Rash	-	1	-	1
Seizure	-	-	1	1
Vomiting	1	-	-	1
Total Events	3	6	1	10
Total Patients*	2	6	1	9

*If one than one event occurred in a single patient, the patient is included in the most severe category.

Local Reactions at the Infusion Site

Local reaction at the infusion site were noted in 2/116 patients (2%) of patients exposed. Both patients received cefepime 1 gram Q12h. One patient discontinued study therapy do to phlebitis at the infusion site. There was no occurrence of local reactions at the infusion site in patients who received cefepime 2 grams Q12h.

Laboratory Test Abnormalities:

Protocol #061 was designed to study the safety and efficacy of cefepime for a variety of indications. The applicant did not organize their data in such a way that laboratory test abnormalities occurring in UTI patients could be separated from laboratory test abnormalities occurring in patients studied for claims of efficacy in other indications. Therefore, no data on laboratory test abnormalities will be included in this study report. However, any laboratory test abnormalities which occurred in UTI patients enrolled in study #061 will be

included in the integrated summary of safety for UTI patients.

Conclusions

Study 411-061 was an open, non-comparative study of the safety and efficacy of cefepime in the treatment of moderate to severe infections. There were 116 patients with urinary tract infections enrolled. 45/116 (39%) were considered evaluable by the applicant and 24/116 (21%) were considered evaluable by the medical officer. The discrepancy in evaluability rates arose from a the different criteria used for the early post-therapy assessment used by the applicant and the medical officer.

The population studied consisted mostly of white females. Most patients had pre-existing medical conditions. In both the applicant's and the reviewer's evaluable populations most UTIs were complicated. Most patient received cefepime at a dose of 1 g BID, however a small number of patients (applicant=3, medical officer=2) received cefepime at a dose of 2 g BID. The average duration of therapy was 7.9 days.

According to the applicant, a satisfactory clinical outcome was seen in 91% of UTI patients (41/45) treated with cefepime. A bacteriologic response of eradication was seen in 45/49 (92%) of infections treated with cefepime.

According to the medical officer, a complete clinical cure was seen in 18/24 patients (75%) after therapy with cefepime. A bacteriologic response of eradication was seen in 20/24 infections (83%) treated with cefepime.

The mortality rate among patients treated with cefepime was 6% (7/111). In all cases the deaths did not appear to be a result of cefepime therapy. Three patients discontinued therapy due to treatment related adverse events. Clinical adverse events were noted in 9/116 UTI patients exposed to cefepime. Two events: vaginal moniliasis and pseudomembranous colitis were felt to be related to cefepime therapy. Laboratory adverse events were not assessed for this population.

The recently released IDSA guidelines for the evaluation of drugs for the treatment of urinary tract infections gives the following expected eradication rates for the 5-9 day post-therapy evaluation: for uncomplicated UTI >85%, for pyelonephritis, >80%, and for complicated UTI > 60%. The eradication rates seen in study 411-061 were for complicated UTI = 82%, for pyelonephritis = 78% and for uncomplicated UTI = 100%. Thus, the experimental eradication rates achieved (83%) compares favorably with the historical values presented in the IDSA guidelines. No safety related concerns were raised by this study.

Since the numbers of patients in each sub-group were small, care must be taken in interpreting the results of this study. Nevertheless, it is the opinion of the medical officer that this study is supportive of the claim of efficacy for cefepime in uncomplicated and complicated UTI including pyelonephritis.

PROTOCOL: 411-140**Introduction**

Protocol #411-140 was designed to study the safety and efficacy of cefepime in the treatment of serious bacterial infections particularly those caused by *Staphylococci*, *Pseudomonas*, and other less common Gram-Negative bacilli. The current study provides safety and efficacy data for cefepime in treating patients with suspected or serious infections of urinary tract (UTI), skin and skin structures (SSTI), or caused by a broad range of pathogens.

Investigational Plan**Design Overview**

This trial was an open, noncomparative clinical study at multiple centers in the United States.

Inclusion/Exclusion Criteria

Study number 411-140 shared many of the inclusion/exclusion criteria that were common to other UTI protocols and were outlined in the preamble to this review. Exceptions to the common UTI protocol inclusion/exclusion criteria will be noted below.

Protocol number 411-140 allowed for the inclusion of:

- Patients with signs or symptoms of shock defined by systolic BP < 80 mm Hg or need for intravenous pressure therapy to maintain blood pressure > 80 mm Hg for > 4 hours.
- Patients with granulocytopenia (PMN < 500 cells/cmm) which was expected to persist seven days or less.

Procedures and Observations

Study 411-140 employed the same pre, during and post-treatment procedures as other UTI protocols.

Study Drug Administration

Patients were administered 2 g doses every 12 hours (or every 8 hours for very severe, life-threatening infections) to be given for a period of up to 28 days.

Population Studied

Three hundred seventy-one patients enrolled between November 6, 1989 and September 23, 1991. Of the 371 patients enrolled, 120 were diagnosed with UTI.

Evaluability for the Assessment of Safety

All 120 patients with UTI received at least one dose of cefepime and, therefore, were evaluable for the assessment of drug safety.

Evaluability for the Assessment of Efficacy

Table-140.1 presents the enrollment and evaluability, according to both the

applicant and the FDA reviewer at each of the study centers.

Table-140.1
Enrollment and Evaluability
Study 411-140

Study Center	Principal Investigator*	Location	Number of Patients		M.O.
			Enrolled	Evaluable EMS	
I-003	Hooker, K. Dale	Kansas City, MO	11	0	0
I-006	McCabe, Robert	Martinez, CA	2	0	0
I-009	Tan, James	Akron, OH	16	8	9
I-010	Hofstetter, Mark	Pittsburgh, PA	1	1	1
I-012	Yangco, Bienvenido	Tampa, FL	8	2	2
I-014	Butler, Thomas	Lubbock, TX	13	5	5
I-016	Stevens, Dennis	Boise, ID	10	3	3
I-020	Brooks, Robert/ Sieger, Barry	Orlando, FL	16	11	10
I-021	Gentry, Layne, M.D.	Houston, TX/ San Jose, Costa Rica	11	0	0
I-022	Najem, Ahmad	East Orange, NJ	1	0	1
I-023	McCloskey, Richard	Philadelphia, PA	2	1	1
I-024	Gelfand, Michael/ Simmons, Bryan	Memphis, TN	7	1	0
I-027	Muder, Robert	Pittsburgh, PA	2	0	0
I-030	Jauregui, Luis	Toledo, OH	5	1	1
I-031	Smith, David	Kansas City, MO	12	2	2
I-032	Sarubbi, Felix	Mountain Home, TN/ Johnson City, TN	2	1	1
I-042	Eng, Robert/ Fan-Havard, Patty	East Orange, NJ	<u>1</u>	<u>0</u>	<u>0</u>
TOTAL UTI			120	36 (30)	36 (30)

COMMENT: Results presented in this report summarize data for all study centers for Protocol 411-140 except Center 021. Due to abnormalities in the manner in which pre-treatment cultures were reported for center 21, the sponsor did not make any claims of efficacy based on the results obtained from that center. Safety experience gained at center 021 is included in the overall analysis of safety.

COMMENT: None of the investigators involved in study #411-140 are listed in the DSI registry of restricted investigators. The DSI accepted assurances from Dr. Michael Gelfand in 1981 for the performance of future studies.

Summary of Non-Evaluability:

According to both the applicant and the reviewer, the most common reason for a patient to be considered not evaluable was the failure to perform the post-treatment assessment within the specified time window.

Table 140.2 summarizes the major reasons for non-evaluability according to both the applicant and the reviewer.

Table 140.2
Summary of Non-Evaluability
Study 411-140

Reason for Exclusion	Number (%) ¹ BMS	Infections Review
UTI	N = 120	N = 120
Total Excluded (Unevaluable)	84 (70)	84 (70)
No pre-Rx culture	3 (3)	3 (3)
No pathogen isolated	9 (8)	14 (11)
Asymptomatic UTI, 1 pre-Rx culture	1 (1)	2 (2)
No pre-kx colony count	4 (3)	
Pre-Rx colony count < 10 ⁵ CFU/ml	8 (7)	
Sensitivity testing not done	7 (6)	3 (3)
Resistant organism	4 (3)	6 (5)
No During Therapy Assessment	4 (3)	4 (4)
Incomplete treatment	10 (8)	
Due to ADR		2 (2)
Due to Death		5 (4)
Due to Patient Decision		1 (1)
Other antibiotic during Rx	4 (3)	
Oral Continuation of Treatment		6 (5)
Infection at Distant Site		6 (5)
Protocol Error		1 (1)
Post-Rx visit out of window	19 (16)	20 (17)
Administrative Decision ²	11 (9)	11 (9)
Evaluable Infections	36 (30)	36 (30)

- 1 Percentages in parenthesis are based on total number of patients enrolled.
- 2 Includes data from center I-021, where patients were excluded for inability to verify the case report forms.

Applicant/Reviewer Evaluability Differences

In the majority of cases the applicant and the reviewer agreed on the assessment of evaluability.

Two patients were considered evaluable by the applicant who were considered not-evaluable by the reviewer. Both patients had received a non-study antimicrobial drug prior to the post-treatment assessment.

Two patients were considered not-evaluable by the applicant who were considered to be evaluable by the reviewer. Both patients were placed on alternative antimicrobial agents for persistence or worsening of symptoms. These patients were considered to have a "presumptive" persistence of their original infection and they were considered to be clinical failures by the reviewer.

DEMOGRAPHIC CHARACTERISTICS

The majority of patients (57%) enrolled in the study were female. Most patients were white (73%). The mean age was 54 years. Table 140.3 presents the demographic characteristics of the enrolled population.

Table 140.3
Demographic Characteristics
of the Enrolled Population
Study 411-140

Parameter	CEFEPIME	
SEX		
FEMALE	68	(57%)
MALE	52	(43%)
RACE		
WHITE	88	(73%)
BLACK	23	(19%)
HISPANIC	9	(8%)
AGE (YR)		
N	120	
MEAN	53.7	
MEDIAN	60	
RANGE		
AGE DISTRIBUTION		
< 18	1	(1%)
18 - 24	18	(15%)
25 - 44	20	(17%)
45 - 64	30	(25%)
65 - 84	44	(37%)
85 +	7	(6%)

The applicant's evaluable population had a similar demographic profile to the enrolled population. Most patients were female (78%) and white (64%). The mean age was younger in the evaluable population (43 years) compared with the enrolled population (54 years). The demographic characteristics of the reviewer's evaluable population were similar to the applicant's. Tables 140.4 and 140.5 presents the demographic characteristics of the applicant's and the reviewer's evaluable populations.

Table 140.4
Demographic Characteristics
Applicant's Evaluable Population
Study 411-140

Table 140.5
Demographic Characteristics
Reviewer's Evaluable Population
Study 411-140

Parameter	CEFEPIME		Parameter	CEFEPIME	
SEX					
FEMALE	28	(78%)	FEMALE	26	(72%)
MALE	8	(22%)	MALE	10	(28%)
RACE					
WHITE	23	(64%)	WHITE	25	(69%)
BLACK	9	(25%)	BLACK	7	(19%)
HISPANIC	4	(11%)	HISPANIC	4	(11%)
AGE (YR)					
N	36		N	36	
MEAN	42.6		MEAN	43.9	
MEDIAN	37		MEDIAN	41	
AGE DISTRIBUTION					
< 18	1	(3%)	< 18	1	(3%)
18 - 24	10	(28%)	18 - 24	10	(28%)
25 - 44	9	(25%)	25 - 44	8	(22%)
45 - 64	7	(19%)	45 - 64	7	(19%)
65 - 84	8	(22%)	65 - 84	9	(25%)
85 +	1	(3%)	85 +	1	(3%)

Medical History

In both the applicant's and the reviewer's evaluable population, pyelonephritis was the most commonly seen relevant medical condition. Among patients with complicated UTI who did not have pyelonephritis, in the applicant's population, the most commonly seen condition was a catheter associated UTI, however, in the reviewer's evaluable population the most commonly seen condition was obstructive uropathy. Table 140.6 summarizes the relevant medical conditions present in the evaluable populations.

Table-140.6
Relevant Medical Conditions
Evaluable Population
Study 411-140

Condition	Number of Patients	
	Applicant ^a	Reviewer ^b
COMPLICATED UTI	N = 34	N = 31
Specific urinary tract conditions:		
Upper UTI	27 (79)	22 (71)
Urinary tract surgery	5 (15)	2 (6)
Obstruction	8 (24)	5 (16)
Urinary tract catheter (all types)	9 (26)	1 (3)
Urethral catheter	7	
Nephrostomy tube	1	
Intermittent catheter	2	
Urinary tract anatomic abnormality	1 (3)	
Other conditions	3 (9)	1 (3)
Diabetes	3 (9)	
UNCOMPLICATED UTI	N = 2	N = 5

a More than one condition may occur in a single patient.

b The most significant conditions was identified for each patient.

Concomitant Drug Therapy

According to the sponsor, of the 116 evaluable patients, 114 (98%) received concomitant medication, including 20 (17%) who received antimicrobial agents (4 of whom received metronidazole) with no known activity against the genus of pathogen involved in the original infection.

Study Drug Administration

According to the applicant, Cefepime was given to 35 (97%) of the 36 evaluable UTI patients at a dose of 2 g BID (the dose for one of these patients was adjusted to 2 g QD due to renal impairment) and to 1 (3%) patient at a dose of 2 g TID. Duration of dosing ranged from 4 to 14 days. Number of doses ranged from 4 to 26. Table 140.8 summarizes the applicant's assessment of duration of drug therapy.

Table 140.7
Duration of Study Drug Therapy
According to the Applicant
Study 411-140

Parameter	<u>Number (%) of Patients</u>	
	2 g BID	2 g TID
Duration of Dosing (days)	N = 35 ^a	N = 1
4	3 (9)	
5	8 (23)	
6	3 (9)	
7	7 (20)	
8	5 (14)	
9	1 (3)	1 (100)
10	2 (6)	
11-14	6 (17)	

a- Includes one patient whose dose was adjusted for renal failure.

All patients in the reviewer's evaluable population received cefepime at a dose of 2 grams BID. Duration of therapy ranged from 4 to 14 days. The mean duration of therapy was 7.4 days. The median duration of therapy was 8.5 days. Table 140.8 summarizes the duration of dosing for the reviewer's evaluable population.

Table 140.8
Duration of Study Drug Therapy
According to the Reviewer
Study 411-140

Parameter	<u>Number (%) of Patients</u>	
	2 g BID	
Duration of Dosing (days)	N = 36	
4	4	(11)
5	8	(22)
6	3	(8)
7	7	(19)
8	6	(17)
9	1	(3)
10	1	(3)
11-14	6	(17)

Clinical Efficacy

According to the applicant, overall, 23/36 patients (64%) were assigned a clinical response of cure. Table-104.9 summarizes the applicant's assessment of the clinical response for the sub-populations of complicated and uncomplicated UTI patients.

Table 140.9
Clinical Response
Study 411-140/UTI
(According to the Applicant)

Number of Diagnoses and Pathogens	----- Number of Patients -----							
	<u>Uncomplicated</u>				<u>Complicated</u>			
	Cured	Imp.	Uns.	Total	Cured	Imp.	Uns.	Total
Total UTI Patients	2	0	0	2	21	5	8	34
Percent	(100)	(0)	(0)		(62)	(15)	(24)	

According to the reviewer, overall, 27/36 patients (75%) were assigned a clinical response of cure at the end of therapy. Table-140.10 summarizes the reviewer's assessment of the clinical response.

Table-140.10
Clinical Efficacy
(According to the Reviewer)
Study #140

Parameter	CEFEPIME
NO. OF EVALUABLE PATIENTS	36
UTI/OVERALL	
CURE	27 (75%)
IMPROV	2 (6%)
FAILURE	7 (19%)
COMPLICATED UTI	9
CURE	3 (33%)
IMPROV	1 (11%)
FAILURE	5 (56%)
PYELONEPHRITIS	22
CURE	19 (86%)
IMPROV	1 (5%)
FAILURE	2 (9%)
UNCOMPLICATED UTI	5
CURE	5 (100%)

COMMENT: The reviewer's complicated UTI population was comprised of 78% males with a mean age of 60. UTI in older males often occurs concomitantly with prostatitis. Since prostatitis tends to be a relapsing and recurring infection which is difficult to cure, the presence of a predominance of males may account for the low rates of clinical cure seen in the complicated UTI population

Bacteriologic Efficacy**Susceptibility of Pathogens**

According to the applicant, *E. coli* was the most common pathogen isolated from patients with UTI, accounting for 54 (49%) of the 111 isolates tested, followed by *K. pneumoniae* in 12 (11%). Only 7 (6%) of 111 isolates tested were resistant to cefepime. Table 140.11 summarizes the susceptibility of pathogens recovered from UTI patients.

Table 140.11
Susceptibility of Pathogens
Study 411-140/UTI

Infection Type/ Pathogen	Number (%) of Pathogens			Total
	----- Type of Sensitivity -----			
	Susceptible	Intermediate	Resistant	
UTI				
<i>Corynebacterium</i> sp.			1 (100)	1
<i>Lactobacillus</i> sp.	1 (100)			1
<i>S. faecalis</i>	1 (25)	1 (25)	2 (50)	4
<i>S. agalactiae</i>	1 (100)			1
<i>Enterococcus</i>			2 (100)	2
Strep. (Group B)	1 (100)			1
<i>S. epidermidis</i>	3 (100)			3
<i>S. epidermidis</i> (MR)		1 (100)		1
<i>P. aeruginosa</i>	9 (82)		2 (18)	11
<i>E. coli</i>	54 (100)			54
<i>C. freundii</i>	1 (100)			1
<i>C. diversus</i>	3 (100)			3
<i>K. pneumoniae</i>	12 (100)			12
<i>E. cloacae</i>	2 (100)			2
<i>E. aerogenes</i>	1 (100)			1
<i>S. marcescens</i>	3 (100)			3
<i>P. mirabilis</i>	6 (100)			6
<i>P. rettgeri</i>	1 (100)			1
<i>P. stuartii</i>	2 (100)			2
<i>O. urethralis</i>	1 (100)			1
Total	102 (92)	2 (2)	7 (6)	111

Bacteriologic Response at the 5 to 9 Days Post-Therapy Evaluation

According to the applicant, overall, 31/38 pathogens (82%) were eradicated by cefepime treatment including 29/36 pathogens (81%) in patients with complicated UTI and 2/2 pathogens (100%) in patients with uncomplicated UTI. Table-140.12 summarizes the applicant's assessment of the bacteriologic response at the 5-9 days post-therapy evaluation.

Table-140.12
Bacteriologic Efficacy at the 5-9 Days Post-Therapy Evaluation
(According to the Applicant)
Study #140

Pathogen	----- Number of Pathogens -----					
	<u>Uncomplicated</u>			<u>Complicated</u>		
	Erad.	Pers.	Total	Erad.	Pers.	Total
S. faecalis				1		1
P. aeruginosa				2	2	4
E. coli				24	3	27
K. pneumoniae	2		2	1		1
E. aerogenes				1		1
S. marcescens					1	1
P. mirabilis				<u>1</u>		<u>1</u>
Total Pathogens*	<u>2</u>	<u>0</u>	<u>2</u>	<u>29</u>	<u>7</u>	<u>36</u>
Percent	(100)	(0)		(81)	(19)	

* Based on 36 patients.

NOTE: Erad. = Eradicated; Pers. = Persisted.

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According to the reviewer, overall, 30/39 pathogens (77%) were eradicated by cefepime therapy, including 7/11 pathogens (64%) in patients with complicated UTI, 18/23 pathogens (78%) in patients with pyelonephritis, and 5/5 pathogens (100%) in patients with uncomplicated UTI. Table-140.12 summarizes the reviewer's assessment of the bacteriologic efficacy at the 5 to 9 days post-therapy assessment.

Table-140.12
Bacteriologic Efficacy at 5 to 9 Days Post-Therapy
(According to the Reviewer)
Study #140

Parameter	CEFEPIME

COMPLICATED UTI	
E. AEROGENES	1/ 1 (100%)
E. COLI	1/ 1 (100%)
K. PNEUMONIAE	1/ 2 (50%)
P. AERUGINOSA	2/ 4 (50%)
P. MIRABILIS	1/ 1 (100%)
P. STUARTII	0/ 1 (0%)
S. MARCESCENS	1/ 1 (100%)
TOTAL/COMP	7/ 11 (64%)

PYELONEPHRITIS	
E. COLI	18/ 21 (86%)
P. AERUGINOSA	0/ 1 (0%)
S. FAECALIS	0/ 1 (0%)
TOTAL/PYELO	18/ 23 (78%)

UNCOMPLICATED UTI	
E. COLI	3/ 3 (100%)
K. PNEUMONIAE	2/ 2 (100%)
TOTAL/UNCOMP	5/ 5 (100%)

TOTAL OVERALL	30/ 39 (77%)

COMMENT: The predominance of males in the complicated UTI group may account for the low eradication rate (See related comment regarding clinical response in this group).

The most commonly recovered organism was *E. coli* which was eradicated in 22/25 infections (88%). *Pseudomonas aeruginosa* was recovered from 5 patients but even at the high dose of medication used in this study, was only eradicated in 2 (40%).

Bacteriologic persistence was seen in infections caused by *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *P. stuartii*, and *S. faecalis*.

Bacteriologic Efficacy at 4 to 6 Weeks Post-Therapy

Table-140.13 presents the applicant's assessment of the bacteriologic efficacy at 4 to 6 weeks post-therapy.

Table-140.13
Bacteriologic Efficacy at 4 to 6 Weeks Post-Therapy
For Evaluable Patients
(According to the Applicant)
Study #140

<u>Parameters</u>	<u>Number (#)+ of Patients</u>
<u>Patients with Complicated UTI</u>	34
Total patients with 4-6 week follow-up culture	7
No follow-up culture	8
Persistence at Day 5-9 post-treatment	6 ¹
Patients with missing information	13
<u>Bacteriologic Response at 4-6 Weeks</u>	
Continued eradication	5 (71)
Eradication with relapse	1 (14)
Eradication with reinfection	1 (14)

* Percentages based on all patients with 4-6 week follow-up.

1 One relapse involved more than one pathogen.

Table-140.15 presents the reviewer's assessment of the bacteriologic efficacy at the 4-6 weeks post-therapy evaluation.

Table-140.15
Bacteriologic Efficacy at the 4 to 6 Weeks Post-Therapy Evaluation
(According to the Reviewer)
Study #140

Parameters	Number (%) of Patients
<u>Patients with Evaluable UTI</u>	36
Persistence at Day 5-9 Post Treatment	7
No Late Follow-Up Evaluation	18
Patients with Late Follow-Up Evaluation	11 (38) ¹
<u>Bacteriologic Response at 4-6 Weeks</u>	
Continued eradication	3 (27) ²
Eradication with relapse	3 (27) ²
Eradication with reinfection	5 (45) ²

- 1 Percent of Patients Eligible for 4-6 week culture (enrolled-early persistence).
- 2 Percent of patients with late follow-up evaluation.

Three patients had relapse of their infection after the 5 to 9 day post-therapy evaluation. One relapse each was caused by *E. coli*, *K. pneumoniae* and *S. marcescens*. All organisms remained susceptible to cefepime at the time of relapse.

There were six reinfections in 5 patients after the 5 to 9 day post-therapy evaluation. Three reinfections were due to *Enterococcus* spp.; one reinfection was due to fungus; one reinfection was due each to *P. aeruginosa* and *P. vulgaris*. Both the *P. aeruginosa* and the *P. vulgaris* were of intermediate susceptibility to cefepime.

COMMENT: The medical officer has not observed the presence of resistant organisms causing reinfection in other UTI studies using lower doses of cefepime. It is interesting to speculate whether treatment with high dose cefepime may result in the emergence of a resistant population.

Safety Analysis

Deaths

There were 119 patients with urinary tract infection who received at least one dose of cefepime and were therefore, included in the analysis of safety.

Cefepime Deaths

Fourteen deaths occurred among the 119 patients with UTI who were exposed to cefepime. The mortality rate was 12%.

COMMENT: This study was designed to assess the efficacy of cefepime in a seriously ill population, thus, a high mortality rate is not unexpected.

Three of the patients who died were receiving cefepime 2 grams TID at the time of their death. The remainder of the patients received cefepime less frequently.

- The patient was a 68 y.o. female with a history of diabetes mellitus, hypertension, arteriosclerotic heart disease, congestive heart failure, CVA and adenocarcinoma of the prostate. The patient was placed on the cefepime protocol for urinary tract infection and sepsis with *Acinetobacter* spp. The patient was critically ill from admission to the study and was placed on "do not resuscitate" status shortly after enrollment. The patient received one dose of cefepime. The patient died four hours after the first dose of cefepime. The cause of death was not known. No autopsy was performed.

- The patient was a 45 y.o. male with history of hypertension; gout and renal stones. The patient was admitted on 10/12 with urosepsis due to *E. coli*. The patient received 3 doses of cefepime (2 grams Q 12H). The patient's sepsis was not controlled. The patient expired due to complication of sepsis.

- The patient was an 83 y.o. male with multiple decubitus ulcers who developed fever, chills, and lethargy. The patient was diagnosed with pneumonia and *E. coli* UTI. The patient was treated with cefepime from 5/5-5/6. The patient expired on 5/6. The patient was believed to be fungemic at the time of death. The source of the fungemia was thought to be the patient's multiple decubiti.

- The patient was a 70 y.o. male with a history of coronary artery disease, congestive heart failure, multiple myocardial infarctions, coronary artery bypass surgery, ulcer disease, benign prostatic hypertrophy and blockage of the carotid artery. The patient was enrolled in the cefepime study for suspected urosepsis with *K. pneumoniae*. The patient was treated with cefepime from 9/30 to 10/13. On day #5 of therapy, the patient had an acute change in mental status which resolved spontaneously. The patient had a deterioration in renal function during the treatment period as evidenced by a creatinine which was 2.0 on admission and rose to 3.9 by 10/13. On 10/13 the patient experienced another decline in mental status. Cefepime therapy was discontinued at this time. Subsequently, the patient had a progressive decline of his cardiac, renal and mental status. The patient died on 11/1 of cerebrovascular insufficiency.

The patient was a 71 y.o. female with a one day history of fever, decreased responsiveness, vomiting and seizure activity. Admission urine and blood cultures were positive for *E. coli* and *P. mirabilis*. The patient was enrolled in the cefepime study and received 4 doses of cefepime. The patient was removed from the study when she was placed on DNR status. The patient died the next day. The cause of death was sepsis.

- the patient was 71 y.o. male who was admitted on 1/1 with symptoms of congestive heart failure. The patient required operative pacemaker insertion for treatment. Peri-operative prophylaxis with vancomycin was given. Post-operatively (on 1/7), patient's blood culture grew *S. aureus*, *S. simulans*, *Enterococcus* spp., and *K. pneumoniae*. The urine culture also grew *K. pneumoniae*. The patient received 5 doses of cefepime. At this time, the patient continued to be febrile, so the patient was removed from the study and placed on vancomycin and ceftazidime. The patient was successfully treated with vancomycin and ceftazidime and was discharged to continue oral treatment with ciprofloxacin. The patient died approximately 3 weeks after removal from the study. The cause of death was congestive heart failure.

- The patient was a 75 y.o. male who was admitted with severe pneumonia. The patient's blood culture grew *S. pneumoniae*. The patient's urine culture grew *E. coli*. The patient was enrolled in the cefepime study and received one dose of study medication. The patient was removed from the study after a respiratory decompensation and transfer to the intensive care unit. The patient was treated with vancomycin, ceftazidime and gentamicin. The patient continued to deteriorate, however, and died 13 days after randomization.

- The patient was an 80 y.o. female with a history of congestive heart failure, multiple decubitus ulcers, cerebrovascular accident and hemiplegia. The patient was enrolled in the cefepime study with a *P. mirabilis* UTI and a "Gram-negative" pneumonia. The patient received cefepime for one day. The patient was removed from the study and started on "triple antibiotics" for deterioration. The patient died 17 days after removal from the cefepime study. The cause of death was not determined.

- The patient was a 65 y.o. male with a history of quadriplegia, pyelonephritis, renal calculi and a decubitus ulcer. The patient was admitted on 2/3 with symptoms of a urinary tract infection. The urine culture grew *Pseudomonas* spp.. The patient was treated with cefepime for 13 days. The original infecting organism was cleared but the patient developed a reinfection with *Enterococcus* spp. The patient became bacteremic with *Enterococci* and died 13 days after the completion of therapy.

with
The patient was a 99 y.o. male with a history of congestive heart failure; arteriosclerotic heart disease; and chronic renal failure. The patient entered the study ~~was~~ an *E. coli* UTI. The patient was treated with cefepime (2 grams Q 12H) from 8/9 to 8/13. On 8/12 the urine culture grew *Enterococcus* spp. which was resistant to cefepime. The patient was discontinued from the study. The patient did not receive any therapy for his *Enterococcus*, but cleared the infection spontaneously by 8/15. On 8/16 the patient died of congestive heart failure. The patient was not believed to have been infected at the time of death.

- The patient was a 73 y.o. female with a history of diabetes mellitus who was admitted with pneumonia and UTI. The urine culture grew *E. coli*. The patient was treated with cefepime for three days. During that time the patient continued to deteriorate clinically and developed bacteremia due to *Proteus* spp. The patient was removed from the study for clinical failure and was treated with amikacin and ciprofloxacin. The patient died seventeen days later of multi-organ failure.

- The patient was a 68 y.o. male with a history of squamous cell carcinoma and hypercalcemia. The patient was enrolled in the cefepime study on 4/5 for the treatment of a UTI due to *Pseudomonas aeruginosa*. On day #2 of therapy, the patient became combative. On day #3 of therapy the patient became unresponsive to verbal stimulation. Cefepime was discontinued at that time and cefotaxime and tobramycin were substituted. The patient remained unresponsive.

A CT scan of the brain showed mild hydrocephalus and atrophy. Of interest, the patient entered the study with hypercalcemia (serum calcium=11.8) which worsened on therapy (serum calcium=12.5 on day #3 of therapy). The patient was placed on "do not resuscitate" status. The patient expired 5 days after randomization. A repeat urine culture prior to death was negative.

- The patient was an 86 y.o. female with a history of aortic stenosis and aortic insufficiency. The patient suffered a cardiac arrest on 9/28 requiring resuscitation and intubation. Post-resuscitation, the patient developed a fever. Blood cultures were sterile but a urine culture yielded *E. coli*. The patient entered the cefepime protocol. Three days after entry the patient developed loss of consciousness and hemoptysis. On the same day, the patient again became asystolic and expired.

- The patient was an 88 y.o. female who was admitted to the hospital after a syncopal episode at home. A urine culture yielded Group-B Streptococci and the patient was entered into the cefepime protocol. A blood culture was sterile. The patient appeared to respond to therapy and was discharged and transudient to oral amoxicillin after 4 days of cefepime. The patient died 3 weeks after randomization from aspiration pneumonia.

COMMENT: Because the population studied all had serious underlying illnesses it is difficult to assess the contribution of cefepime to the death of these 14 patients. In seven patients the death was clearly unrelated to cefepime. One patient died 4 hours after the first dose of cefepime. In four patients death with at least contributed to by a lack of therapeutic effect. Of note, in two instances the patient experienced acute changes in mental status while on cefepime therapy.

DISCONTINUATIONS

Eight patients were removed from cefepime therapy due to treatment related adverse events.

- The patient is a 20 y.o. female with *E. coli* UTI who developed hives and shortness of breath after the first dose of cefepime.

- 70 y.o. male who experienced two episodes of mental status change while on cefepime therapy. (See reports of deaths).

The patient is a 74 y.o. male with a *S. marcescens* pyelonephritis. Cefepime was discontinued on day #4 due to disorientation.

- The patient is a 45 y.o. female with *E. coli* UTI. Cefepime was discontinued on day #10 due to a rash.

- The patient is a 66 y.o. with UTI due to *P. mirabilis*. Cefepime was discontinued after the 4th dose due to the development of obtundation and confusion. The symptoms resolved after removal of the drug.

- 68 y.o. male who was removed from cefepime therapy when he became combative. (See report of deaths)

- 72 y.o. female who after 6 days of cefepime therapy refused further therapy because she felt "listless and unwell" after each infusion.

- 56 y.o. female with E. coli urosepsis who was removed from cefepime therapy on day #9 after the development of a red, raised rash.

COMMENT: Five of the eight patient who discontinued cefepime therapy were removed from the study after they experienced an acute mental status change. All of these patient were over 60 years of age. In all cases the patients were taking concomitant medications that have been reported to cause mental status changes (e.g. trazodone, cimetidine, lasix, metaclopramide). Therefore, the relationship to cefepime therapy is unclear.

CLINICAL ADVERSE EVENTS

Clinical adverse events were reported for 35 of the 119 patients (29%) exposed to at least one dose of cefepime. In total 73 clinical adverse events were reported. Clinical adverse events occurred most frequently within the gastrointestinal- (35%) and nervous (29%) systems. Table 140.16 presents the clinical adverse events reported by body system.

Table 140.16
Clinical ADE by Body System
Study 411-140/UTI

Body System	# of ADE (Percent)
Body as a Whole	3 (6)
Cardiovascular	3 (6)
Gastrointestinal	18 (35)
Genitourinary	3 (6)
Musculo-skeletal	1 (2)
Neurological	15 (29)
Respiratory	3 (6)
Skin	4 (8)
Special Senses	1 (2)
Any System	35

The most commonly reported clinical adverse events was diarrhea (8 reports). Most clinical adverse events were of mild severity (51%); there was one life-threatening clinical adverse event (ventricular arrhythmia). Table 140.17 presents the clinical adverse events reported by severity.

Table 140.17
Clinical Adverse Events by Severity
Study 411-140/UTI

Body System/ Event	Mild	Number of Events		Total
		Moderate (Life-Threatening)	Severe	
Body as a Whole				
Anaphylaxis	0	0	1	1
Diaphoresis	0	1	0	1
Fever	0	1	0	1
Cardiovascular				
Arrhythmia, Atrial	0	0	1	1
Arrhythmia, ventric.	0	0	(1)	1
Hypotension	1	0	1	1
Gastrointestinal				
Anorexia	0	1	0	1
Constipation	0	1	0	1
Diarrhea	5	3	0	8
Hematemesis	1	0	0	1
Hemorrhage, Upper	0	1	0	1
Jaundice	1	0	0	1
Nausea	4	1	0	6
Pain, Epigastric	1	0	0	1
Pain, Abdominal	2	0	0	2
Vomiting	6	1	0	7
Genitourinary				
Renal Failure	0	0	1	1
Vaginal Inflamm.	1	0	0	1
Vaginal Moniliasis	0	1	0	1
Musculo-Skeletal				
Neck Stiffness	1	0	0	1
Pain, Chest	1	0	0	1

Table 140.17-Continued
 Clinical Adverse Events by Severity
 Study 411-140/UTI

Body System/ Event	Number of Events			Total
	Mild	Moderate (Life-Threatening)	Severe	
Nervous				
Depression	0	1	0	1
Dizziness	1	0	0	1
Headache	2	2	0	4
Insomnia	1	0	0	1
Lethargy	1	0	1	2
Loss of Conscious	0	0	2	2
Mental Status Change	1	0	4	5
TIA	0	0	1	1
Tremors	0	1	0	1
Weakness	1	1	0	2
Special Senses				
Conjunctivitis	0	1	0	1
Skin/Skin Structures				
Hives	1	0	0	1
Pruritus	0	1	0	1
Rash	1	2	0	3
Respiratory				
Congestion	0	1	0	1
Cough	1	0	0	1
Epistaxis	1	0	0	1
Hiccups	2	0	0	2

There were 29 clinical adverse events (40%) that were considered to be of possible or unknown relationship to the study drug. Table 140.18 presents the clinical adverse events of possible or unknown relationship to the study drug.

Table 140.18
ADE of Probably or Unknown Relation to Drug
Study 411-140/UTI

ADE	Mild	Mod.	Severe	Total
Anaphylaxis	0	0	1	1
Cough	1	0	0	1
Diarrhea	3	2	0	5
Epistaxis	1	0	0	1
Headache	2	1	0	3
Hiccups	1	0	0	1
Hypotension	1	0	0	1
Lethargy	1	0	0	1
Loss of Consciousness	0	0	1	1
Monilia, vaginal	0	1	0	1
Nausea	1	1	0	2
Pruritus	0	1	0	1
Rash/Hives	2	1	0	3
Tremors	0	1	0	1
Vomiting	3	1	0	4
Weakness	1	0	0	1

Local Intolerance

There were 12 instances of infiltration or inflammation at the intravenous infusion site. One patient who received cefepime by intramuscular injection experienced pain at the injection site. No patients were removed from therapy because of local reactions at the site of cefepime administration.

Laboratory Test Abnormalities

Protocol #140 was designed to study the safety and efficacy of cefepime for a variety of indications in a population of seriously ill individuals. The applicant did not organize their data in such a way that laboratory test abnormalities occurring in UTI patients could be separated from laboratory test abnormalities occurring in patients studied for claims of efficacy in other indications. Therefore, no data on laboratory test abnormalities will be included in this study report. However, any laboratory test abnormalities which occurred in UTI patients enrolled in study #140 will be included in the integrated summary of safety for UTI patients.

Conclusions

Study #411-140 was designed to assess the safety and efficacy of high-dose cefepime (2 grams Q 12H to 2 grams Q 8H) in the treatment of severe infections. Patients with symptoms of septic shock and profound neutropenia were included. The protocol specifically was designed to assess "severe" Gram-negative infections such as infections due to *Pseudomonas* spp. and *Enterobacter* spp..

One hundred nineteen patients with urinary tract infections were enrolled in study #411-140. The majority of UTI patients were treated with cefepime 2 grams Q 12H. The duration of study drug administration ranged from 4 to 14 days.

According to the applicant, the bacteriologic eradication at the 5-9 days post-therapy assessment was 82% (31/38 pathogens). According to the reviewer, the overall bacteriologic eradication rate at the 5-9 days post-therapy assessment was 77% (30/39 pathogens). Of note, the overall bacteriologic eradication rate for *Pseudomonas aeruginosa* was 40% (2/5 isolates).

COMMENT: A lower overall eradication rate was seen in the reviewer's analysis because of the inclusion of patients who were treated with non-study antimicrobials prior to the post-therapy culture as bacteriologic failures.

The analysis of safety was performed on the entire 119 patients enrolled since all patients received at least one dose of cefepime. There were 14 deaths among UTI patients (mortality rate = 12%). Four of the 12 deaths were due to lack of effective treatment.

Seven patients were removed from cefepime therapy due to treatment related adverse events. Five of the seven patients (4% of the safety population) were removed from therapy because of alterations in mental status.

One life-threatening episode of ventricular arrhythmia occurred which was not related to cefepime therapy.

The majority of clinical adverse events, however, were mild and occurred within the gastrointestinal and nervous systems. Vomiting and diarrhea were the adverse events reported most frequently.

Overall, study 411-140 was supportive of the claim of efficacy for cefepime in the treatment of patients with urinary tract infections. This study, however, can not be considered supportive of the claim of efficacy in complicated UTI because of the low bacteriologic eradication rate (64%) and the low clinical cure rate (56%) seen in this population. Furthermore, study 411-140 can not be considered supportive of the claim of efficacy of cefepime in UTI due to *Pseudomonas aeruginosa*.

A potential safety concern is raised by the five patients who required discontinuation of study therapy due to acute alterations in mental status. Since the patients involved in study 411-140 were seriously ill at enrollment it is not clear whether this effect is a function of the high dose of medication used in this study or if it is, instead, a function of the patient's underlying disease. The significance of this observation awaits corroboration from studies of high-dose cefepime in indication other than UTI.

EUROPEAN NON-COMPARATIVE STUDIES**PROTOCOL: 411-067****Introduction****Objectives:**

To evaluate the safety and the clinical and bacteriologic efficacy of cefepime when administered intravenously at a dose of either 1g Q12h or 2g Q12h for the treatment of acute infections of the urinary tract, acute uncomplicated infections of the lower respiratory tract and mild to moderate infections of the skin and skin structure.

Investigational Plan**Design Overview**

This Phase II trial was an open, non-comparative clinical study at multiple centers in Europe.

Patient Selection and Study Procedures

Study #067 used the inclusion criteria that are common to all UTI protocols. One difference present in study 411-067 is the possibility to be assigned to two different doses of cefepime. The applicant states that patients with "serious" infections were assigned to the high-dose treatment group (2 grams Q12h). Serious was defined by the applicant as:

"A serious and/or complicated urinary tract infection includes, but is not limited to, an infection occurring in the presence of known anatomic abnormalities of the genitourinary tract, stones, stents, nephrostomy tubes or indwelling catheters."

While non-serious infections, which were to be randomized to low-dose therapy (1 gram Q12h) were defined as:

urinary tract infection such as pyelo-
cystitis, pyelonephritis, pyelitis.

COMMENT: In actuality, the patient population enrolled in the two treatment groups did not differ significantly in terms of the proportion of patients with complicated UTI. Please refer to medical history tables for information on relevant medical conditions.

Study Drug Administration:

Cefepime was supplied by Bristol-Myers Squibb Company in vials containing 1 gram of either a lyophilized mixture of cefepime and NaCl or a dry-powder blend of cefepime dihydrochloride and L-arginine. Investigators prepared cefepime of either formulation for infusion and administered the resulting solution intravenously over 30 minutes.

One cohort of patients, designated as "low-dose" received doses of 1 g Q12h for up to 14 days. A second cohort of patients, designated as "high-dose" received 2 g Q12h for up to 14 days.

Procedures and Observations

The procedures employed and the observations collected were consistent with those found in other UTI protocols and described in the preamble to this review.

Population Studied

In total, 346 patients were enrolled between September 19, 1987 and December 29, 1989. Among the 346 patients enrolled, 152 patients had urinary tract infection. Of the 152 urinary tract infection patients enrolled, 109 received low-dose cefepime (1 gram Q12H) and 43 received high-dose cefepime (2 grams Q12H).

Evaluability for the Assessment of Safety

All UTI patients received at least one dose of cefepime and, therefore, were evaluable for the assessment of safety.

Evaluability for the Assessment of Efficacy

Table-067.1 presents the enrollment; the applicant's assessment of evaluability; and the reviewer's assessment of evaluability at each study center.

Table-067.1
Enrollment and Evaluability
Study #067

Site	Principal Investigator	Location	Number of Patients		
			Enrolled	Evaluable (Percent) Applic.	Reviewer
LOW DOSE					
I-001	H. Van Landuyt	Brugge, Belgium	14	10 (16)	8 (15)
I-002	K.G. Naber	Straubing, Germany	22	18 (30)	17 (32)
I-003	M. Glauser	Lausanne, Switzerland	1	1 (2)	0
I-004	H. Giamarellou	Athens, Greece	12	5 (8)	5 (9)
I-006	F. Debruyne	Nijmegen, Holland	2	2 (3)	2 (4)
I-008	J. Berger	Vevey, Switzerland	1	0	0
I-009	Y. Mouton	Tourcoing, France	6	2 (3)	3 (6)
I-010	G. Humbert/ J. Leroy	Rouen, France	16	7 (11)	6 (11)
I-011	P. Veyssier	Compiègne, France	14	10 (16)	9 (17)
I-012	J. Modai	Paris, France	7	2 (3)	2 (4)
I-016	H. Mattie	Leiden, Holland	14	4 (7)	2 (4)
		TOTAL	109	61 (56)	54 (50)
HIGH DOSE					
I-009	Y. Mouton	Tourcoing, France	9	3 (20)	3 (20)
I-010	G. Humbert/ J. Leroy	Rouen, France	1	0	1 (7)
I-011	P. Veyssier	Compiègne, France	9	5 (33)	5 (33)
I-012	J. Modai	Paris, France	4	1 (7)	1 (7)
I-018	A. Bertrand	Montpellier, France	2	1 (7)	1 (7)
I-020	P. Dellamonica	Nice, France	13	4 (27)	3 (20)
I-021	M. Micoud/J.P.	Stahl Grenoble, France	4	1 (7)	1 (7)
I-022	J. Jourdan	Nîmes, France	1	0	0
		TOTAL	43	15 (35)	15 (35)

Summary of Non-Evaluability

According to the applicant, the most common reason for exclusion from the efficacy analysis was the failure to document a pathogen, occurring in 19/152 (13%) enrolled patients, the next most common reason was the failure to perform the post-treatment assessment at the appropriate time, occurring in 15/152 (10%) of enrolled patients. In contrast, the most common reason for which the medical officer considered patients to be not-evaluable was the failure to perform the post-treatment assessment at the appropriate time, occurring in 32/152 (21%) enrolled patients. The applicant accepted post-treatment assessments performed on day 3 post-therapy or later, however, the medical officer only accepted post-treatment assessments performed on day 5 post-therapy or later, thus accounting for the observed discrepancy.

Table-067.2 presents the major reasons for which patients were excluded from the analysis of efficacy by the medical officer.

Table-067.2
- Exclusions from the Analysis of Efficacy
Study #067

Reason	Number (%) of Unevaluable Infections (Percent) ¹
Total Enrolled	152
Total Excluded	83 (55%)
No Pre-Treatment Assessment or Out of Window	6 (4%)
No Pathogen Isolated	18 (12%)
Resistant Organism Isolated	2 (1%)
No During Treatment Assessment or Out of Window	5 (3%)
Incomplete Treatment/ADR	4 (3%)
Incomplete Treatment/Secondary Infection	1 (<1%)
Incomplete Treatment/Patient Request	2 (1%)
Incomplete Treatment/Ran Out of Drug	1 (<1%)
Protocol Error ²	3 (2%)
Other Antimicrobial Administered ³	9 (6%)
No Post-Treatment Assessment or Out of Window	32 (21%)
Total Evaluable	69 (45%)

1 Percent of Total Enrollment

2 Includes: Improper dosage administered

3 Patients in whom other antimicrobials drugs were administered for reasons other than clinical or bacteriological failure.

Applicant/Reviewer Evaluability Differences

Ten patients that were considered evaluable by the applicant were considered not-evaluable by the reviewer. In nine patients the post-treatment culture was performed out of the accepted range of 5 to 14 days after therapy. One patient was placed on bactrim prior to the post-therapy culture as "an oral follow-up to successful IV treatment".

Three patients who were considered not-evaluable by the applicant were considered

evaluable by the reviewer. In all cases, the patients were started on non-study antimicrobial drugs for persistence or worsening of symptoms. The patients were considered evaluable failures by the reviewer.

Demographic Characteristics

The majority of UTI patients enrolled were female (61%). Most patients were white (94%). The majority of patients were between 65 and 84 years of age. Table 067.3 presents the major demographic details of the enrolled UTI population.

Table 067.3
Demographic Characteristics
The Enrolled Population
Study 411-067

Parameter	CEFEPIME	
SEX		
FEMALE	93	(61%)
MALE	59	(39%)
RACE		
WHITE	143	(94%)
BLACK	8	(5%)
OTHER	1	(1%)
AGE (YR)		
N	152	
MEAN	56.5	
MEDIAN	62	
AGE DISTRIBUTION		
< 18	2	(1%)
18 - 24	15	(10%)
25 - 44	27	(18%)
45 - 64	35	(23%)
65 - 84	70	(46%)
85 +	3	(2%)

The determination of evaluability had little impact on the demographics of the study population. Both the applicant's and the reviewer's evaluable population had very similar demographic characteristics to the enrolled population. In both cases, most patients were white females. The age group most represented was the 65-84 year old groups, however the mean age for both populations was approximately 56 years. Tables 067.4 and 067.5 presents the demographic characteristics of the applicant's and the reviewer's evaluable populations respectively.

Table 067.4 Demographics of Evaluable Population Applicant's Analysis		Table 067.5 Demographics of Evaluable Population According to Reviewer	
Parameter	CEFEPIME	Parameter	CEFEPIME
SEX		SEX	
FEMALE	46 (61%)	FEMALE	40 (58%)
MALE	30 (39%)	MALE	29 (41%)
RACE		RACE	
WHITE	73 (96%)	WHITE	66 (96%)
BLACK	3 (4%)	BLACK	3 (4%)
AGE (YR)		AGE (YR)	
N	76	N	69
MEAN	55.9	MEAN	55.5
MEDIAN	60	MEDIAN	60
RANGE		RANGE	
AGE DISTRIBUTION		AGE DISTRIBUTION	
< 18	1 (1%)	< 18	1 (1%)
18 - 24	5 (7%)	18 - 24	5 (7%)
25 - 44	17 (22%)	25 - 44	14 (20%)
45 - 64	18 (24%)	45 - 64	19 (28%)
65 - 84	34 (45%)	65 - 84	29 (42%)
85 +	1 (1%)	85 +	1 (1%)

Medical History

Table-067.6 summarizes the medical conditions associated with the genitourinary system present in evaluable patients as determined by the applicant.

COMMENT: Fifty one percent of patients in the low-dose (1 gram Q12h) group have complicated UTIs, however, only 20% of patients in the high-dose (2 grams Q12h) group have complicated UTIs. This fact is interesting in light of the fact that patients in the high-dose (2 grams Q12h) were supposed to have more "serious" infections.

Table-067.6
Relevant Medical Conditions
According to the Applicant
Study: 411-067

Disease Type/ Medical Condition	Number (%) of Patients	
	All	Evaluable
<u>Low Dose Group</u>		
<u>Patients with UTI</u>	N = 109	N = 61
<u>Patients with complicated UTI</u>	50 ²	31 (51)
Diabetes		7 (23)
Obstruction		17 (55)
Cancer of the Urinary Tract		5 (16)
Urinary Tract Catheter		20 (65)
<u>Patients with Uncomplicated UTI</u>		30 (49)
<u>High Dose Group</u>		
<u>Patients with UTI</u>	43 ²	15
<u>Patients with Complicated UTI</u> ¹		3 (20)
Upper UTI		2 (67)
Anatomic Abnormality		2 (67)
Diabetes		1 (33)
Obstruction		1 (33)
UTI Surgery		1 (33)
<u>Patients with Uncomplicated UTI</u>		11 (73)
<u>Patients with UTI Unable to Determine</u>		1 (7)

1 Some patients had more than one complicating factor.
2 Specific diagnosis not provided for enrolled population.

Table-067.7 presents the relevant medical conditions existing in evaluable patients. In the low-dose (1 gram Q12h) patients with complicated UTI made up the largest group. In contrast, among patients who received high-dose (2 grams Q12h) therapy, patients with upper UTI made up the largest group.

Table-067.7
Relevant Medical Conditions
According to the Reviewer
Study: 411-067

Condition	Number of Patients	
	Low Dose	High Dose
Evaluable Patients	54	15
COMPLICATED UTI	28 (52)	3 (20)
Anatomic Abnormality	1 (4)	1 (33)
BPH	7 (25)	1 (33)
Catheter Associated	1 (4)	0
Functional Abnormality	1 (4)	1 (33)
Male > 40 years	5 (18)	0
U.T. Neoplasia	5 (18)	0
Obstruction	1 (4)	0
Recent Surgery	2 (8)	0
Stones	5 (18)	0
PYELONEPHRITIS	16 (30)	7 (47)
UNCOMPLICATED UTI	10 (19)	5 (33)

Concomitant Drug Therapy

According to the sponsor, 90% of patients received concomitant drug therapy. In both the low-dose group and the high-dose group, CNS drugs were the most frequent concomitant medication prescribed. No evaluable patients in either treatment groups received concomitant antimicrobials active against common UTI pathogens. One patient in the low-dose group received fluconazole.

Study Drug Therapy

Table 067.8 details the duration of study therapy. Patients were treated from 4 to 15 days. The mean duration of therapy for both the high and low dose groups was approximately 8.5 days. As this was a multiple-indication trial, the sponsor did not present data on the duration of therapy for the UTI population, therefore, only the reviewer's analysis is presented.

Table-067.8
Duration of Study Drug Therapy
According to the Reviewer
Study 411-067

Duration of Therapy(Days)	Low Dose	High Dose
Number of Patients	54	15
4	0	1 (7)
5	1 (2)	2 (13)
6	5 (9)	1 (7)
7	13 (24)	2 (13)
8	10 (19)	4 (27)
9	5 (9)	1 (7)
10	11 (20)	0
11	4 (7)	0
12	2 (4)	1 (7)
13	1 (2)	0
14	1 (2)	2 (13)
15	1 (2)	1 (7)
Mean Duration	8.7	8.7
Median Duration	9.5	7.5
Modal Duration	7	8

Efficacy Evaluation**Clinical Efficacy**

According to the applicant, overall, a satisfactory clinical outcome was achieved in 58/91 patients (95%) who received low-dose cefepime (1 gram Q12H) and in 14/15 patients (93%) who received high-dose cefepime (2 grams Q12H). The clinical response for the sub-groups of complicated and uncomplicated UTI are presented in table-067.9.

Table-067.9
Clinical Efficacy
According to the Applicant
Study 411-067

Parameter	CEFEPIME	
	Low Dose (1 gram Q12h)	High Dose (2 grams Q12h)
NO. OF EVALUABLE PATIENTS	61	15
UTI/COMP		
SATIS	48 (96%)	10 (91%)
UNSAT	2 (4%)	1 (9%)
UTI/UNCOMP		
SATIS	10 (91%)	4 (100%)
UNSAT	1 (9%)	

According to the medical officer, overall, 49/54 patients (91%) who received low-dose (1 gram Q12H) cefepime were clinically cured at the 5-9 day post-therapy evaluation and 11/15 patients (73%) who received high-dose (2 grams Q12H) cefepime were clinically cured at the 5-9 day post-therapy evaluation. Table-10 presents the reviewer's assessment of the clinical efficacy for the sub-groups of patients with complicated UTI, pyelonephritis and uncomplicated UTI.

Table-067.10
Clinical Efficacy
According to the Medical Officer
Study 411-067

Parameter	CEFEPIME	
	Low Dose (1 gram Q12h)	High Dose (2 grams Q12h)
UTI/ALL PATIENTS	54	15
CURE	49 (91%)	11 (73%)
IMPROVED	0	1 (7%)
FAILURE	5 (9%)	3 (20%)
COMPLICATED UTI	28	3
CURE	25 (89%)	3 (100%)
FAILURE	3 (11%)	0
PYELONEPHRITIS	16	7
CURE	15 (94%)	6 (86%)
FAILURE	1 (6%)	1 (14%)
UNCOMPLICATED UTI	10	5
CURE	9 (90%)	2 (40%)
IMPROVED	0	1 (20%)
FAILURE	1 (10%)	2 (40%)

Bacteriologic Efficacy**Bacteriologic Efficacy at the 5-9 Days Post-Therapy Evaluation**

According to the applicant, overall, 60/67 pathogens (90%) were eradicated in patients who received low-dose (1 gram Q12H) cefepime and 14/15 pathogens (93%) were eradicated in patients who received high-dose (2 grams Q12H) cefepime. Table-067.11 presents the bacteriologic response at 5-9 days post-therapy for the sub-groups of patients with complicated and uncomplicated UTI.

Table-067.11
Bacteriologic Efficacy at the 5-9 Days Post-Therapy Evaluation
(According to the Applicant)
Study #067

Parameter	CEFEPIME	
	Low Dose (1 gram Q12h)	High Dose (2 grams Q12h)
UTI/COMP		
A. ANITRATUS	1/ 1 (100%)	
C. FREUNDII	1/ 1 (100%)	
E. COLI	32/ 35 (91%)	9/ 10 (90%)
K. PNEUMONIAE	2/ 2 (100%)	
P. AERUGINOSA	1/ 4 (25%)	
P. MIRABILIS	3/ 3 (100%)	
P. VULGARIS	1/ 1 (100%)	
S. AGALACTIAE	1/ 1 (100%)	
S. AUREUS	1/ 1 (100%)	
S. EPIDERMIDIS	2/ 2 (100%)	
S. FAECALIS	0/ 1 (0%)	
S. SAPROPHYTICUS	1/ 1 (100%)	
STREP. (ALPHA HEMOLYTIC)	1/ 1 (100%)	
STREP. GROUP-D		1/ 1 (100%)
OVERALL	47/ 54 (87%)	10/ 11 (91%)
UTI/UNCOMP		
E. COLI	9/ 9 (100%)	4/ 4 (100%)
P. AERUGINOSA	1/ 1 (100%)	
P. MIRABILIS	2/ 2 (100%)	
S. FAECALIS	1/ 1 (100%)	
OVERALL	13/ 13 (100%)	4/ 4 (100%)
TOTAL UTI	60/ 67 (90%)	14/ 15 (93%)

According to the reviewer, overall, 48/58 pathogens (83%) treated with low-dose (1 gram Q12h) cefepime were eradicated and 12/15 pathogens (80%) treated with high-dose cefepime were eradicated.

E. coli was the most commonly isolated organism in all sub-groups. *P. aeruginosa* was seen in 5 patients with complicated UTI. All 5 patients with *P. aeruginosa* UTI were treated with low-dose (1 gram Q12h) cefepime. The organism was eradicated in 2/5 patients (40%).

Table-067.12 presents the bacteriologic efficacy at the 5-9 day post-therapy evaluation.

Table-067.12
Bacteriologic Efficacy at the 5 to 9 Days Post-Therapy Evaluation
(According to the Reviewer)
Study #067

Parameter	CEFEPIME	
	Low Dose (1 gram Q12h)	High Dose (2 grams Q12h)
COMPLICATED UTI		
A. ANITRATUS	1/ 1 (100%)	
E. COLI	11/ 15 (73%)	3/ 3 (100%)
K. PNEUMONIAE	2/ 2 (100%)	
P. AERUGINOSA	2/ 5 (40%)	
P. MIRABILIS	2/ 2 (100%)	
P. VULGARIS	0/ 1 (0%)	
S. AGALACTIAE	1/ 1 (100%)	
S. EPIDERMIDIS	2/ 2 (100%)	
S. FAECALIS	0/ 1 (0%)	
S. SAPROPHYTICUS	1/ 1 (100%)	
TOTAL/COMP	22/ 31 (71%)	3/ 3 (100%)
PYELONEPHRITIS		
E. COLI	14/ 15 (93%)	5/ 7 (71%)
S. AUREUS	1/ 1 (100%)	
TOTAL/PYELONEPHRITIS	15/ 16 (94%)	5/ 7 (71%)
UNCOMPLICATED UTI		
E. COLI	9/ 9 (100%)	3/ 4 (75%)
P. MIRABILIS	1/ 1 (100%)	
S. FAECALIS	1/ 1 (100%)	
STREP GROUP-D		1/ 1 (100%)
TOTAL/UNCOMP	11/ 11 (100%)	4/ 5 (80%)
TOTAL/ALL PATIENTS	48/ 58 (83%)	12/ 15 (80%)

Bacteriologic Efficacy at the 4-6 Weeks Post-Therapy Evaluation

COMMENT: The applicant did not report on the results of the 4-6 week post-therapy evaluation, therefore, all of the following information is derived from the reviewer's analysis of the data.

The majority of patients in both the low-dose (1 gram Q12h) and the high-dose (2 grams Q12h) groups were not assessed at 4-6 weeks post-therapy. Of those assessed, 8/13 (62%) of patients in the low-dose (1 gram Q12h) groups had continued eradication of their pathogens. In the high dose group 3/6 (50%) of patients had continued eradication of their pathogens. Table 067.13 summarizes the bacteriologic results at the 4-6 week post-therapy evaluation.

Table 067.13
Bacteriologic Response
At The 4-6 Week Assessment
According to the Reviewer
Study 411-067

Outcome	Low Dose	High Dose
Total Patients	54	15
Early Persistence	10	3
Not Assessed	31	6
Patients with Late Follow-up	13 (24%)	6 (40%)
Continued Eradication	8 (62%)	3 (50%)
Eradication with Relapse	2 (15%)	0
Eradication with Reinfection	3 (23%)	3 (50%)

Analysis of Relapses

Two patients in the low-dose group relapsed after the 5-9 day post-therapy assessment. Both relapses occurred in patients infected with *E. coli*. One of the *E. coli* isolates was still susceptible to cefepime at the time of relapse; the other isolates was not tested for susceptibility.

No patients in the high-dose group relapsed.

Analysis of Reinfections

Three patients in the low-dose group had reinfection with a new organism after the 5-9 day post-therapy assessment. Two patients had a reinfection with *S. faecalis*. One isolate of *S. faecalis* was resistant to cefepime, the other was not tested. One patient had a reinfection due to *E. cloacae* which was susceptible to cefepime.

Three patients in the high-dose group had reinfections with new organisms after the 5-9 day post-therapy assessment. Two patients had relapses with *Enterococcus* spp. One of the isolates was of intermediate susceptibility to cefepime, the other isolate was resistant. One patients had a reinfection with *E. cloacae* which was susceptible to cefepime.

Safety Analysis

Cefepime Deaths

Four deaths occurred among UTI patients who participated in protocol 411-067. Two deaths occurred among the 109 patients with UTI who received low-dose (1 gram Q12h) therapy. Two deaths occurred among the 43 patients who received high-dose (2 grams Q12h) therapy. A brief summary for each patient who died during the study period follows.

- The patient was a 53 y.o. male with history of carcinoma of the right kidney. The patient was treated with low-dose cefepime from 7/15/88 to 7/21/88 for a complicated UTI due to *P. aeruginosa*. The infection was eradicated and clinical symptoms resolved. Two months after the conclusion of therapy, the patient died of his underlying illness.

- The patient was a 62 y.o. male with history of lung cancer with metastasis to lung and liver. The patient also had a history of chronic lymphocytic leukemia, and was neutropenic at the time of randomization from chemotherapy. The patient was treated with low-dose cefepime for 11 days for an *E. coli* UTI. Thirteen days after completing the study therapy, the patient developed respiratory insufficiency. The patient became acidotic and suffered a cardio-pulmonary arrest.

- The patient was an 84 y.o. female with history of cardiovascular and neurovascular disease. The patient was treated with high-dose cefepime for pyelonephritis due to *E. coli*. The infection was eradicated during therapy culture, and the signs and symptoms of infection were reported to resolve. The patient died 9 days after completion of therapy. The cause of death was reported to be complication of cerebro-vascular accident.

- The patient was an 86 y.o. male with senile dementia and a history of multiple decubitus ulcers. The patient was treated with high-dose cefepime for a UTI due to *P. mirabilis*. The infection was eradicated but recurred 32 days post-therapy. The patient's recurrence was successfully treated with ampicillin and tobramycin. The patient died 2 months after the conclusion of cefepime therapy.

COMMENT: In three of the patients, the underlying medical conditions clearly contributed to the patient's demise. In one patient the cause of death was unknown, but since the death occurred 2 months after the conclusion of study drug therapy, the relationship to cefepime is doubtful.

Cefepime Discontinuations

Six patients discontinued cefepime therapy due to treatment related adverse events. All patients who discontinued medication were treated with low-dose (1 G Q12h) cefepime. Brief summaries of the reasons for discontinuation follow.

- The patient is a 41 y.o. female who discontinued cefepime therapy on day #6 due to phlebitis.

- The patient is a 68 y.o. female who discontinued cefepime because of a rise in liver function tests. The SGOT rose from 20 mg/dL at baseline to 51 mg/dL on study day #2. The SGPT rose from 47 mg/dL at baseline to a high of 122 mg/dL on study day #2. All values returned to normal after discontinuation of the

drug.

- The patient is an 80 y.o. female who discontinued cefepime therapy on day #5 due to phlebitis.

- The patient is a 43 y.o. female who discontinued cefepime therapy on day #6 due to the occurrence of a rash. The patient has a history of penicillin allergy and had experienced similar rashes after antimicrobial use in the past.

The patient is a 27 y.o. female who discontinued cefepime therapy on day #6 due to multiple episodes of phlebitis.

- The patient is a 76 y.o. female who discontinued cefepime therapy on day #7 due to the occurrence of a rash of moderate severity.

COMMENT: The overall incidence of phlebitis or other reactions at the infusion site was 11/109 patients (10%) in the low-dose group and 6/43 (14%) in the high-dose group. Three patients discontinued therapy due to phlebitis.

Clinical Adverse Events

Among the patients treated with low-dose cefepime, there were 9 clinical adverse events reported among the 109 patients exposed. The incidence of adverse events for the low-dose group was 8%. Five of the 9 events were considered probably related to drug use. Most events occurred within the gastrointestinal system and were of mild severity. No adverse events were considered severe.

There were no clinical adverse events reported among the 43 patients exposed to high-dose cefepime.

The following table details the clinical adverse events reported.

Table 067.14
 Clinical Adverse Events
 According to the Reviewer
 Study No. 411-067

Organ System Adverse Event	# of Events			Total
	Mild	Mod.	Sev.	
Gastrointestinal	4	3	-	7
Diarrhea	1	3	-	4
Nausea	2	-	-	2
Tongue Ulcer	1	-	-	1
Skin	-	2	-	2
Rash	-	2	-	2

Local Reactions at the Infusion Site

Among the 109 patients enrolled in the low-dose (1 gram Q12H) cefepime group there were 11 reported cases (10%) of phlebitis or other local reactions at the infusion site. Among the 43 patients enrolled in the high-dose (2 grams Q12H) cefepime group there were 6 reported cases (14%) of phlebitis or other local reactions at the infusion site. The difference between the two groups in the rate of occurrence of local reactions at the infusion site is not significant ($p > 0.05$).

Laboratory Test Abnormalities

Protocol #067 was designed to study the comparative safety and efficacy of two doses of cefepime in patients with UTI and a variety of other disease entities. The applicant did not organize their data in such a way that laboratory test abnormalities occurring in UTI patients could be separated from laboratory test abnormalities occurring in patients studied for claims of efficacy in other indications. Therefore, no data on laboratory test abnormalities will be included in this study report. However, any laboratory test abnormalities which occurred in UTI patients enrolled in study #067 will be included in the integrated summary of safety for UTI patients.

Conclusions

Protocol 411-067 described an open, non-randomized trial of two different doses of cefepime for the treatment of multiple indications including complicated and uncomplicated urinary tract infections.

Patients were assigned, by the investigator, to receive either a low-dose of cefepime (1 gram Q12h) or a high-dose of cefepime (2 grams Q12h) based on the "severity" of their infection. The judgement of severity was left to the individual investigators and was not well defined.

At the 5-9 days post-therapy evaluation; according to the applicant, the causative organism was eradicated in 60/67 cases (89%) treated with low-dose (1 gram Q12h) cefepime and in 14/15 cases (93%) treated with high-dose cefepime. According to the medical officer, at the 5-9 day post-therapy evaluation, the causative organism was eradicated in 48/58 cases (83%) treated with low-dose (1 gram Q12h) cefepime and in 12/15 (80%) of patients treated with high-dose cefepime. *Pseudomonas aeruginosa* was recovered from 5 patients, the infection was eradicated in 2 patients. The eradication rate for *P. aeruginosa* was 40%. There was a trend toward increasing efficacy with increasing dose in the applicant's evaluable population but not in the medical officer's evaluable population. The medical officer's evaluable population did not include patients whose post-therapy evaluation were performed prior to day 5 (post-therapy) while the applicant accepted, in some cases, evaluations performed 3 days or more after the conclusion of therapy. Patients evaluated closer to the conclusion of therapy are more likely to appear to have eradicated their infection.

In addition, the medical officer's population included several patients who were placed on alternative antimicrobials for persistence or worsening of clinical symptoms. The patients were considered evaluable clinical and bacteriological failure by the medical officer. In contrast, these patients were considered not-evaluable by the applicant because of non-study antimicrobial use.

Both of the above mentioned factors probably contributed to the overall lower eradication rates seen in the medical officer's evaluable population, however, they do not explain the failure to demonstrate a dose-response effect. Demographic characteristics of the medical officer's evaluable population and the applicant's evaluable population did not differ significantly and therefore, do not explain the observed discrepancy.

This study may be considered supportive of the comparative studies included in the NDA in support of the uncomplicated and complicated (including pyelonephritis) indication.

Because of the low eradication rate (40%), this study is not considered to be supportive of the inclusion of *Pseudomonas aeruginosa* as a pathogen effectively treated by cefepime.

Based on the medical officer's analysis, this study does not support an increased effectiveness of the high-dose (2 grams Q12h) compared with the low-dose (1 gram Q12h) in the treatment of UTI.

EFFICACY SUMMARY**Introduction**

The applicant has requested approval to include the indications: complicated UTI, including pyelonephritis; and uncomplicated UTI in the approved product label for Maxipime®. The applicant requests that a dose of 500 mg to 1 gram Q12H be approved for "mild to moderate" UTI and a dose of 2 grams Q12H be approved for "...severe infections...including UTI". The applicant states that the usual duration of dosing is 7 to 10 days.

COMMENT: Only the medical officer's analysis is presented in the summary section. The applicant's interpretation of the data may be found in the individual study reports.

In the new drug application for Maxipime®, the applicant submitted data on 1585 patients with urinary tract infections: 1164 patients were treated in comparative clinical studies—designed to study patients with UTI; 387 were treated in non-comparative studies designed to study patients with UTI; 1 patient was studied under an emergency IND; and 33 patients were enrolled in clinical trials designed to study indications other than UTI but were noted to have a concurrent UTI.

Only the data from studies designed to assess the safety and efficacy of cefepime in patients with UTI were considered, by both the applicant and the medical officer, in support of the applicant's claim of efficacy. The comparative studies were considered to be pivotal; among the 1164 patients who were enrolled in comparative studies, 647 patients treated with cefepime and 517 patients treated with ceftazidime.

Table ES.1 gives additional information regarding the location and dose studied. In addition, table ES.1 summarizes the medical officer's determination of the number of patients who were evaluable for efficacy in each study.

The mean duration of cefepime administration was 8.1 days. The mean duration of ceftazidime administration was 8.7 days. Table-ES.2 summarizes the mean and median duration of therapy for each study submitted.

The majority of patients were treated via the intravenous route, however, 61 evaluable patients (cefepime=41, ceftazidime=20) in study #083 and 20 evaluable patients (cefepime = 11, ceftazidime=9) in study #108 were treated via the intramuscular route

Table-ES.1
Enrollment and Evaluability
UTI Studies

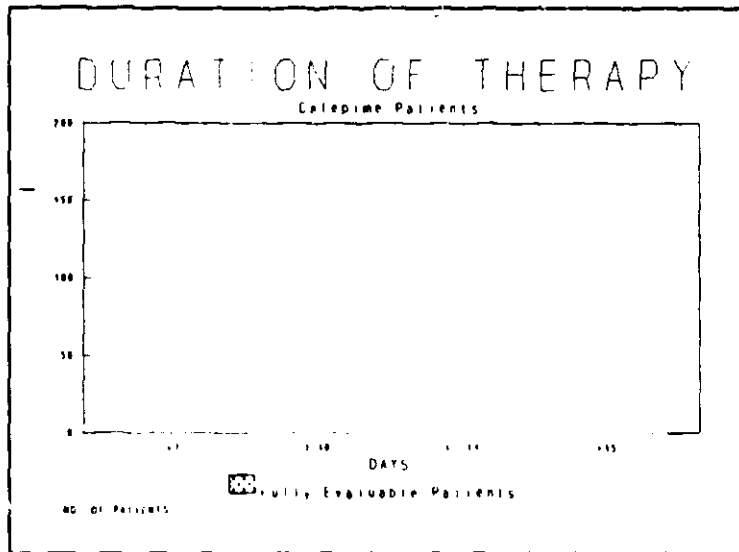
Dose	Study No.	Cefepime		Ceftazidime	
		Enrolled	Eval.	Enrolled	Eval.
North American Comparative Trials					
0.25 grams BID	411-071	32	21	16	11
0.5 grams BID	411-083	246	121	125	64
	411-108	39	29	41	19
2 grams BID	411-097	215	67	226	69
European Comparative Trials					
0.5 grams BID	411-083-E	59	21	36	18
2 grams BID	411-111-E	56	15	73	23
North American Non-Comparative Trials					
1 gram BID	411-061	116	24		
2 grams BID	411-140	119	36		
European Non-Comparative Trials					
1 gram BID	411-067-LD-E	109	54		
2 grams BID	411-067-HD-E	43	15		
Emergency IND					
	411-999	1	0		
Non-UTI Studies					
Varied	Multiple	22	0	11	
Total Enrollment					
		1057	403	528	204

Table-ES.2
Duration of Drug Administration
Medical Officer's Evaluable Population

Dose	Study No.	Cefepime		Ceftazidime	
		Duration of Therapy (Days)		Duration of Therapy (Days)	
		Mean	Median	Mean	Median
North American Comparative Trials					
0.25 grams BID	411 071	5.7	6.0	6.0	6.0
0.5 grams BID	411-083	8.9	9.5	8.9	9.0
	411-108	6.4	10.5	6.9	10.5
2 grams BID	411-097	8.3	9.5	9.6	9.5
European Comparative Trials					
0.5 grams BID	411-083	6.9	7.0	7.5	7.0
2 grams BID	411-111	9.4	9.5	10.2	10.0
North American Non-Comparative Trials					
1 gram BID	411-061	7.9	8.0		
2 grams BID	411-140	7.4	8.5		
European Non-Comparative Trials					
1 gram BID	411-067-LD	8.5	7.5		
2 grams BID	411-067-HD	8.5	6.5		
All UTI Trials					
All UTI		8.1		8.7	

The following figure shows the frequency distribution of the duration of therapy. The frequency distribution is approximately normally distributed with a slight skew toward shorter duration of therapy. The majority of patients were treated from 7 to 10 days.

Figure ES.1
 Duration of Therapy
 Medical Officer's Evaluable Patients
 All UTI Studies



Complicated UTI

The medical officer considered comparative studies to be pivotal in the determination of the efficacy of cefepime in patients with complicated UTI. All conclusions stated in the following sections are based on the medical officer's analysis of the data. In all cases reference to complicated UTI includes those patients with pyelonephritis as well as those patients with other anatomic or functional factors generally thought to make a UTI complicated (Please refer to the introduction to this review). Three doses of cefepime were studied for this indication: 250 mg twice daily, 500 mg twice daily, and 2.0 grams twice daily. Within each dosage level, similar study protocols using similar inclusion and exclusion criteria were employed. Therefore, the medical officer felt justified in combining the results of all studies within a dosage level to obtain an estimate of the comparative efficacy of cefepime and ceftazidime.

The lowest dose, 250 mg twice daily, was studied in only one comparative study (#411-071) which enrolled only 12 evaluable patients with complicated UTI in the cefepime group and only 5 evaluable patients with complicated UTI in the ceftazidime group. The 5-9 day bacteriologic eradication rate (by pathogen) was 8/12 (67%) in the cefepime treatment group, and 5/5 (100%) in the ceftazidime treatment group. The 95% confidence interval around the true difference in eradication rates was [-74%, +8%]; the wide confidence interval being a consequence of the small number of patients studied at this dose. The applicant does not propose to include this dose in the final package insert for cefepime.

The mid-level cefepime dose studied was 500 mg twice daily. The applicant proposes this dose for patients with mild to moderate infection of the urinary tract. The 500 mg twice daily dose was studied in three comparative studies (411-083, 108, and 083 (European)) which enrolled 138 evaluable patients (146 evaluable pathogens) with complicated UTI in the cefepime treatment group and 78 evaluable patients (81 evaluable pathogens) with complicated UTI in the ceftazidime treatment group. The 5-9 day bacteriologic eradication rate (by pathogen) was 115/146 (79%) in the cefepime treatment group, and 62/81 (77%) in the ceftazidime treatment group. The 95% confidence interval around the true difference in eradication rates was [-10%, +15%]. Since the lower bound of the 95% confidence interval is less than -20%, the medical officer concludes that the two studied treatments are equivalent.

The highest dose studied was 2.0 grams twice daily. The applicant proposes this dose for patients with severe infections of the urinary tract. The 2.0 gram twice daily dose was studied in two comparative studies (#411-097, -111 (European)) which enrolled 70 evaluable patients (82 evaluable pathogens) with complicated UTI in the cefepime treatment group and 76 evaluable patients (81 evaluable pathogens) with complicated UTI in the ceftazidime treatment group. The 5-9 day bacteriologic eradication rate (by pathogen) was 64/82 (78%) in the cefepime treatment group, and 65/81 (80%) in the ceftazidime treatment group. The 95% confidence interval around the true difference in eradication rates was [-16%, +12%]. Since the lower bound of the 95% confidence interval approximates -15%, the medical officer concludes that the two studied treatments are equivalent.

Eradication rates in non-comparative clinical trials of UTI patients were similar to those obtained from the comparative trials and therefore were considered by the medical officer to be supportive of the above conclusions.

Table-ES.3 summarizes the bacteriologic efficacy (by pathogen) of cefepime determined at the 5-9 day post-therapy assessment in patients with complicated UTI.

Table-ES.3
Bacteriologic Efficacy at the 5-9 Days Post-Therapy Evaluation
Complicated UTI (Including Pyelonephritis)
Medical Officer's Analysis

Dose	Study #	Evaluable Pathogens ¹ #Eradicated/#Evaluable				95% CI ²
		Cefepime		Ceftazidime		
		Number	Percent	Number	Percent	
Comparative Trials (North American and European)						
0.25 grams BID	411-071	8/ 12	67%	5/ 5	100%	[-74%, +8%]
	-					
0.5 grams BID	411-083	88/109	81%	41/ 55	75%	[-10%, +15%]
	411-108	18/ 22	82%	10/ 13	77%	
	411-083E ³	9/ 15	60%	11/ 13	85%	
	Total	115/146	79%	62/ 81	77%	
2 grams BID	411-097	53/ 67	79%	52/ 62	84%	[-16%, +12%]
	411-111E	11/ 15	73%	13/ 19	68%	
	Total	64/ 82	78%	65/ 81	80%	
Non-Comparative Trials (North American and European)						
1 gram BID	411-061	16/ 20	80%			
	411-067-LD-E	37/ 47	79%			
	Total	53/ 67	79%			
2 grams BID	411-140	25/ 34	74%			
	411-067-HD-E	8/ 10	80%			
	Total	33/ 44	75%			

- 1 Some patients may have had more than one pathogen, therefore, the number of evaluable pathogens is equal to or greater than the number of evaluable patients.
- 2 Corrected 95% confidence interval around the true difference in eradication rates.
- 3 Study numbers ending in E were performed at European centers.

Similar eradication rates, at the 5-9 day post-therapy evaluation, were seen in both the 500 mg twice daily dose group (Eradication rate = 79%) and the 2 gram BID dose group (eradication rate = 78%). In response to a query by the reviewer, the applicant compared their evaluable populations exposed to each dose with respect to seven presumed risk factors for poor outcome in UTI. The results of the applicant's comparison analysis are summarized in table ES.4. Patients in the 2 gram twice daily dose group were more likely to have pyelonephritis, a urinary catheter and a concurrent positive blood culture. However, patients in the 500 mg twice daily dose group were more likely to have obstruction or cancer of the urinary tract. There were no significant differences in the proportion of patients 65 years or older or the proportion of patients with diabetes.

Table-ES.4
Comparison of Low and High Dose Populations
in BMS Evaluable Patients with Complicated UTI
North American Comparative Trials (83, 097, 108)

Factor	Response	Cefepime		P-Value ¹
		500 mg BID	2 G BID	
Number of BMS Evaluable Patients in each dose group		112	56	
> 65 years	Yes	47 (42)	27 (48)	
	No	65 (58)	29 (52)	0.510
Pyelonephrit.	Yes	27 (24)	27 (48)	
	No	85 (76)	29 (52)	0.003
Diabetes	Yes	15 (13)	10 (18)	
	No	97 (87)	46 (82)	0.493
Blood Culture	Positive	9 (8)	12 (21)	
	Negative	103 (92)	44 (79)	0.024
Catheter	Yes	35 (31)	30 (54)	
	No	77 (69)	26 (46)	0.007
Obstruction	Yes	59 (53)	20 (36)	
	No	53 (47)	36 (64)	0.049
Neoplasm	Yes	14 (12)	4 (7)	
	No	98 (88)	52 (93)	0.428

¹Calculated using Fisher's Exact Test

Comment: The above table was prepared using the applicant's evaluable complicated UTI patients. The applicant's evaluable population and the reviewer's evaluable population differed in that the reviewer considered a larger proportion of the enrolled patients to have complicated UTI than did the applicant. Therefore, caution must be exercised in extending conclusions based on the above table to the medical officer's evaluable population.

Complicated UTI - Demographics

Table-ES.5 presents the eradication rate at the 5-9 days post-therapy evaluation listed by study location, sex, age, and race.

COMMENT: The values presented in the following tables represent a meta-analysis of all patients involved in comparative cefepime trials. This approach is considered to be valid by the M.O. because of the similarity in protocols, however, the limitations imposed by such an approach should be appreciated.

Table-ES.5
Determinants of Efficacy
Complicated UTI (Including Pyelonephritis)
Patients Enrolled in Comparative Trials Only
(411-071, 083, 097, 108, 111)
Medical Officer's Analysis

Group	Evaluable Pathogens ¹ #Eradicated/#Evaluable				95 % ² Confidence Interval
	Cefepime		Ceftazidime		
	No.	%	No.	%	
All UTI	187/240	78	132/169	78	[-9%, +8%]
NORTH AMERICAN	167/210	80	108/135	80	[-10%, +8%]
EUROPEAN	20/30	67	24/32	75	[-34%, +17%]
MALES	102/139	73	73/ 99	74	[-13%, +12%]
FEMALES	85/101	84	59/709	84	[-12%, +12%]
> 65 YEARS OLD	93/123	76	75/ 89	84	[-20%, +3%]
WHITE	124/160	78	89/ 117	76	9%, +12%]
AFRICAN AMERICAN	50/62	81	34/ 38	89	[-24%, +7%]
OTHER RACES	13/18	72	9/ 14	64	[-31%, +46%]

¹ Evaluable patients may have more than one evaluable pathogen.

² Corrected 95% confidence interval around the difference in eradication rates.

Statistical equivalence, by the 95% confidence interval approach, in 5-9 day post-therapy eradication rates were seen in males, females and white patients. Statistical equivalence was not achieved for patients 65 year of age or older despite a relatively large sample size in this group. The reason for the trend toward inferior performance of cefepime compared with ceftazidime in the geriatric age group is not clear.

In addition, statistical equivalence between the two treatment groups was not demonstrated for African American patients and patients of races other than White or African American. The small sample sizes of these sub-groups make drawing conclusions regarding the significance of this observation difficult.

Complicated UTI - Clinical and Bacteriological Response

At the 500 mg dosage level (studies: 083, 083-EU, and 108), medication was administered via both the intravenous and intramuscular routes.

According to the medical officer, 105 pathogens in 99 evaluable patients were treated with cefepime via the intravenous route. These patients were compared with 63 pathogens in 60 evaluable patients who were treated with ceftazidime via the intravenous route. The clinical and bacteriologic efficacy determined by the medical officer for intravenous administration of cefepime 500 mg BID (pooled data from studies 083, 083-EU, and 108) are reported in the following table.

Table ES.6A
 Efficacy of Cefepime 500 mg BID Compared with Ceftazidime 500 mg TID
 in Complicated UTI
 Intravenous Administration
 According to the Medical Officer

Parameter	CEFEPIME 500 mg BID	CEFTAZID 500 mg TID
CLINICAL RESPONSE		
CURE	64 (65%)	39 (65%)
IMPROV	18 (16%)	11 (18%)
UNDET	0	2 (3%)
UNSAT	17 (17%)	8 (13%)
BACTERIOLOGIC ERADICATION		
A. CALCOACETICUS	1/ 1 (100%)	0
C. DIVERSUS	0	0/ 1 (0%)
C. FREUNDII	0	1/ 1 (100%)
E. AEROGENES	2/ 2 (100%)	1/ 1 (100%)
E. CLOACAE	1/ 2 (50%)	4/ 4 (100%)
E. COLI	47/ 62 (76%)	22/ 31 (71%)
K. OXYTOCA	2/ 2 (100%)	2/ 2 (100%)
K. PNEUMONIAE	6/ 8 (75%)	3/ 5 (60%)
P. AERUGINOSA	4/ 8 (50%)	8/ 9 (89%)
P. MIRABILIS	8/ 10 (80%)	4/ 4 (100%)
S. AUREUS	1/ 2 (50%)	1/ 1 (100%)
S. EPIDERMIDIS	2/ 3 (67%)	0
S. FAECALIS	0	2/ 2 (100%)
S. HOMINIS	0/ 1 (0%)	0
S. MARCESCENS	2/ 3 (67%)	0
S. WARNERI	0	0/ 1 (0%)
STREP. (GROUP B)	1/ 1 (100%)	1/ 1 (100%)
TOTALS	77/105 (73%)	49/ 63 (78%)

Comment: The 95% confidence interval for the medical officer's bacteriologic eradication rates is {-18%, +9%} which supports the claim of equivalent efficacy.

According to the medical officer, 41 pathogens in 39 evaluable patients were treated with cefepime via the intramuscular route. These patients were compared with 18 pathogens in 18 evaluable patients who were treated with ceftazidime via the intramuscular route. The clinical and bacteriologic efficacy (pooled from studies 083, 083-EU, and 108) reported by the applicant for intramuscular administration of cefepime 500 mg BID are reported in the following table.

Table ES.6D
Efficacy of Cefepime 500 mg BID Compared with Ceftazidime 500 mg TID
in Complicated UTI
Intramuscular Administration
According to the Medical Officer

Parameter	CEFEPIME 500 mg BID	CEFTAZID 500 mg TID
CLINICAL RESPONSE		
SATIS	29 (74%)	9 (50%)
IMPROV	5 (13%)	4 (22%)
UNSAT	5 (13%)	5 (28%)
BACTERIOLOGIC ERADICATION		
ACINETOBACTER SP.	0	1/ 1 (100%)
C. FREUNDII	1/ 1 (100%)	1/ 1 (100%)
E. CLOACAE	1/ 1 (100%)	0
E. COLI	21/ 21 (100%)	5/ 10 (50%)
ENTEROBACTER SP.	1/ 1 (100%)	0
K. OXYTOCA	1/ 1 (100%)	0
K. PNEUMONIAE	2/ 3 (67%)	2/ 2 (100%)
P. AERUGINOSA	7/ 9 (78%)	2/ 2 (100%)
P. MIRABILIS	2/ 2 (100%)	1/ 1 (100%)
P. RETTGERI	1/ 1 (100%)	0
PROTEUS SP.	1/ 1 (100%)	0
SHIGELLA SP.	0	1/ 1 (100%)
TOTALS	38/ 41 (93%)	13/ 18 (72%)

Comment: The 95% confidence interval for the medical officer's eradication rates is {-6, +46} which is consistent with the claim of equivalent bacteriologic efficacy for cefepime and ceftazidime when given via the intramuscular route.

In summary, the medical officer was able to demonstrate the statistical equivalence of bacteriologic outcome in patients with complicated UTI for cefepime and ceftazidime at the 500 mg dosage level for both intravenous and intramuscular administration. In fact, there is a trend toward superior performance of cefepime compared with ceftazidime when administered by the intramuscular route.

E. coli, *P. mirabilis*, *K. pneumoniae* and *P. aeruginosa* were isolated from a sufficient number of evaluable patients who were treated via the intravenous route to draw valid conclusions. Similar eradication rates were seen for cefepime and ceftazidime for patients with infections due to *E. coli* and *K. pneumoniae*. There was a trend toward inferior performance for cefepime compared with ceftazidime in patients with infections due to *P. mirabilis* (cefepime=8/10 (80%), ceftazidime=4/4 (100%) and *P. aeruginosa* (cefepime=4/8

(50%), ceftazidime=8/9 (89%).

Only *E. coli* was isolated from a sufficient number of evaluable patients, treated via the intramuscular route, to draw valid conclusions. There was a trend toward superior performance of cefepime compared with ceftazidime in the eradication of *E. coli* in patients treated via the intramuscular route.

With regard to clinical efficacy, the rates of clinical cure for patients with complicated UTI treated with cefepime was similar to or greater than the rate of clinical cure for patients treated with ceftazidime, administered at the 500 mg dosage level, regardless of route of administration.

The 2.0 gram dosage level was studied in two comparative clinical trials (studies: 097 and 111). Medication was administered via the intravenous route.

According to the medical officer, 82 pathogens in 70 evaluable patients were treated with cefepime. These patients were compared with 81 pathogens in 76 evaluable patients who were treated with ceftazidime. The clinical and bacteriologic efficacy determined by the medical officer for intravenous administration of cefepime 2.0 g BID (pooled data from studies 097, and 111) are reported in the following table.

Table ES.7
Bacteriologic Response of Pathogens Recovered from Patients with
Complicated UTI (Including Pyelonephritis)
5-9 Days Post-Therapy Evaluation
According to the Medical Officer

	CEFEPIME 2.0 grams BID	CEFTAZID 2.0 grams TID
CLINICAL RESPONSE		
SATIS	57 (81%)	58 (76%)
IMPROV	1 (1%)	4 (5%)
UNSAT	12 (17%)	14 (18%)
COMPLICATED UTI PATHOGENS		
C. AMALONATICUS	0	1/ 1 (100%)
C. DIVERSUS	1/ 2 (50%)	0
C. FREUNDII	0	1/ 1 (100%)
E. AGGLOMERANS	0/ 1 (0%)	0
E. CLOACAE	1/ 1 (100%)	1/ 1 (100%)
E. COLI	36/ 39 (92%)	41/ 46 (89%)
ENTEROBACTER SP.	1/ 1 (100%)	1/ 1 (100%)
ENTEROCOCCUS	0/ 1 (0%)	0
H. ALVEI	1/ 1 (100%)	1/ 1 (100%)
K. ORNITHINOLYTICA	0	1/ 1 (100%)
K. OXYTOCA	0/ 2 (0%)	2/ 2 (100%)
K. PNEUMONIAE	8/ 9 (89%)	6/ 8 (75%)
KLEBSIELLA SP.	2/ 2 (100%)	1/ 2 (50%)
P. AERUGINOSA	2/ 7 (29%)	3/ 8 (38%)
P. MIRABILIS	4/ 7 (57%)	4/ 6 (67%)
PSEUDOMONAS SP.	0	1/ 1 (100%)
S. AUREUS	4/ 4 (100%)	0/ 1 (0%)
S. FAECALIS	0/ 1 (0%)	0
S. MARCESCENS	0	1/ 1 (100%)
S. VIRIDANS	1/ 1 (100%)	0
S REP. (GROUP B)	3/ 3 (100%)	0
ALL COMPLICATED PATHOGENS	64/ 82 (78%)	65/ 81 (80%)

The 95% confidence interval for the medical officer's bacteriologic eradication rates is (-16%, +12%). Only *E. coli* was recovered from greater than 10 evaluable cefepime patients. The bacteriologic responses of cefepime and ceftazidime were equivalent by the 95% confidence interval approach for *E. coli* isolates (-11, +18).

Similar overall clinical cure rates were seen in both treatment groups.

Table ES.7C presents the bacteriologic response of pathogens recovered from patients with UTI in non-comparative clinical trials.

Table ES.7C
Bacteriologic Response of Pathogens Recovered from Patients with
Complicated UTI (Including Pyelonephritis)
5-9 Days Post-Therapy Evaluation
According to the Medical Officer

CEFEPIME 1.0 GRAMS BID	
A. ANITRATUS	1/ 1 (100%)
E. AEROGENES	2/ 2 (100%)
E. COLI	36/ 43 (84%)
K. PNEUMONIAE	3/ 4 (75%)
P. AERUGINOSA	3/ 6 (50%)
P. MIRABILIS	2/ 2 (100%)
P. VULGARIS	0/ 1 (0%)
S. AGALACTIAE	1/ 1 (100%)
S. AUREUS	1/ 1 (100%)
S. ENTERITIDIS	1/ 1 (100%)
S. EPIDERMIDIS	2/ 2 (100%)
S. FAECALIS	0/ 1 (0%)
S. SAPROPHYTICUS	1/ 1 (100%)
ALL 1.0 GRAM	53/ 67 (79%)
CEFEPIME 2.0 GRAMS BID	
E. AEROGENES	1/ 1 (100%)
E. COLI	27/ 32 (84%)
K. PNEUMONIAE	1/ 2 (50%)
P. AERUGINOSA	2/ 5 (40%)
P. MIRABILIS	1/ 1 (100%)
P. STUARTII	0/ 1 (0%)
S. FAECALIS	0/ 1 (0%)
S. MARCESCENS	1/ 1 (100%)
ALL 2.0 GRAM	33/ 44 (75%)

Complicated UTI - Clinical Efficacy

Table ES.8 summarizes the clinical response to treatment assessed at the 5-9 days post-therapy evaluation for patients with complicated UTI. -In comparative clinical trials comparing cefepime and ceftazidime, statistically equivalent clinical cure rates were seen, by the 95% confidence interval approach, for both the 500 mg twice daily and the 2.0 gram twice daily dosage groups.

Table-ES.8
Clinical Efficacy at the 5-9 Days Post-Therapy Evaluation
Complicated UTI (Including Pyelonephritis)
Medical Officer's Analysis

Dose	Study #	Evaluable Patients' #Cured/#Evaluable				95% CI ¹
		Cefepime		Ceftazidime		
		Number	Percent	Number	Percent	
Comparative Trials (North American and European)						
0.25 grams BID	411-071	9/ 12	75%	5/ 5	100%	[-64%, +14%]
0.5 grams BID	411-083	74/103	72%	35/ 55	64%	[-8%, +20%]
	411-108	11/ 21	52%	7/ 13	54%	
	411-083E ²	8/ 14	57%	6/ 10	60%	
	Total	93/ 138	67%	48/ 78	62%	
2 grams BID	411-097	48/ 58	83%	44/ 58	76%	
	411-111E	9/ 12	75%	14/ 18	77%	
	Total	57/ 70	81%	58/ 76	76%	[-9%, +20%]
Non-Comparative Trials (North American and European)						
1 gram BID	411-061	15/ 20	75%			
	411-067-LD-E	40/ 44	91%			
	Total	55/ 64	86%			
2 grams BID	411-140	22/ 31	71%			
	411-067-HD-E	9/ 10	90%			
	Total	31/ 41	76%			

¹ Corrected 95% confidence interval around the true difference in clinical cure rates.

² Study numbers ending in E were performed at European centers.

Complicated UTI - Pyelonephritis - Subset

For the sub-group of complicated UTI patients with pyelonephritis who were treated with 500 mg twice daily of either cefepime or ceftazidime, the eradication rate was 31/38 (82%) in the cefepime treatment group and the eradication rate was 17/24 (71%) in the ceftazidime treatment group. The corrected 95% confidence interval was [-15, +36]. Again, as for the complicated UTI population as a whole statistical equivalence was demonstrated.

For the sub-group of complicated UTI patients with pyelonephritis who were treated with either 2 grams BID of cefepime or 2 grams TID of ceftazidime, the bacteriologic eradication rate at the 5-9 day post-therapy evaluation was 26/30 (87%) in the cefepime treatment group and 25/31 (81%) in the ceftazidime treatment group. The corrected 95% confidence interval was [-16, 25]. Although, the eradication rate for cefepime is actually greater than the eradication rate for ceftazidime, when the 95% C.I criteria for equivalence are strictly applied, the results do not lead to the conclusion of equivalence between the two treatment groups in the pyelonephritis sub-group.

Table-ES.9 summarizes the bacteriologic eradication rate at the 5-9 day post-therapy evaluation for the sub-group of complicated UTI patients with pyelonephritis.

Table-ES.9
 Bacteriologic Efficacy at the 5-9 Days Post-Therapy Evaluation
 Pyelonephritis Sub-Group
 Medical Officer's Analysis

Dose	Study #	Evaluable Pathogens #Eradicated/#Evaluable				95% CI ¹
		Cefepime		Ceftazidime		
		Number	Percent	Number	Percent	
Comparative Trials (North American and European)						
0.5 grams BID	411-083	24/ 30	80%	14/ 19	74%	{-15, +36}
	411-108	6/ 7	86%	3/ 4	75%	
	411-083-E	1/ 1	100%	0/ 1	0%	
	Total	31/ 38	82%	17/ 24	71%	
2 grams BID	411-097	22/ 25	88%	19/ 23	83%	{-16, +25}
	411-111	4/ 5	80%	8/ 8	100%	
	Total	26/ 30	87%	25/ 31	81%	
Non-Comparative Trials (North American and European)						
1 gram BID	411-061	7/ 9	78%			
	411-067-LD-E	15/ 16	94%			
	Total	22/ 25	88%			
2 grams BID	411-140	18/ 23	78%			
2 grams BID	411-067-HD-E	5/ 7	71%			
	Total	23/ 30	77%			
All Pyelonephritis Patients						
		102/123	83%	44/ 55	80%	[-11, +17]

¹The number of patients in each sub-group is too small to perform meaningful confidence interval analysis.

Uncomplicated UTI

Table-ES.10 presents the bacteriologic eradication rate at the 5-9 day post-therapy evaluation for patients with uncomplicated UTI. For the overall group of patients with uncomplicated UTI the bacteriologic eradication rates at the 5-9 days post-therapy evaluation were shown to be statistically equivalent by the 95% confidence interval approach. In the 500 mg twice daily and the 2.0 gram twice daily dosage levels, similar eradication rates were observed in both the cefepime and the ceftazidime treatment groups, however, the number of patients studied was too small to perform a meaningful confidence interval analysis on each dosage group.

Table ES.11 presents the eradication rate at the 5-9 day post-therapy evaluation in patients with uncomplicated UTI listed by study location, sex, age and race. As was observed in the complicated UTI population, there seemed to be a trend toward inferior efficacy in the cefepime treatment group compared with the ceftazidime treatment group in patients who are 65 years of age or older.

Table ES.12 presents the bacteriologic response at the 5-9 days post-therapy evaluation for each pathogen recovered from patients with uncomplicated UTI. *E. coli* was the most commonly isolated pathogen, it was eradicated in 56/63 patients (89%) in the cefepime treatment group and in 28/33 (85%) in the ceftazidime treatment group. No other pathogens were recovered in large numbers from patients with uncomplicated UTI.

Table ES.12 presents the clinical response at the 5-9 days post-therapy evaluation for patients with uncomplicated UTI. The small numbers of patients with uncomplicated UTI has lead to highly variable results. In the 500 mg twice daily dosage group, the clinical cure rate was higher in the ceftazidime treatment group (21/23, 93%) than in the cefepime treatment group (23/33, 70%). However, in the 2 grams twice daily dosage group, the clinical cure rate in the cefepime treatment group (11/12, 92%) was higher than in the ceftazidime treatment group (11/16, 69%).

Table-ES.10
 Bacteriologic Eradication Rates at the 5-9 Days Post-Therapy Evaluation
 Uncomplicated UTI
 Medical Officer's Analysis

Dose	Study #	Evaluable Pathogen #Eradicated/#Evaluable				95% CI
		Cefepime		Ceftazidime		
		Number	Percent	Number	Percent	
Comparative Trials (North American and European)						
0.25 grams BID	411-071	7/ 9	78%	7/ 7	100%	
0.5 grams BID	411-083	17/ 19	89%	8/ 9	89%	
	411-108	7/ 8	88%	5/ 6	83%	
	411-083-E	6/ 7	86%	8/ 9	89%	
	Total	30/ 34	88%	21/ 24	88%	
2 grams BID	411-097	8/ 9	89%	11/ 13	85%	
2 grams BID	411-111-E	2/ 3	67%	3/ 5	60%	
	Total	10/ 12	83%	14/ 18	78%	
Non-Comparative Trials(North American and European)						
1 gram BID	411-061	4/ 4	100%			
	411-067-LD	11/ 11	100%			
	Total	15/ 15	100%			
2 grams BID	411-140	5/ 5	100%			
	411-067-HD	4/ 5	80%			
		9/ 10	90%			
All Uncomplicated UTI						
		71/ 80	89%	42/ 49	86%	[-10, +17]

The number of patients in each dosage group is too small for meaningful confidence interval analysis.

Uncomplicated UTI - Bacteriologic Efficacy by Demographic Group

Table-ES.11
 Determinant of Efficacy
 Uncomplicated UTI
 Patients Enrolled in Comparative Trials Only
 (411-071, -083, -108, -111)
 Medical Officer's Analysis

Group	Evaluable Pathogens ¹ #Erad/#Eval				95% ² Confidence Interval
	Cefepime		Ceftazidime		
	No.	%	No.	%	
ALL UTI	47/ 55	85%	42/ 49	86%	
NORTH AMERICAN	39/ 45	87%	31/ 35	89%	
EUROPEAN	8/ 10	80%	11/ 14	79%	
MALES	8/ 11	73%	1/ 2	50%	
FEMALES	39/ 44	88%	41/ 47	87%	
>65 YEARS OLD	26/ 31	84%	20/ 22	91%	
WHITE	38/ 45	84%	30/ 37	81%	
AFRICAN AMERICAN	6/ 6	100%	8/ 8	100%	
OTHER RACES	3/ 4	75%	4/ 4	100%	

- 1 Some patients may have more than one evaluable pathogen, therefore, the number of evaluable pathogens will be greater than or equal to the number of evaluable patients.
- 2 The numbers of patients in each sub-group are too small for meaningful confidence interval analysis.

COMMENT: The difference in eradication rates between males and females suggests that despite the fact that the "uncomplicated males" did not fulfill any of the medical officer's criteria for complicated UTI, that probably all UTI in males is complicated.

Uncomplicated UTI - Bacteriologic Response by Infecting Pathogen

Table ES.12 summarizes the bacteriologic response by infecting pathogen in patients with uncomplicated UTI. Table ES.12A presents the bacteriologic response for pathogens treated with cefepime 500 mg BID compared with the response for pathogens treated with ceftazidime 500 mg TID.

Table ES.12A
Bacteriologic Response of Pathogens Recovered from Patients with
Complicated UTI (Including Pyelonephritis)
5-9 Days Post-Therapy Evaluation
According to the Medical Officer

	CEFEPIME 500 mg BID	CEFTAZIDIME 500 mg TID
UNCOMPLICATED UTI PATHOGENS		
E. AEROGENES	0	1/ 1 (100%)
E. AGGLOMERANS	0	1/ 1 (100%)
E. COLI	24/ 28 (86%)	15/ 17 (88%)
ENTEROCOCCUS	0	1/ 1 (100%)
K. PNEUMONIAE	1/ 1 (100%)	2/ 2 (100%)
M. MORGANII	1/ 1 (100%)	0
P. MIRABILIS	4/ 4 (100%)	0/ 1 (0%)
S. MITIS	0	1/ 1 (100%)
ALL UNCOMPLICATED PATHOGENS	30/ 34 (88%)	21/ 24 (88%)

Only *E. coli* was recovered from greater than 10 cefepime patients with uncomplicated UTI. Because of the small number of isolates, equivalence in bacteriologic outcome could not be demonstrated, for *E. coli* by the 95% confidence interval approach (-27%, +22%). Nevertheless, the observed eradication rates are similar in the two treatment groups.

Table ES.12B presents the bacteriologic response for pathogens treated with cefepime 2.0 grams BID compared with the response for pathogens treated with ceftazidime 2.0 grams TID.

Table ES.12B
Bacteriologic Response of Pathogens Recovered from Patients with
UNComplicated UTI 7/26/97
5-9 Days Post-Therapy Evaluation
According to the Medical Officer

	CEFEPIME 2.0 grams BID	CEFTAZID 2.0 grams TID
UNCOMPLICATED UTI PATHOGENS		
C. DIVERSUS	1/ 1 (100%)	1/ 1 (100%)
E. CLOACAE	1/ 1 (100%)	0
E. COLI	7/ 9 (78%)	8/ 11 (73%)
K. PNFUMONIAE	0	3/ 3 (100%)
KLEBSIELLA-SP.	1/ 1 (100%)	0
P. AERUGINOSA	0	1/ 2 (50%)
S. LIQUIFACIENS	0	1/ 1 (100%)
ALL UNCOMPLICATED PATHOGENS	10/ 12 (83%)	14/ 18 (78%)

No pathogens were isolated from more than 10 patients treated with cefepime 2.0 grams BID. E. coli was the most frequently isolated pathogen. Because of the small number of E. coli isolates, equivalence in bacteriologic response for cefepime and ceftazidime could not be demonstrated by the 95% confidence interval approach (-43%, +53%).

Table ES.12C presents the bacteriologic response of pathogens recovered from patients with UTI in non-comparative clinical trials.

Table ES.12C
Bacteriologic Response of Pathogens Recovered from Patients with
(U)Complicated UTI 7/26/94 DA
5-9 Days Post-Therapy Evaluation
According to the Medical Officer

CEFEPIME 1.0 GRAMS BID	
E. COLI	12/ 12 (100%)
K. PNEUMONIAE	1/ 1 (100%)
P. MIRABILIS	1/ 1 (100%)
S. FAECALIS	1/ 1 (100%)
ALL 1.0 GRAM PATHOGENS	15/ 15 (100%)
CEFEPIME 2.0 GRAMS BID	
E. COLI	6/ 7 (86%)
K. PNEUMONIAE	2/ 2 (100%)
STREP. (GROUP D)	1/ 1 (100%)
ALL 2.0 GRAM PATHOGENS	9/ 10 (90%)

Uncomplicated UTI - Clinical Efficacy

Table-ES.13
 Clinical Efficacy at the 5-9 Days Post-Therapy Evaluation
 Uncomplicated UTI
 Medical Officer's Analysis

Dose	Study #	Evaluable Patients ¹ #Cured/#Evaluable				95% CI ¹
		Cefepime		Ceftazidime		
		Number	Percent	Number	Percent	
Comparative Trials						
0.25 grams BID	411-071	8/ 9	89%	6/ 6	100%	
0.5 grams BID	411-083	10/ 18	56%	9/ 9	100%	
	411-108	6/ 8	75%	6/ 6	100%	
	411-083E	7/ 7	100%	6/ 8	75%	
	Total	23/ 33	70%	21/ 23	91%	
2 grams BID	411-097	9/ 9	100%	8/ 11	73%	
	411-111E	2/ 3	67%	3/ 5	60%	
	Total	11/ 12	92%	11/ 16	69%	
Non-Comparative Trials						
1 gram BID	411-061	3/ 4	75%			
	411-067-LD-E	9/ 10	90%			
	Total	12/ 14	86%			
2 grams BID	411-140	5/ 5	100%			
	411-067-HD-E	2/ 5	40%			
	Total	7/ 10	70%			

- 1 Confidence interval analysis not performed due to small numbers of patients in each dosage group.
 2 Study numbers ending in E were performed at European centers.

Long-Term (4-6 Weeks Post-Therapy) Follow-Up

In the majority of UTI protocols⁶ submitted in support of this application, a long-term follow-up visit was requested only of patients with complicated UTI. In practice, however, although only a small number of patients actually underwent a long-term follow-up evaluation, patients with both complicated and uncomplicated UTI were assessed. Because of the small number of patients involved, the medical officer will present the results of the long-term follow-up evaluation for the combined (complicated + uncomplicated) populations together.

Table ES.13 presents the bacteriologic efficacy at the long-term (4-6 weeks post-therapy) evaluation. Because of the small numbers of patients involved, it is difficult to draw conclusions from this data. However, in each dosage group the percentage of patients in the cefepime treatment group who were assigned the outcome of continued eradication at long-term follow-up was equal to or greater than the percentage of patients in the ceftazidime treatment group.

Table ES.14
Bacteriologic Efficacy at The Long Term (4-6 Weeks Post-Therapy)
Evaluation
Patients with Complicated and Uncomplicated UTI
Enrolled in Comparative Studies (071, 083, 083E, 097, 108, 111E)
According to the Medical Officer

Study	4-6 Week Eligible ¹		Not Assessed		Continued Eradication		Relapse ²		Reinfection	
	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz
071	15	11	0	0	-	-	-	-	-	-
083	99	47	45 (45) ³	22 (47)	32 (32)	16 (34)	6 (6)	3 (6)	16 (16)	6 (13)
108	26	16	8 (31)	0	14 (54)	11 (69)	4 (15)	4 (25)	0 (0)	1 (6)
083E	14	15	7 (50)	10 (69)	4 (29)	2 (13)	1 (7)	0 (0)	2 (14)	3 (19)
500 mg	139	79	60 (43)	33 (41)	50 (37)	29 (37)	11 (8)	7 (9)	18 (13)	10 (13)
097	55	57	38 (69)	42 (74)	8 (15)	3 (5)	4 (7)	7 (12)	5 (9)	5 (9)
111E	10	15	5 (50)	11 (73)	3 (30)	1 (7)	1 (10)	3 (20)	1 (10)	0 (0)
2000 mg	65	72	43 (66)	53 (74)	11 (17)	4 (5)	5 (7)	10 (15)	6 (8)	5 (7)

- 1- 4-6 Week Eligible = M.O. Evaluable Failures at 5-9 Days.
- 2- Includes 3 patients with relapse and reinfection.
- 3- Numbers in parenthesis are percent of 4-6 week eligible patients.

Table ES.14-A, on the following page, presents the cumulative rates of bacteriologic success and failure as determined at the end of the study (4-6 weeks post-therapy).

*no chart located in document on diskette
02/7/94*

Conclusions

In support of their claim of efficacy for cefepime in patients with complicated and uncomplicated UTI, the applicant has submitted data from five comparative and three non-comparative studies. In general the studies were well designed and executed according to their stated protocols.

With regard to patients with complicated UTI, the medical officer's analysis of the data leads to the conclusion that the overall bacteriologic response to treatment with cefepime and ceftazidime, evaluated at 5-9 days post-therapy, is statistically equivalent by the 95% confidence interval approach when administered at the dose of 500 mg twice daily and at the dose of 2.0 grams twice daily.

Patients who received the dose of 2.0 grams twice daily were more likely to have pyelonephritis, a urinary catheter and concurrent bacteremia than patients who received the dose of 500 mg twice daily. Therefore, patients who received the dose of 2.0 grams twice daily may have had more severe disease than patients who received the dose of 500 mg twice daily, since the bacteriologic eradication rates are similar for the two dosage regimens (500mg: 115/146(79%), 2.0 grams:64/82(78%)) one may infer that there is an incremental increase in efficacy at the higher dosage level.

E. coli, *K. pneumoniae*, *P. aeruginosa*, and *P. mirabilis* were studied in greater than 10 evaluable patients treated with cefepime 500 mg BID. The bacteriologic response of cefepime treated patients was equivalent to the response of ceftazidime treated patients for *E. coli* by the 95% confidence interval approach. There were insufficient numbers of evaluable patients with *K. pneumoniae*, *P. aeruginosa* and *P. mirabilis* for a meaningful confidence interval analysis. However, in patients infected with *K. pneumoniae*, similar eradication rates were seen in the cefepime and ceftazidime treatment groups. In patients infected with *P. aeruginosa* and *P. mirabilis* there was a trend toward inferior eradication rates among patients treated with cefepime (see page 216).

E. coli was the only organism studied in greater than 10 evaluable patients treated with cefepime 2.0 grams BID. The bacteriologic response of cefepime treated patients was equivalent to the response of ceftazidime treated patients for *E. coli* by the 95% confidence interval approach (see page 217).

Of concern, is the trend toward inferior performance of cefepime when compared with ceftazidime in persons over 65 years of age. The 95% confidence interval was [-20%, +3%], failing to demonstrate equivalence for this age group.

The two treatment regimens were demonstrated to be equivalent with respect to clinical cure rates in patients with complicated UTI by the 95% confidence interval approach.

With regard to patients with uncomplicated UTI, the small number of patients studied makes it difficult to make statement regarding the effectiveness of individual dosage regimens. Overall (including all dosage groups) the eradication rate at the 5-9 day post-therapy evaluation was 71/80 (89%) in the cefepime treatment group and 42/49 (86%) in the ceftazidime treatment group. The 95% confidence interval around the true difference in eradication rates is [-10%, +17%] which fulfills the regulatory definition for equivalence.

Only *E. coli* was studied in greater than 10 patients with uncomplicated UTI treated with cefepime 500 mg BID. Statistical equivalence between cefepime and ceftazidime was not demonstrated for *E. coli* at this dosage level because of the

small number of evaluable patients studied (see page 225). Nevertheless, the eradication rates observed in the two treatment groups were similar and the bacteriologic performance of cefepime and ceftazidime was shown to be equivalent, at this dosage level, in patients with complicated UTI due to *E. coli*. (see page 216).

No pathogens were isolated in greater than 10 patients with uncomplicated UTI treated with cefepime 2.0 grams BID. *E. coli* was the most commonly isolated pathogen, however, it was only isolated from nine cefepime patients in comparative trials. Nevertheless, similar eradication rates were seen in both the cefepime and ceftazidime treatment groups in patients infected with *E. coli* and treated at this dosage level (see page 226). Also, the bacteriologic performance of cefepime and ceftazidime was shown to be equivalent, at this dosage level, in patients with complicated UTI due to *E. coli*. (see page 217).

The favorable results achieved in patients with complicated UTI should be supportive of the claim of efficacy for patients with uncomplicated UTI.

With regard to route of administration, forty-one patients in the 500 mg twice daily dosage group were treated via the intramuscular route, however, only a small number of patients (approximately 7 according to the applicant) in the 2.0 gram twice daily dosage group were treated via the intramuscular route. Therefore the efficacy of intramuscular technique has only been verified at the 500 mg twice daily dosage level in mild to moderate infections.

With regard to duration of therapy, the applicant states that the "usual duration of dosing is 7 to 10 days". The mean duration of therapy was 6.1 days in the cefepime treatment group. Referring to the frequency histogram (figure-ES.1) the duration of therapy was normally distributed with the center at the 7-10 day range. Therefore, the medical officer concludes that the duration of therapy suggested by the applicant (7-10 days) is supported by the data.

Therefore, the medical officer concludes that the applicant has sufficiently demonstrated the efficacy of cefepime at a dose of 500 mg IM/IV twice daily in patients with mild to moderate complicated and uncomplicated UTI due to *E. coli* and *K. pneumoniae*. The applicant has also demonstrated the efficacy of cefepime at a dose of 2.0 grams IV twice daily in patients with severe complicated and uncomplicated UTI due to *E. coli*.

SAFETY SUMMARY

The safety of cefepime was assessed in 647 patients enrolled in the cefepime treatment group in comparative studies of patients with UTI; these patients were compared with 517 patients who received ceftazidime in the same studies. An additional 387 patients were treated with cefepime in non-comparative studies of patients with UTI. Also 22 patients with UTI were treated with cefepime and 11 patients with UTI were treated with a comparator in studies designed to assess the safety and efficacy of cefepime in patients with infections other than UTI.

Comment: The 33 patients who were enrolled in studies designed to assess the safety and efficacy of cefepime in patients with infections other than UTI but who had concomitant UTI will not be discussed here, instead they will be addressed in the sections of the NDA review that discuss the primary indication for which these patients were studied.

Finally one patient was treated with cefepime for a UTI under an emergency IND.

Table SS.1 summarizes the population evaluable for the assessment of drug safety.

Table SS.1
Patients Evaluable for the Safety Assessment

Study	Enrollment	
	Cefepime	Ceftazidime
Comparative Studies		
250 mg Twice Daily		
411-071	32	16
500 mg Twice Daily		
411-083	246	125
411-108	39	41
411-083-E	59	36
Total	344	202
2.0 Grams Twice Daily		
411-097	215	226
411-111-E	56	73
Total	271	299
All Comparative Studies		
	647	517
Non-Comparative Studies		
411-061	116	
411-140	119	
411-067-E	152	
Emergency IND		
	1	
Total UTI		
	1035	517
Other Experience¹		
Multiple	22	11

1 Patients with UTI enrolled in studied primarily designed to study other indications, not included in this review.

Deaths

Sixty patients with UTI who were exposed to cefepime died during the clinical investigation of the safety and efficacy of cefepime. Please see the individual study reports for a brief summary of each patients who died. In addition to those patients who died during the clinical UTI studies there was one patients who died after treatment with cefepime for a UTI under an Emergency IND.

Patient : The patient was a 45 year old female with a history of severe thrombotic thrombocytopenic purpura requiring immunosuppressive therapy. The patient developed a UTI due to a multiply resistant isolate of *P. aeruginosa* and septicemia due to *E. cloacae*. Because of the resistance pattern of the *Pseudomonas* isolate and Emergency IND for cefepime was requested and granted. Cefepime was administered, in combination with amikacin for six days. The patients infections were clinically and bacteriologically cured. However, the patient died 23 days after the completion of therapy due to fungal sepsis.

Thirty-two patients with UTI who were exposed to ceftazidime died during the clinical investigation of the safety and efficacy of cefepime. Please see the individual study reports for a brief summary of each patients who died.

Overall, comparative studies, there was no significant difference in the mortality rate between patients in the cefepime treatment group (34/647, 5%) and patients in the ceftazidime treatment group (32/517, 6%). The mortality rates seen in non-comparative studies were similar to those seen in comparative studies of the same doses. Table-SS.2 presents summarizes the deaths occurring in UTI patients.

Table-SS.2
Deaths Occurring in Cefepime Studies

Study	Enrollment		Deaths (Deaths/Enrollment)	
	Cefepime	Ceftazidime	Cefepime	Ceftazidime
Comparative Studies				
250 mg Twice Daily				
411-071	32	16	0 (0)	1 (6)
500 mg Twice Daily				
411-083	246	125	6 (2)	3 (2)
411-108	39	41	2 (5)	1 (2)
411-083-E	59	36	2 (3)	3 (8)
Total	344	202	10 (3)	7 (3)
2.0 Grams Twice Daily				
411-097	215	226	17 (8)	14 (6)
411-111-E	50	73	7 (13)	10 (14)
Total	271	299	24 (9)	24 (8)
All Comparative Studies				
	647	517	34 (5)	32 (6)
Non-Comparative Studies				
411-061	116		7 (6)	
411-140	119		14 (12)	
411-067-E	152		4 (3)	
Other Experience¹				
Multiple	1		1	
Totals	1035	517	60 (6)	32 (6)

¹ Studied under emergency IND.

Discontinuations

Overall, in comparative studies, 14/647 patients (3%) were removed from cefepime therapy due to adverse clinical or laboratory events. In contrast, 7/517 patients (1%) were removed from ceftazidime therapy due to adverse clinical or laboratory events. The difference in the discontinuation rate between the two treatment groups was not significant (p=0.18). An additional 16/387 (4%) patients enrolled in non-comparative or other studies were also removed from therapy due to adverse clinical or laboratory events.

Table-SS.3 lists the clinical and laboratory adverse events that resulted in discontinuation of therapy. Rash was the most common reason for discontinuation of both cefepime and ceftazidime therapy.

Table-SS.3
Adverse Events Resulting in Discontinuation
UTI Studies

Event	Cefepime No. of Patients	Ceftazidime No. of Patients
Rash	12	3
Change in Mental Status	5	0
Infiltration/Phlebitis	5	0
Lack of Effect	2	0
Moniliasis	1	0
Hypotension	1	0
Leg Pain	1	0
Seizure	0	1
Dizziness	0	1
Nausea/Vomiting	0	1
Leukopenia	0	1
Eosinophilia	1	0
Elevated LFT	1	0
Elevated Creatinine	1	0
TOTAL	30	7

Clinical Adverse Drug Events

Overall, at least one clinical adverse drug events (CADE) was reported for 189 of the 1035 patients (18%) exposed to cefepime; 169 patients experienced at least one CADE that was of probable or unknown relation to the study drug. At least one CADE was reported for 116 of the 517 patients (22%) exposed to ceftazidime; 77 patients experienced at least one CADE that was of probable or unknown relation to the study drug. A significantly greater ($X^2=7.94$, $p<<0.05$) proportion of the patients in the ceftazidime group experienced at least one CADE compared with the cefepime group, however, there was no statistically significant difference in the proportion of patients experiencing a CADE of probable or unknown relationship to the study drug ($X^2=0.01$, $P=1$).

Table-SS.4 presents the CADE reporting rates by location of study. The CADE

reporting rate is higher for North American than for European centers.

Table-SS.4
Clinical Adverse Drug Events Reporting Rate
By Location of Study Center
UTI Studies

Location	Cefepime			Ceftazidime		
	N	# of CADE	Prob or Unk CADE	N	# of CADE	Prob or UNK CADE
North Amer.	768	173 (23%)	156 (20%)	408	112 (27%)	73 (18%)
Europe	267	16 (6%)	13 (5%)	109	4 (4%)	4 (4%)

Table-SS.5 presents the CADE reporting rate by the dose of medication administered. A higher incidence of CADE reporting is seen with increasing doses of both cefepime and ceftazidime. The dose-response effect seen is likely to have been contributed to by both the increasing amount of drug administered and the increasing severity of disease in the patients in whom high doses of drug were administered.

Table-SS.5
Clinical Adverse Drug Events Reporting Rate
Listed by Dose of Drug Administered
North American Comparative UTI Studies

Dose	Cefepime			Ceftazidime		
	N	# ADR (Per)	Prob/Unk (Per)	N	# ADR (Per)	Prob/Unk (Per)
250 BID	32	2 (6)	2 (6)	16	1 (6)	1 (6)
500 BID	285	52 (18)	37 (13)	166	33 (20)	18 (11)
2 g BID	215	76 (35)	40 (19)	226	78 (34)	52 (23)

Table-SS.6 presents the number of CADE reported for the studies in which the investigation was conducted in a blinded manner (#097BL, #108). There is no significant difference in the rate of CADE reporting between the treatment groups at the blinded centers.

Table-SS.6
Clinical Adverse Drug Events Reporting Rate
Blinded Centers
UTI Studies

Dose	Cefepime			Ceftazidime		
	N	# ADR (Per)	Prob/Unk (Per)	N	# ADR (Per)	Prob/Unk (Per)
Blinded	74	29 (39)	22 (30)	74	30 (41)	19 (26)

Table-SS.7 presents the number of patients experiencing at least one CADE within each major organ system. The digestive system was the organ system most frequent site of CADEs for both treatment groups. A statistically significant difference in the CADE reporting rate for the skin system was observed ($X^2 = 6.48$, $p < 0.05$); no other statistically significant differences were observed.

Table-SS.7
 Clinical Adverse Drug Events
 Number of Patients Experiencing at least One CADE
 in the Indicated System
 UTI Studies

Organ System	Cefepime Number of Pts. (Percent)	Ceftazidime Number of Pts. (Percent)
Patients in Database	1035	517
Body as a Whole	10 (1%)	3 (<1%)
Cardiovascular	20 (2%)	10 (2%)
Digestive	70 (7%)	47 (9%)
Musculo/Skeletal	14 (1%)	14 (1%)
Nervous	44 (4%)	26 (5%)
Respiratory	12 (1%)	15 (3%)
Skin and Appendages*	25 (2%)	25 (5%)
Special Senses	2 (<1%)	4 (:1%)
Urogenital	13 (1%)	13 (3%)

Table-SS.8 lists all individual adverse events that occurred in North American clinical trials which were judged by the investigator to be either possibly or of unknown relationship to the study therapy. The most commonly reported CADE among patients exposed to cefepime were headache (2.61%), diarrhea (1.65%), vomiting (2.2%), and nausea (1.1%). The same CADEs were also the most common events seen in patients exposed to ceftazidime.

Table-SS.8
 Clinical Adverse Drug Events
 of Probably or Unknown Relationship to Drug Therapy
 All Cefepime Courses

ADR	CEFEPIME		CEFTAZIDIME	
	NUMBER	RATE	NUMBER	RATE
BODY AS WHOLE				
Aesthesia	5	1%	2	<1%
Allergic	1	<1%		0%
Cold	2	<1%	1	<1%
Diaphoresis	1	<1%		0%
Fever	1	<1%	1	<1%
Pain	3	<1%		0%
Pain, Back	1	<1%	1	<1%
Pain, Chest	3	<1%	3	1%
Pain, Dental			1	<1%
Pain, Extr	2	<1%	5	1%
Pain, Facial			1	<1%
Pain, Neck	1	<1%		0%
Pain, Throat			4	1%
Thirst	1	<1%		0%
CARDIOVASCULAR				
Arrhy, atrial	1	<1%		0%
Arrhy, ventric	1	<1%		0%
Cardiac Arrest	1	<1%		0%
Embolus	1	<1%		0%
Hypertension			1	<1%
Hypotension	1	<1%	1	<1%
Vasodilation	2	<1%	1	<1%
DIGESTIVE SYSTEM				
Anorexia	1	<1%	0	0%
Colitis, PMC	3	<1%	0	0%
Constipation	2	<1%	6	2%
Diarrhea	12	2%	11	3%
Dyspepsia	1	<1%	0	0%
Hematemesis	1	<1%	0	0%
Ileus	1	<1%	0	0%
Melena	0		1	<1%
Monilia, O	2	<1%	3	1%
Nausea	8	1%	9	2%
Pain, Abd	10	1%	6	2%
Stomatitis	0		1	<1%
Ulceration	0	0%	0	0%
Vomiting	16	2%	10	3%

Table-SS.9 - Continued
 Clinical Adverse Events
 of Probably or Unknown Relation to Study Drug
 All Cefepime Courses

ADR	CEFEPIME NUMBER	RATE	CEFTAZIDIME NUMBER	RATE
METABOLIC AND NUTRITIONAL SYSTEM				
Edema, Ext	3	<1%	1	<1%
Edema, Gen	1	<1%	2	1%
NERVOUS SYSTEM				
Agitation	0	0%	1	<1%
Anxiety	0	0%	1	<1%
Coma/Stupor	1	<1%	0	0%
Confusion	4	1%	2	1%
Depression	0		2	1%
Dizziness	2	<1%	2	1%
Headache	19	3%	10	3%
Insomnia	5	1%	2	1%
Paresthesia	1	<1%	1	<1%
Seizures	1	<1%	2	1%
Tremors	1	<1%		0%
RESPIRATORY SYSTEM				
Cough	2	<1%	2	1%
Dyspnea	2	<1%	4	1%
Epistaxis	2	<1%	0	0%
Hiccups	1	<1%	1	<1%
Lung Disorder	1	<1%	0	0%
Lung Edema	0	0%	1	<1%
Sputum	0	0%	1	<1%
SKIN				
Hives	1	<1%	1	<1%
Pruritus	6	1%	3	1%
Rash	3	<1%	11	3%
SPECIAL SENSES				
Blurred Vision	0	0%	1	<1%
UROGENITAL SYSTEM				
Herpes, Exac	0		1	<1%
Monilia, V	3	<1%	2	1%
Vaginitis	3	<1%	5	1%
TOTAL	147	20%	128	33%

Most CADE associated with cefepime exposure were of mild or moderate severity (4%). One patients experienced a life-threatening cardiac arrhythmia that was not believed to be related to cefepime therapy. Forty-three patients experienced severe CADEs. Of the 43 severe CADE 12 events (cefepime=3, ceftazidime=3) were considered of probably or unknown relation to the study drug therapy. Table-SS.9 presents severe CADE of probably or unknown relation to study drug therapy.

Table-SS.9
Severe Clinical Adverse Drug Events
of Unknown or Probable Relation to Drug
UTI Studies

Event	Cefepime Number of Events	Ceftazidime Number of Events
Anaphylaxis	1	0
Agitation	1	0
Chills	1	0
Constipation	1	0
Loss of Consciousness	1	0
Peripheral edema	1	0
Pseudomemb. Colitis	2	0
Pulmonary Embolus	1	0
Insomnia	0	1
Extremity Pain	0	1
Pulmonary Edema	0	1

Local Reactions at the Infusion Site

Overall, 68/1035 patients (7%) exposed to cefepime experienced a local reaction at the infusion site. In comparison, 29/517 patients (6%) exposed to ceftazidime experienced local reaction at the infusion site. The difference in the incidence rates for local reactions between the two treatment groups is not significant ($X^2=0.54$, $p<0.05$).

Table-SS.10 presents the incidence of local reactions, occurring in North American studies, as a function of the dose of study drug administered. In general an increasing incidence of local reactions is seen with increasing doses of cefepime.

Table-SS.10
Local Reactions at the Infusion Site
by Dose of Drug Administered
UTI Studies

Dose Received	Cefepime		Ceftazidime	
	#	Reactions (Percent)	#	Reactions (Percent)
250 mg BID	32	0	16	0
500 mg BID	285	11 (4%)	166	14 (8%)
2 grams BID	215	16 (7%)	226	11 (5%)
>2 grams BID	120	12 (10%)		

Laboratory Test Abnormalities

Table-SS.11 presents the number of patients, enrolled in North American clinical trials who had normal pre-treatment laboratory test parameters but developed abnormal values either during or after treatment.

Table-SS.11
Laboratory Test Abnormalities
In Patients with a Normal Pre-Treatment Value
North American Studies
All Dosage Levels

Test	Cefepime		Ceftazidime	
	N	Abn. (%)	N	Abn (%)
Hematocrit	309	18 (5%)	164	4 (2%)
Platelet	626	11 (2%)	312	4 (1%)
WBC	706	5 ($\leq$ 1%)	355	3 ($\leq$ 1%)
Neutrophil Count	641	2 ($\leq$ 1%)	333	1 ($\leq$ 1%)
Eosinophil Count	594	27 (5%)	313	17 (5%)
PT	440	4 ($\leq$ 1%)	214	4 (2%)
PTT	480	5 ($\leq$ 1%)	249	8 (3%)
Alk. Phosphatase	489	4 ($\leq$ 1%)	230	2 ($\leq$ 1%)
AST	529	24 (5%)	254	8 (3%)
ALT	518	23 (4%)	246	8 (3%)
Total Bilirubin	589	8 ($\leq$ 1%)	279	3 (1%)
BUN	520	9 (2%)	253	4 (2%)
Creatinine	580	5 ($\leq$ 1%)	266	3 (1%)
Sodium	517	6 (1%)	259	1 ($\leq$ 1%)
Potassium	561	14 (3%)	281	7 (3%)
Calcium	373	7 (2%)	208	6 (3%)
Phosphorous	425	51 (12%)	229	15 (7%)

Greater than 1% of the population exposed to cefepime developed abnormalities in hematocrit; platelet count; eosinophil count; AST; ALT; BUN; potassium; calcium; and phosphorous. Compared with the patients who were exposed to ceftazidime, a statistically greater proportion of patients in the cefepime treatment group developed abnormalities in hematocrit ($\chi^2=2.77$, $p<0.05$) and phosphorous ($\chi^2=4.87$, $p<0.05$). In contrast a statistically greater proportion of patients in the ceftazidime treatment group developed an abnormality in PTT ($\chi^2=4.41$, $p<0.05$) compared with the cefepime treatment group.

Table-SS.12 compares cefepime and ceftazidime in patients with abnormal results of laboratory tests at pre-treatment. In general, because of the small numbers of patients involved, statistically significant differences were not demonstrated for most tests. However, a greater proportion of patients with abnormalities in renal function worsened in the cefepime treatment group than in the ceftazidime treatment group.

Table-SS.12
Laboratory Test Abnormalities
In Patients with Abnormal Pre-Treatment Values
North American Studies
All Dosage Levels

Test	Cefepime		Ceftazidime	
	N	Abn (%)	N	Abn (%)
Hematocrit	393	10 (3%)	186	9 (5%)
Platelet	42	2 (5%)	34	3 (9%)
WBC	29	2 (7%)	14	0
Neutrophil Count	19	0	8	1 (13%)
Eosinophil Count	40	1 (3%)	13	1 (8%)
Prothrombin Time	162	14 (8%)	88	3 (3%)
PTT	75	3 (4%)	30	0
Alkaline Phosphatase	168	3 (2%)	86	0
AST	139	7 (3%)	64	6 (9%)
ALT	98	9 (9%)	54	4 (7%)
Total Bilirubin	71	4 (5%)	35	2 (6%)
BUN	194	22 (11%)	95	3 (3%)
Creatinine	140	9 (6%)	84	0
Sodium	205	1 (<1)	95	0
Potassium	161	0	72	1 (<1%)
Calcium	194	6 (3%)	94	3 (3%)
Phosphorous	136	10 (7%)	75	2 (3%)

Table-SS.13 compares the incidence of laboratory test abnormalities in the two different dosage groups of cefepime. The low-dose group received < 2 grams per day of cefepime and the high-dose group received > 2 grams per day of cefepime. Statistically significant increases were seen in the proportion of patients who developed abnormalities in hematocrit, AST, ALT, BUN, creatinine, and phosphorous in the high-dose group.

Table-SS.13
 Laboratory Test Abnormalities
 in Patients with Normal Pre-Treatment Values
 By Dose of Cefepime Received
 North American Studies

Test	< 2 grams /Day		> 2 grams/Day	
	N	Abn (%)	N	Abn (%)
Hematocrit	157	4 (3%)	56	6 (11%)
Platelet	255	4 (2%)	147	3 (2%)
White Blood Cells	282	2 (≤1%)	165	1 (≤1%)
Neutrophils	259	1 (≤1%)	156	0
Eosinophil	237	8 (3%)	144	4 (3%)
Prothrombin Time	201	2 (1%)	81	0
PTT	223	2 (≤1%)	94	2 (2%)
Alk. Phosphatase	223	1 (≤1%)	106	1 (≤1%)
AST	214	7 (3%)	120	11 (9%)
ALT	231	6 (3%)	114	13 (11%)
Total Bilirubin	248	2 (≤1%)	139	2 (1%)
BUN	232	2 (≤1%)	120	5 (4%)
Creatinine	244	0	132	3 (2%)
Sodium	223	1 (≤1%)	116	0
Potassium	240	7 (3%)	127	2 (2%)
Calcium	188	2 (1%)	86	3 (3%)
Phosphorous	208	15 (7%)	106	17 (16%)

Table-SS.14 presents the incidence of laboratory test abnormalities in patients with normal pre-treatment laboratory test results who were enrolled in clinical trials at European centers. There were no significant differences in the incidence of laboratory test abnormalities between the treatment groups at the European centers.

Table-SS.14
Laboratory Test Abnormalities
in Patients with Normal Pre-Treatment Values
European Centers
All Dosage Groups

Test	Cefepime		Ceftazidime	
	N	Abn (%)	N	Abn (%)
Hematocrit	126	4 (3%)	34	2 (6%)
Platelet	184	6 (3%)	74	1 (1%)
White Blood Cells	227	7 (3%)	85	2 (2%)
Neutrophils	191	4 (2%)	79	0
Eosinophil	173	8 (5%)	79	5 (6%)
Prothrombin Time	33	0	24	0
Prothrombin Ratio	122	1 ($\leq$ 1%)	38	0
PTT	133	0	50	1 (2%)
Alk Phosphatase	154	1 ($\leq$ 1%)	48	1 (2%)
AST	170	3 (2%)	61	2 (3%)
ALT	175	8 (5%)	65	5 (8%)
Total Bilirubin	156	3 (2%)	57	0
BUN	96	1 (1%)	17	1 (6%)
Blood Urea	52	2 (4%)	39	0
Creatinine	167	1 ($\leq$ 1%)	63	1 (2%)
Sodium	166	2 (1%)	56	1 (2%)
Potassium	170	3 (2%)	68	3 (4%)
Calcium	52	2 (3%)	45	0
Phosphorous	48	6 (13%)	45	4 (9%)

Conclusions

There were no significant differences in the rate of deaths between the cefepime and the ceftazidime treatment groups at any dosage level.

There were no statistically significant differences in the rate of discontinuation between the cefepime and ceftazidime treatment groups.

Considering all clinical adverse events, a greater proportion of patients experienced at least one clinical adverse event in the ceftazidime group (23%) than in the cefepime group (18%), this difference is significant ($\chi^2=7.94$, $p<0.05$). If only events of probable or unknown relation to the study drug are considered then no significant difference could be noted between the two treatment groups.

Most clinical adverse events were of mild or moderate severity. The most frequently reported adverse events, that were considered of probable or unknown relationship to the study drug therapy, were headache (2.7%), diarrhea (2.7%), vomiting (2.2%) and nausea (1.9%). There was a trend toward increasing incidence of clinical adverse events with increasing doses of both cefepime and ceftazidime.

There was no significant difference in the incidence of local reactions at the infusion site between the patients exposed to cefepime and the patients exposed to ceftazidime. A trend was noted toward increasing incidence of local reactions at the infusion site with increasing doses of cefepime.

More patients in the cefepime treatment group developed abnormalities in hematocrit and phosphorous either during or after therapy. Patients with abnormal renal function tests tended to worsen more frequently on cefepime therapy than with ceftazidime therapy. When high-dose (>2 grams per day) and low-dose (< 2 grams per day) were compared the incidence of laboratory test abnormalities was the same or higher in the high dose group for every parameter tested. The difference was statistically significant for 6 tests (hematocrit, alkaline phosphatase, AST, BUN, Creatinine, phosphorous).

Cefepime appears to be comparable to ceftazidime in terms of the studied safety parameters. There appears to be a trend toward increasing adverse drug events with increasing doses of cefepime.

OVERALL CONCLUSIONS

The applicant has demonstrated in three adequate and well controlled studies, performed in North America, that cefepime has comparable efficacy and safety to ceftazidime for the treatment of patients with uncomplicated and complicated UTI including pyelonephritis.

The conclusions reached based on the North American comparative studies were supported by the experience in Europe and the experience in non-comparative studies.

Efficacy has been demonstrated in complicated UTI for *E. coli*, *K. pneumoniae* and *P. mirabilis*. Efficacy was not demonstrated for *P. aeruginosa* because the eradication rates were not statistically equivalent, by the 95% confidence interval approach to the eradication rates for ceftazidime. Efficacy was not demonstrated for *Enterobacter* species because of the low number of evaluable patients studied.

Efficacy was demonstrated at two dosage levels: 500 mg IV/IM BID and 2 grams BID. Most patients at both dosage levels were treated from seven to ten days. Patients studied at 2 grams IV BID were more likely to have pyelonephritis, a catheter and concurrent bacteremia than patients studied at 500 mg BID, yet the eradication rates for the two dosage groups were similar, thus there may be a role for the higher dosage level in patients with UTI.

In general cefepime seemed to have a similar safety profile to ceftazidime. The medical officer has some concerns regarding the deterioration in renal function seen in patients treated with cefepime who had abnormalities of renal function prior to treatment. Conclusion regarding this issue must await the large numbers of patients that will be reviewed for the integrated safety summary for the complete application.

RECOMMENDED REGULATORY ACTION

In the opinion of the medical officer:

(P)

The claim of efficacy for uncomplicated UTI due to E. coli should be approved

The claim of efficacy for complicated UTI including pyelonephritis due to E. coli, and K. pneumoniae should be approved.

The claim of efficacy for complicated UTI including pyelonephritis due to P. aeruginosa, P. mirabilis, and Enterobacter species is not approvable.

The dose of 500 mg IM/IV every 12 hours for the treatment of mild to moderate complicated and uncomplicated UTI is should be approved.

The dose of 2 grams IV every 12 hours for the treatment of moderate to severe complicated and uncomplicated UTI is should be approved.

The requested duration of therapy of 7 to 10 days is supported by the data.

William A. Erhardt MD 3/1/94

William A. Erhardt, M.D.
MO/HFD-520

- cc:orig. NDA
- HFD-340
- HFD-520
- HFD-520/MO/Werhardt
- HFD-520/MO/LSherman
- HFD-520/SMO/RAlbrecht
- HFD-520/Pharm/Mainigi
- HFD-520/Micro/Soprey
- HFD-520/Chem/Roy
- HFD-520/CSO/DeBellas

Concurrence Only:
HFD-520/DivDir/MLumpkin
HFD-520/DepDir/LGavrilovich

ra 3/8/94
discrepancies
noted; see
addendum -
ra 6/14/94

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MAXIPIME®

REVIEWER INTRODUCTION

The applicant, Bristol Myers Squibb is seeking approval for the treatment of pneumonia as subsets of and pneumonia. Because the applicant approached these two indications are discussed concurrently in the following review.

Labelling Request

The applicant has submitted several studies to support efficacy claims for pneumonia. Specifically, the applicant has requested the following statements in their proposed label.

PACKAGE INSERT REQUEST

"MAXIPIME" is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Recommended Dosage Schedule for MAXIPIME®:

Site:	Dose:	Frequency:
Mild to moderate infections including pneumonia skin and skin-structure infections.	1 g IV or 1 g IM	Q12h
Severe infections including pneumonia, urinary tract infections, skin and skin-structure infections.	2 g IV	Q12h

General Comments

Before commencing the review, the reviewer would like to make a few comments on the study design as a whole. The applicant approached their development program on the basis of how cefepime

compared to a marketed third generation cephalosporin (ceftazidime or cefotaxime) in the treatment

The applicant had two protocol designs. One was specifically targeted to study [redacted] and one was to study multiple indications (of which pneumonia [redacted] were subsets) under a single protocol. Both these protocol types had similar evaluability and procedural requirements. Minimum case definition of appropriate patients was non-specific (i.e. inclusion of patients with signs and symptoms consistent with a [redacted] Unlike the IDSA guidelines, parameters such as fever, leukocytosis and increased sputum volume were not entry requirements. Pneumonia was distinguished [redacted] by the presence or absence of an infiltrate on a chest X-ray.

The "points to consider" document clarifies the "indication" as follows:

The definition of "indication" as applied to antimicrobial drug products has evolved over time. In the past it assumed a broader interpretation, such as [redacted] or [redacted]. More recently, a more definitive interpretation, such as [redacted] has been applied. This recent change recognizes the different pathophysiologies of certain infectious diseases and the inability to extrapolate effectiveness in one disease to effectiveness in another disease when pathophysiology or microbiology are different. This change in perspective has been undertaken in an effort to fulfill the mission of the Agency to inform physicians, as accurately as possible, about the established effectiveness of a product and to limit manufacturer promotion of products only to those indications for which adequate effectiveness and safety have been established. (no. 2, p. 4)

The applicant has addressed this recognized need of the physician to distinguish different disease processes and has requested more specific terminology in their label. They have requested, for example, [redacted] In their studies, however, patients with these disease processes were not specifically identified and/or differentiated.

The applicant enrolled many types of patients - patients with underlying chronic obstructive pulmonary disease, patients with no prior history of pulmonary disease, patients with neoplasia (either pulmonary or other), patients with chronic congestive heart failure, patients in a chronic vegetative state, etc. - all of whom had an [redacted] illness. These patients were distributed in all the applicant's clinical trials. However, the applicant failed to identify exactly which patients were supportive of the treatment of [redacted] which were supportive of the treatment of [redacted] which were supportive of the treatment of secondary infection and which were supportive of the treatment [redacted]

This issue was addressed by the applicant in the efficacy summary of [redacted] as follows (volume 280, page 17):

"For the purposes of this summary, and where deemed appropriate, pneumonias of all etiologies were grouped under the classification of pneumonia. [redacted] were not defined a priori in the protocols. The Sponsor elected to distinguish between the pathogens which are usually involved with pneumonias acquired in the community and those which are characteristic of hospital-acquired pneumonias.

Since the protocols were not designed to classify patients with _____ into subtypes of disease, no attempt was made to separate the _____ patients into patients with an _____ superimposed on an episode of viral respiratory infectic _____

Furthermore, to be able to address the efficacy of treatment in pneumonia _____ patients, certain elements of diagnosis should be present. Because the case summaries/case report forms did not capture what the reviewer believes to be key descriptive elements, validation of the applicant's patient population was difficult. (It should be noted that there were individual differences between protocols and also between individual investigators.)

To validate the disease process, certain clinical terms are expected in the case report form. These clinical parameters are then followed during the course of treatment and during the post-therapy follow-up evaluation period. The applicant provided some descriptive terminology to document the process. The most frequently employed terms were "fever, chills, chest pain, cough, sputum, rales and dyspnea." However, notably absent from the applicant's documentation of respiratory illness were the following parameters: baseline and changes in respiratory rate, descriptions of sputum production changes (voluminous, scanty, mucoid, blood tinged), descriptions of pulmonary signs (E to A changes, dullness to percussion, fremitus, wheezes), arterial blood gases and oxygenation requirements.

To determine the etiological agent of a disease process, an appropriate bacteriological specimen must be secured. To be validated during the review process, the method of specimen collection and the results of the specimen gram stain must be recorded. Then and only then, can the pathogen isolated upon culture be placed in its proper perspective. The applicant's protocols requested that appropriate samples be obtained; however, the applicant did not adequately define which specimens would be suitable and which specimens would not. Recording of gram stain information was not required.

Expectorated sputum (which microscopically had >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low magnification field), transtracheal aspirates, pleural fluid, and biopsy material usually provide adequate bacterial samples. In general, specimens aspirated from endotracheal tubes do not provide useful specimen material. The clinical trials submitted in support of this application did not provide valid gram stain and/or type of specimen collection in over 67% of enrolled patients.

In sum, the applicant enrolled 1608 patients with signs and symptoms of _____ infections. On the basis of radiological information and investigator assessment, fifteen hundred ten patients were classified as having pneumonia

The reviewer examined the available patient information in two ways. For the minority of patients with positive blood cultures and/or adequately documented gram stains, both a clinical and bacteriological evaluation was made. These patients were termed "strictly evaluable." Because of the general lack of bacterial specimen information, all patients who were otherwise evaluable were assessed on clinical grounds alone ("clinically evaluable" patients). Outcome was assessed on the basis of clinical performance in comparison to the known marketed comparator drug.

In patients with an infiltrate and physical symptoms consistent with consolidation, a clinical evaluation was meaningful. In contrast to the diagnosis of pneumonia which can be confirmed by the presence of an infiltrate, _____ is a diagnosis of exclusion. For this reason, the reviewer considers the clinical evaluation of these patients is useful, but not definitive.

Review Organization

The organization of the review is as follows. Each of the supporting studies are discussed separately as an individual unit. Each study report follows the same discussion format as outlined below. Although all protocols are similar; they are presented for the sake of completeness. Reviewer comments with regard to individual protocol differences can be located within the text of the applicant's protocol summary. Many of the reviewer concerns cited above are expanded upon within the body of each study report. At the conclusion of the individual study reports, there is a summary section which combines the outcome of each of the individual studies. The applicant did not present separate safety analyses for each study and/or indication. Therefore, at the reviewer's request, safety tables for _____ as a whole _____ pneumonia) were submitted as an amendment. These tables are presented at the conclusion of this report. Lastly, the reviewer's recommendations are given.

STUDY ENROLLMENT

<u>NUMBER</u>	<u>DOSE*</u>	<u>COMPAR.</u>	<u>NA/EUROPE</u>	<u>BLIND</u>	<u>PNEUMONIA</u> (<u>CEF/CTL</u>)
061	1g	NO	NAMERICA	NO	221 (221/ 0)
067	1g, 2g	NO	EUROPE	NO	168 (168/ 0)
070	1g	YES	NAMERICA	NO	269 (180/ 89)
070B	1g	YES	NAMERICA	YES	60 (39/ 21)
070E	1g	YES	EUROPE	NO	122 (83/ 39)
097	2g	YES	NAMERICA	NO	281 (143/ 138)
097B	2g	YES	NAMERICA	YES	80 (46/ 34)
106	1g, 2g	YES	EUROPE	NO	52 (36/ 16)
111	2g	YES	EUROPE	NO	124 (65/ 59)
115	2g	NO	EUROPE	NO	11 (11/ 0)
140	2g	NO	NAMERICA	NO	122 (122/ 0)
TOTALS:					1510

(*IND FOR CEF/NO FOR CTL)

Each report has a similar FORMAT which is as follows:

1. Applicant Review of the Protocol with Reviewer Comments
2. Applicant and Reviewer Criteria for Evaluability and Assessment
3. Table of Enrolled and Evaluable Patients per Applicant and Reviewer
4. Table of Available Specimen Information
5. Reasons Patients were Excluded from the Efficacy Analysis
6. Demographics of Evaluable Patients per Applicant and Reviewer
7. Tables of Clinical and Microbiological Efficacy per Applicant and Reviewer
8. Tables of Clinical Efficacy by Demographic Variable
9. Tables of Efficacy Based on Underlying Respiratory Status/Disease
10. Abbreviated Safety Evaluation including Death Narratives
11. Conclusions per Study

PNEUMONIA**PROTOCOL A1411-061 All North American Investigators** (NDA volumes 1.154 - 1.168)

TITLE: A Phase II Multi-Investigator Non-Comparative Study of Cefepime in the Treatment of Infections of the Urinary Tract, and Skin and Skin Structures

MEDICAL OFFICER'S COMMENTS:

The following protocol description was excerpted from the applicant's study summary (volume 1.154); the reviewer has made minor editorial changes. This study was initiated with the use of [REDACTED] lyophilized in a mixture with sodium chloride. As the study was underway, a dry blend of cefepime dihydrochloride with L-arginine replaced the formulation of the [REDACTED]. The protocol was designed to study patients with many infections; however, the discussion that follows will be limited to the [REDACTED]. [REDACTED] infections included patients with [REDACTED] pneumonia and occasionally other infections such as [REDACTED]. For this review, pneumonia and [REDACTED] were analyzed separately for safety and efficacy; patients with other respiratory diagnoses were analyzed for safety only. It should also be noted that the protocol did not make any separate provisions to distinguish [REDACTED] patients versus patients with pneumonia.

STUDY DESIGN:

This trial was a Phase II, Multi-Investigator, Non-Comparative Study of Cefepime in the Treatment of Infections of the Urinary Tract, and Skin and Skin Structures. There were a total of twenty-seven centers who enrolled patients in the United States; twenty-four centers enrolled patients with [REDACTED] infections. (There were six amendments.)

Inclusion Criteria:

1. Male or female patients at least 18 years old of any race.
2. If female, had a negative pregnancy test immediately prior to enrollment, was taking oral contraceptives in the prescribed manner, was surgically sterilized, or post-menopausal.
3. Had symptoms consistent with mild to severe, acute, pneumonia).
4. Had an infection suspected to be caused by a pathogen(s) susceptible to cefepime.
5. Participant, parent, or legal guardian agreed to the patient's participation in the study by signing the Informed Consent Form.

Exclusion Criteria:

A patient was to be excluded if any of the following conditions applied:

1. History of a serious reaction to penicillin or a cephalosporin.
2. Impaired renal function (serum creatinine of ≥ 1.7 mg/dL), or on renal dialysis.
3. Impaired hepatic function.
4. Infection not yet established (e.g., antibiotic therapy for the initial management of extensive physical trauma).
5. Likelihood of receiving other antimicrobials concomitantly.
6. Previous enrollment in the study.
7. Medically significant disease or disorder that in the opinion of the investigator could influence the results of the study.
8. Pregnancy or nursing.
9. Infection that was likely to require long-term antimicrobial therapy.
10. A patient with _____ was to be excluded if there was underlying chronic obstructive pulmonary disease (e.g., cystic fibrosis) which would negate a valid evaluation of the response to short-term therapy.
11. A patient with acute, _____ was to be excluded if there was infection (e.g., _____ pneumonia, etc.) requiring long-term therapy (more than 14 days for patients receiving cefepime/arginine; according to Amendment 4, more than 30 days for patients receiving cefepime

NOTE: Amendments 3 and 4 modified the inclusion and exclusion criteria of the original Protocol to allow patients who were not hospitalized and female patients taking oral contraceptives to enroll in the study. These modifications were applied retroactively to include all patients enrolled in the study. Amendment 1 to the Replacement Protocol allowed investigators 004, 007, 011, 028, and 048 to enroll patients with severe infections, and was applied retroactively to all patients at those centers.

MEDICAL OFFICER'S COMMENTS:

It should be noted that on the case report forms patients with more severe, _____ were not distinguished from those patients with _____ generally less virulent infections. The investigators did classify patients with regard severity and type of pneumonia e.g. moderate, lobar pneumonia

Procedures and Observations Outlined in the Protocol and Amendments

The table below lists the procedures and observations that were specified in the Protocol and Amendments for pneumonia infections.

Study Schedule
Study 411-061

Procedure	Pretreatment Within 48 hrs	During Treatment Day 3-5	Post-Treatment Day 1-14
Eligibility	X	-	-
Informed Consent	X	-	-
Medical History	X	-	-
Laboratory Tests	X	X	X
Physical Examination	X	X ^a	X
Clinical Evaluation	X	X	X
Bacteriologic Tests ^b	X	X	X
Chest X-ray	X ^c	X ^d	X ^e

a Abbreviated physical examination.

b Bacteriologic Tests include culture, subculture, and susceptibility tests. Subcultures and susceptibility tests were performed only if there was a source to culture.

c Pretreatment chest X-ray requested within 72 hours before or 24 hours after beginning treatment.

d During-treatment chest X-ray requested only as deemed appropriate by the investigator.

e Requested only for patients with confirmed diagnosis of pneumonia.

Pre-therapy Procedures

1. Within 48 hours before treatment began, a medical history was recorded and a physical examination was completed.
2. The presence of clinical signs and symptoms of infection was to be evaluated within 48 hours before beginning therapy.
3. Bacteriologic confirmation of the infection was to be obtained by culturing the infected site(s) within 48 hours before beginning treatment. For a suctioned sputum specimen or a deep-cough, purulent, expectorated sputum sample was to be obtained.

MEDICAL OFFICER'S COMMENTS:

One of the most useful and meaningful parameters in the evaluation of pneumonia is the description of the quality and quantity of the sputum specimen. Examples of pertinent facts include whether the sputum is blood

tinged or mucoid. The specimen should also be assessed for adequacy e.g. a predominance of a single organism, ≥ 25 PMNs and ≤ 10 epithelial cells under low power magnification. In this protocol, there was no reference made to the adequacy of a gram stain or the importance of any descriptive parameter. The case report form, however, did provide a section where a gram stain description could be recorded.

For example, (411-061-004-026) a gram stain is recorded as "few gram positive cocci in pairs, WBC > 25 and epithelial cells > 25." This specimen is not an appropriate gram stain, because of the large number of epithelial cells. However, neither the investigator nor the applicant made an assessment with regard to adequacy of the specimen and the organism isolated. Other examples were as follows: (411-061-003-041) "Many gram negative cocci present"; (411-061-016-013) "Many WBCs, many gram negative bacilli"; or (411-061-038-004) "Gram stain of sputum prior to beginning therapy revealed multiple WBCs and gram positive diplococci - diagnosis - pneumococcus." There were a few centers who appropriately recorded a predominant organism and quantified the polymorphonuclear and epithelial cells (e.g. center 004 and 013).

4. Each pathogen(s) was to be identified and tested for susceptibility to cefepime by disc or Minimum Inhibitory Concentration methods.
5. In most cases, subcultures of pathogens were prepared and shipped to Bristol-Myers Squibb Company.
6. A chest X-ray was to be done on each patient with symptoms of within 72 hours before or 24 hours after the beginning of cefepime treatment.
7. Laboratory studies were requested within 48 hours before treatment. Additional laboratory tests were done at the discretion of the investigator. All laboratories that performed tests were to be accredited through a local or state agency, or participate in a recognized quality control program. The requested assessments were:

HEMATOLOGY

Hemoglobin
Hematocrit
Leukocyte count, total and differential
Platelet count or estimate from smear
Erythrocyte Sedimentation Rate
Prothrombin Time (PT)
Partial Thromboplastin Time (PTT)

SERUM CHEMISTRY

Aspartate aminotransferase (AST/SGOT)
Alanine aminotransferase (ALT/SGPT)
Total bilirubin
Alkaline phosphatase
Blood Urea Nitrogen (BUN)
Creatinine
Glucose
Electrolytes (sodium, potassium, calcium*, phosphorus*) - *Added by Amendment 3

URINALYSIS

Specific gravity
pH
Albumin
Glucose
Microscopic Examination (WBC, RBC, Casts, Crystals)

During-Treatment Procedures

Investigators were requested to observe their patients at least once during treatment.

1. An abbreviated physical examination was requested on Day 3-5 of treatment.
2. The Protocol requested that clinical signs and symptoms of infection be assessed on Day 3-5.
3. The Protocol requested a culture be prepared from an appropriate specimen obtained on Day 3-5.
 - a. All pathogens from a positive culture were to be isolated and identified. After testing each pathogen's susceptibility, the investigator was to subculture it for shipment to Bristol-Myers Squibb, and at the same time, the investigator was to determine whether a patient with a positive culture should be discontinued and/or placed on other therapy.
 - b. The occurrence of a negative culture was to be recorded.
 - c. If a specimen could not be obtained for culturing because sputum could not be produced, the attempt and date were to be noted on the CRF with the statement "NO SOURCE TO CULTURE."
4. Pathogens from concurrent infections that developed were to be appropriately cultured and tested for susceptibility.
5. The Protocol requested chest X-rays be repeated as needed for patients with
6. Laboratory tests requested as pretreatment evaluation were to be repeated on Day 3-5; values obtained on Day 2 to the end of treatment were accepted.

Post-Treatment Procedures

Investigators were requested to complete the procedures listed below 1-14 days after the last dose of cefepime.

1. A physical examination was requested.
2. The Protocol requested clinical signs and symptoms of infection be evaluated once during post-treatment Day 1-14 for patients with

MEDICAL OFFICER'S COMMENTS:

At the end of Phase II meeting which took place on February 14, 1989, both the Division and the Applicant agreed that the appropriate follow-up period for infections was 5-14 days post treatment. (This trial was conducted from 6/11/87 to 12/10/88.) The reviewer believes that patients who were not followed for at least five days post-therapy cannot be adequately assessed.

3. The Protocol requested a post-treatment culture be obtained during post-treatment Day 1-14 for patients. Any pathogen cultured was to be identified and tested for susceptibility, then subcultured and sent to Bristol-Myers Squibb Company. The lack of a suitable specimen source was to be recorded with the statement "NO SOURCE TO CULTURE."

- The Protocol requested at least one post-treatment chest X-ray be done on any patient with a confirmed diagnosis of pneumonia.

MEDICAL OFFICER'S COMMENTS:

The term "requested" is from the applicant's protocol summary. However, a follow-up chest X-ray was required. The protocol stated as follows: "Subsequent X-ray examination should be repeated as deemed appropriate for during treatment assessments of all patients with infections; HOWEVER, at least one post therapy chest X-ray is required for all patients with a confirmed diagnosis of pneumonia after completion of drug therapy." The reviewer and the IDSA in their guideline concur that a post-therapy chest X-ray is essential for evaluation of new drug therapy in the treatment of infections.

- The Protocol requested laboratory assessments be repeated on post-treatment Day 1-14 for patients

Drug Information and Dose Selection

Cefepime was supplied by Bristol-Myers Squibb Company in vials containing 500 mg or 1 g of either a lyophilized mixture of cefepime and NaCl or a dry-powder blend of cefepime dihydrochloride and L-arginine (added by Amendment 2). Conditions for storage were specified on the label of each vial; the NaCl mixture required refrigeration, the arginine blend did not.

Investigators were to administer cefepime/NaCl or cefepime/arginine by intravenous infusion over 30 minutes. Patients were to receive 1 g every 12 hours for up to 14 days for cefepime/arginine or 30 days for cefepime/NaCl (the original Protocol specified 10 days). Patients must have received seven doses of cefepime in 96 hours to be eligible for evaluation of efficacy (Amendment 3; the original Protocol specified at least eight consecutive doses).

MEDICAL OFFICER'S COMMENTS:

The reviewer disagrees with the Protocol's request for a minimum number of doses (either 7 or 8 of cefepime) required for efficacy. In general, a parenteral product is targeted primarily at the more severely ill patient. Therefore, a minimum of five days of therapy should be required; this concurs with the IDSA guideline of treatment for an evaluable patient with pneumonia/bronchitis.

Amendment 1 to the Replacement Protocol allowed investigators 004, 007, 011, 028, and 048 to administer other doses. Depending on the severity of their infections, patients could receive doses of 500 mg, 1 g, or 2 g every 12 hours, or 2 g every 8 hours, for up to 14 days. Only patients with very severe life-threatening infections were put on the 2 g TID regimen.

Concomitant Therapy

The Protocol allowed medications, except for systemic antimicrobial agents, to be administered as indicated to enrolled patients. Use of any non-study medication was to be recorded on the CRF.

Microbiology Assessments

Bacterial isolates were tested for susceptibility to cefepime by disc sensitivity or MIC method. Based on the disc sensitivity method, isolates were defined as susceptible if the zone diameter was 18 mm or greater, resistant if the zone diameter was 14 mm or less, and intermediate if the zone diameter was 15 mm to 17 mm. Based on results of MIC testing, isolates were defined as susceptible if the MIC was 8 mcg/ml or less, resistant if the MIC was 32 mcg/ml or greater, and intermediate if the MIC was

16 mcg/ml.

The identity of each isolate was recorded on the microbiology page of the CRF. Based on the investigator's clinical judgment, each isolate was assigned to one of the following categories: causative pathogen, colonizer, contaminant, normal flora, or other. Isolates assigned to the category of other by the investigators were reassigned by Bristol-Myers Squibb personnel to one of the other four categories.

MEDICAL OFFICER'S COMMENTS:

It was unclear how the classification was accomplished without guidelines for the adequacy of a sputum culture and gram stain.

Applicant Criteria for Evaluability

A patient was considered evaluable for efficacy only if the following criteria were met. Any additional or altered requirements from the original Protocol are indicated.

1. An acute or chronic _____ was diagnosed on clinical grounds and confirmed by positive pretreatment culture. (Amendment 1 to the Replacement Protocol allowed patients with severe _____ for investigators 004, 007, 011, 028, and 048.)
2. Pretreatment clinical and bacteriologic assessments were conducted within 48 hours before beginning treatment and after termination of any previous antimicrobial therapy.
3. Any causative pathogen isolated in the pretreatment culture was identified and shown to be susceptible to cefepime.
4. During-treatment clinical and bacteriologic assessments were requested between Day 2 and the last day of treatment (the Protocol requested Day 3-5). These assessments were not required if all other evaluability criteria were met.
5. Post-treatment clinical assessments were conducted on post-treatment Day 1-14.
6. Post-treatment bacteriologic assessments were conducted on post-treatment Day 1-14, if there was a source to culture. If there was no source available, a "NO SOURCE TO CULTURE" was documented on the case report form for that date.
7. Patients diagnosed as having pneumonia had a pretreatment chest X-ray that confirmed the diagnosis. The X-ray was performed within 72 hours before beginning treatment and 24 hours after starting treatment. A follow-up chest X-ray was required from during-treatment Day 3 onward. (The Protocol requested post-treatment Day 1 onward.) NOTE: A few patients had clinical signs and symptoms of pneumonia and were diagnosed by the investigator as having pneumonia even though the pretreatment chest X-ray did not confirm this diagnosis; if all other evaluability criteria were met, these patients were considered evaluable.
8. Patients diagnosed as having _____ had a pretreatment chest X-ray that did not support a diagnosis of pneumonia.

9. After the pretreatment clinical assessment and culture, no concomitant systemic antimicrobial agent (that, according to official labeling published in the 1990 PDR, had activity against the genus of pathogen being treated) was allowed before the during- or post-treatment clinical and bacteriologic assessments. (The Protocol did not allow any concomitant systemic antimicrobial agent.)
10. Cefepime was administered intravenously at the dose, frequency, and duration specified in the appropriate Protocol or amendment; except for treatment failures, a minimum of seven doses was received within a 96-hour period for the BID administration (Amendment 3), or 11 doses within 96 hours for TID administration for investigators 004, 007, 011, 028, and 048 (Amendment 1 to the Replacement Protocol).

Applicant Efficacy Criteria Definitions

Patients were to be examined and assigned a Clinical Response category at their final acceptable visit. Cultures obtained both during and after therapy were used to determine Bacteriologic Response.

Clinical Response

After treatment was completed, each patient was to be assessed by the investigator and assigned to a Clinical Response category:

Satisfactory: All signs and symptoms of the infection that were present prior to therapy were improved or resolved, and no new signs or symptoms of the infection were present at the post-treatment follow-up.

Unsatisfactory: One or more signs or symptoms of the infection persisted or worsened, or one or more new signs or symptoms of the infection were evident at the post-treatment follow-up.

Undetermined: All cases where a response could not be determined (e.g., no follow-up evaluation).

Bacteriologic Response

Cultures obtained both during- and post-treatment were to be used to assess Bacteriologic Response. Each pathogen was assigned a response as follows:

Eradicated: The pathogen was not present in the post-treatment culture.

Persisted: The continued presence of the pathogen in the post-treatment culture.

Undetermined: The response could not be evaluated (e.g., no follow-up evaluation).

NOTE: For evaluable patients only, if the investigator's assessment of Clinical or Bacteriologic Response did not conform to the Protocol definitions, Bristol-Myers Squibb corrected the response to the Protocol specifications.

MEDICAL OFFICER'S COMMENTS

To be strictly evaluable by the reviewer, a patient had to have:

1. met the inclusion and exclusion criteria established by the applicant.
2. at least two signs and/or symptoms consistent with a infection. Pneumonia was
differentiated by the presence of an infiltrate on chest X-ray.

NOTE:

a. To support the observed diagnosis, the investigator could document the presence of signs and symptoms from a list of pre-selected terms. They were as follows:

Fever	Chills
Chest Pain	Cough
Sputum	Circumoral Cyanosis
Rales	Pleural Effusion
Chest Retractions	Tachypnea
Diminished Breath Sounds	

b. Respiratory rates were not recorded for any patient. Sputum production was not characterized with regard to quantity, quality or relationship to baseline. In patients with chronic respiratory disease, a change in sputum production and/or cough was also not noted.

c. The IDSA states that leukocytosis and pyrexia should be present to support the diagnosis of a infection. In this indication, many patients were afebrile and without
a significant elevation of the white count. The study was not designed to capture information with respect to chronic administration of steroids and/or the use of acetaminophen or aspirin products. Therefore, this information could not be used as diagnostic criteria.

d. For a reviewer to validate the diagnosis of a specific respiratory illness, certain minimal clinical and laboratory information is necessary. In some instances, this includes baseline respiratory conditions and/or recent medications. Other helpful supporting data are respiratory rates or arterial oxygen content. This study as others in this indication had limited information to precisely characterize the respiratory condition; however, there was sufficient data to determine that a pulmonary process was present. To the reviewer, the minimum clinical observations required to support the diagnosis of pneumonia were cough, sputum
production, and/or abnormal auscultatory sounds.

3. a culture documented pathogen susceptible to cefepime.

NOTE:

a. A gram stain was requested by the applicant. However, a written description was provided at the discretion of the investigator.

b. For the most part, the type of specimen was not identified, e.g. transtracheal aspirate, deep expectorated sputum, etc., nor was the quality described e.g. mucoid, voluminous, blood tinged, etc.

c. Those patients with a documented, valid gram stain and/or positive blood culture constituted the "strictly evaluable" reviewer population.

4. received 24 hours or less of pre-study antimicrobial drug with activity against the identified pathogen or a demonstration of a pathogen resistant to the pre-study antimicrobial drug.

NOTE:

The reviewer believes that this criterion is critical in this study; because treatment by applicant definition could be short (i.e. 3.5 days) and the influence of the pre-study antibiotic is unknown. Second, because validated gram stains were not a study requirement, sputum samples could not always differentiate between a colonizing organism and a true pathogen. The applicant did not address the issue of pre-study antimicrobials in their protocol or study report. The reviewer refers the reader to the published IDSA general guideline which states that: "Patients may be enrolled if they have received < 24 hours of treatment with a presumably effective anti-infective drug for an infectious process though (on the basis of published reference material) to require a standard duration of therapy of ≥ 7 days." The only extenuating circumstances where a patient may exceed the suggested 24 hour limit of pre-study therapy are illnesses which require lengthy therapy e.g. osteomyelitis and endocarditis or patients infected with a pathogen

resistant to the initial anti-infective drug and sensitive to the study drug. (pp. S17-18)

Exceptions to this requirement were those patients who had an acceptable interval (five half-lives) between the administration of alternative systemic antimicrobials and study drug.

5. received a minimum of 4.5 days of therapy (i.e. 9 doses of cefepime) for success. This requirement is consistent with the general IDSA guidelines which recommends a minimum 5 days of therapy for pneumonia. (However, a patient could be classified as a failure after only five cefepime doses.)
6. received a maximum of 18 days therapy. (Amendments to the protocol specified 14 days of therapy with cefepime/arginine and 30 days for cefepime/NaCl.)
7. had neither concomitant nor post-study antimicrobial therapy with activity against the identified pathogen in excess of a single dose.
8. had the minimum of three clinical evaluations: pre-therapy visit, during therapy visit and the follow-up visit (5-21 days).

NOTE:

In instances when an in-person test-of cure visit was not possible: The reviewer accepted telephone follow-up information provided by the patient (not a third party, e.g. relative), because this mechanism was mutually accepted during the development program. However, the reviewer would like to state her opinion that this information is of dubious value. There was no standard questionnaire to provide consistent data collection and documentation of these telephone conversations. Therefore, each investigator could ask a different battery of questions.

9. had evidence of bacterial clearance ("sputum production resolved") or a statement with regard to "No source to culture" at the follow-up visit (5-21 days).
10. had a pre-treatment chest X-ray and a post-treatment (either end of treatment or follow-up) chest x-ray. The IDSA guideline recommends that: "A chest radiograph will be obtained 3 days after the initiation of therapy, within 72 hours of completion of therapy, and at any other time the investigator deems necessary." (p. S85) It should be noted that the post-treatment X-ray was a requirement in the original protocol.

Clinical Response:

Satisfactory: Improvement and/or resolution of all pre-treatment signs and symptoms diagnostic of pneumonia/ at the test of cure visit (5-21 days). The end of treatment/follow-up chest X-ray had to show either improvement or lack of progression of the pneumonic process.

Unsatisfactory: Persistence or worsening of any clinical signs or symptoms associated with pneumonia/ during treatment or at the time of the follow-up evaluation (5-21 days). The end of treatment/follow-up chest X-ray showed no improvement or worsening.

Unevaluable: Assessment of the clinical outcome could not be determined e.g. the patient did not return for follow-up evaluation.

Bacteriologic Response:

Eradication - Either the causative pathogen(s) was not isolated from the follow-up culture or there was a presumptive eradication because there was no material available for culture.

Persistence - The original pathogen(s) was isolated from the follow-up culture or the patient was a clinical failure with a presumed pathogen persistence.

Unevaluable - It was not possible to determine a bacteriological response, e.g. because the patient did not return for follow-up.

The reviewer conducted an assessment of the "strictly evaluable" population based on the criteria described above. However, the reviewer feels that the design of this study was severely deficient. Problematic areas were as follows:

- a. Inadequate gram stain assessments/documentation
- b. The lack of description with respect to quality and quantity of sputum samples
- c. The lack of description of the method in which a sputum sample was collected
- d. The absence of characterization of "change" of described signs and symptoms from baseline (especially in the patient with chronic lung disease)
- e. The lack of a gradation system with respect to the improvement of signs and symptoms
- f. The lack of assessments with respect to pre-treatment antibiotics on selected patients
- g. The absence of correlation with white blood cell counts (elevations and/or bacteremia) and temperature
- h. The absence of definition and attempts to clarify the setting of the pneumonic processes for either pneumonia (i.e. not all pneumonias : infections are alike.)
- i. The absence of pre-determined format or questionnaire to gather telephone follow-up data

Not unexpectedly, there were few "strictly evaluable" patients. However, a secondary analysis of a "clinically evaluable" patient population was conducted. The "clinically evaluable" population met all the criteria described above with the exception of the valid pathogen requirement. These patients fell into four categories: a) those patients with an inadequate gram stain, b) those patients whose organism did not have sensitivities done, c) those patients with an inadequate gram stain and a resistant organism and d) those patients in which no organism was isolated. Obviously, this population subset contained patients whose respiratory illness was viral/other and not necessarily bacterial in origin. The reviewer believes that the outcome results of this population are more reflective of the "real world" clinical situation and are more consistent with how the drug will perform when used empirically.

New Infections

According to the Protocol, a new infection occurred if a different pathogen was cultured from the original infection site after the pretreatment culture. Patients were also considered to have a new infection if either the original pathogen or a new pathogen caused an infection at a body site unrelated to the original site of infection.

Safety Assessments

All patients who received cefepime were evaluable for safety. Each adverse clinical event (ACE) was documented by type, associated body system, frequency, severity, outcome, and relationship to study drugs. Deaths that occurred during or within 30 days after the last dose of study drug were to be reported.

Investigators were to record on the CRF whether cefepime was well-tolerated or poorly tolerated at the infusion site or site of injection.

Laboratory tests for which results were abnormal were to be repeated at appropriate intervals until the values returned to normal (baseline for patient). Laboratory data were evaluated by comparing during- and post-treatment values with laboratory normal ranges and with pretreatment values.

For safety analyses, the laboratory tests listed below were selected as the most appropriate indicators of toxicity. To identify clinical abnormalities, "direction of toxicity" was defined for each of the selected tests as follows (BMSq clinically relevant levels are provided for each test):

<u>Below lower limit of normal for:</u>	Clinically <u>Relevant</u>	<u>Above upper limit of normal for:</u>	Clinically <u>Relevant</u>
Hematocrit:	≤ 23.9 vol%	Alkaline phosphatase:	≥ 3 x UNL
Neutrophil:	≤ 500 /cmm	AST, ALT:	≥ 3 x UNL
WBC:	≤ 2000 /cmm	Total bilirubin:	≥ 3.0 mg/dL
Platelet:	$\leq 50,000$ /cmm	BUN:	≥ 50.0 mg/dL
		Creatinine:	≥ 3.0 mg/dL
		Prothrombin:	> 15 sec
		PTT:	> 45 sec
		Eosinophil:	≥ 1000 /cmm

<u>Outside normal limits for:</u>	Clinically <u>Relevant</u>
Sodium:	≤ 119 or ≥ 160 mEq/dL
Potassium:	≤ 2.4 or ≥ 6.5 mEq/dL
Calcium:	≤ 7.0 or ≥ 12.0 mg/dL
Phosphorus:	≤ 1.7 or ≥ 6.1 mg/dL

Additional criteria were implemented in testing for neutropenia and eosinophilia.

Absolute eosinophil count = % eosinophils x total WBC count.

Absolute neutrophil count = $\frac{\text{sum (\% neutrophils \& \% immature neutrophilic forms)}}{\text{x total WBC count.}}$

The APPLICANT applied the following definitions to laboratory values:

Abnormal: Outside the normal range limit in the direction of toxicity. (Abnormal results were classified into the following categories: mild [Class II]; moderate [Class III]; or clinically relevant [Class IV].)

Normal: All other laboratory values were defined to be normal (Class I).

Discontinuations

The Protocol stated that any of the following conditions could justify the early discontinuation of a patient from treatment. However, investigators sometimes continued cefepime therapy for patients who improved clinically.

1. No pathogen isolated from the pretreatment culture.
2. *In vitro* susceptibility testing indicated that the pathogen had an MIC (or correlated disc diffusion zone size) defined as resistant to cefepime.
3. A poor Clinical Response was evident within 72 hours of therapy.
4. A serious or alarming adverse event, including an ACE, abnormal laboratory result, or severe reaction at the infusion site. When an ACE resulted in a discontinuation, the patient was to be examined as frequently as deemed necessary to ensure that the reaction had subsided and effects did not persist.
5. Intercurrent illness.
6. Patient decision not to participate further.
7. Investigator decision that it was in the best interest of the patient to discontinue treatment.

Deaths and discontinuations are summarized at the end of this report.

RESULTS:

There were 594 patients enrolled in this study. Of these patients, 553 were treated with cefepime/NaCl and 41 with cefepime/arginine. All but 11 patients were treated in the hospital. Because this was a multi-indication protocol, patients were enrolled with infections of the urinary tract, the skin

Twenty-three investigators enrolled 221 patients diagnosed with pneumonia

STUDY 061 - PNEUMONIA PATIENTS
N = 221

CENTER	INVESTIG./ STATE	CEFEPIME ENROLLED	BMS EVALUABLE	NO CLIN ¹ EVALUABLE	NO STRICT ² EVALUABLE
002	SORG-OH	1	0	1	0
003	FARKAS-OH	16	10	1	0
004	SCHWARTZ-FL	12	6	1	0
005	NEU-NY	26	8	3	1
006	YANGO-FL	18	3	4	0
007	LEFROCK-FL	*4	1	3	0
011	RAMIREZ-PR	*8	6	3	2
012	LANE-NC	11	2	1	0
013	MCCABE-CA	42	26	3	0
015	HANDWERGER-NY	2	1	1	0
016	GELFAND-TN	7	2	0	0
020	HALL-ME	1	0	0	0
023	MOGABGAB-LA	5	1	1	0
028	GREENBERG-MO	*2	0	0	0
030	FORLENZA-NY	1	0	0	0
031	WORMSER-NY	6	2	3	0
035	GAINER-WV	3	2	2	0
037	IANNINI-CT	18	7	3	0
038	DALL-MO	6	1	1	0
040	RYAN-CT	14	7	8	0
042	CHRISTOU-GUJ	8	2	5	0
043	JENSEK-NC	5	4	2	0
048	GREEN-VA	*1	1	0	0
050	OLANS-MA	4	0	2	0
TOTAL		221	92	44	3

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PNEUMONIA/

PROTOCOL A411-061

*Some of these patients received 2g BID instead of 1g BID as per protocol. Six patients were given 2g BID as follows:

Center:	Number	Evaluable per BMS
007	2	1
011	1	0
028	2	0
048	1	1

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Below is a table with the demographic information with regard to the REVIEWER'S two evaluable populations.

DEMOGRAPHICS TABLE
PNEUMONIA
N = 221

PARAMETER	CLINICALLY EVALUABLE N = 48	STRICTLY EVALUABLE N = 3
SEX		
FEMALE	1 (2%)	
MALE	37 (77%)	3 (100%)
RACE		
WHITE	39 (81%)	2 (67%)
BLACK	9 (19%)	1 (33%)
HISPANIC		
AGE (yr)		
N	48	3
MEAN	61.9	65.7
MEDIAN	66	65
RANGE		
AGE DISTRIBUTION		
18-24	3 (6%)	
25-44	9 (19%)	1 (33%)
45-64	8 (17%)	
65-84	23 (48%)	1 (33%)
85+	5 (10%)	1 (33%)
WEIGHT (kg)		
N	39	2
MEAN	67.11	62.35
MEDIAN	64.9	62.4
RANGE		
HEIGHT (cm)		
N	38	2
MEAN	170.65	174.0
MEDIAN	170.2	174.0
RANGE		

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CLINICAL EFFICACY:

PNEUMONIA (N = 221)

CLINICAL RESPONSE	BMS	MO CLINICALLY EVAL	MO STRICTLY EVAL
SATISFACTORY	75 (82%)	20 (42%)	1 (33%)
UNSATISFACTORY	17 (18%)	28 (58%)	2 (67%)
UNEVALUABLE	129	173	218
TOTALS (N)	221	221	221

The BACTERIOLOGICAL responses for pneumonia based on patients that were strictly evaluable are as follows:

<i>S. epidermidis</i>	1/1 (100%)
<i>S. pneumoniae</i>	0/1 (0%)
<i>Strep. (Group B)</i>	0/1 (0%)

The BACTERIOLOGICAL response for bronchitis based on the patient that was strictly evaluable is as follows:

<i>S. pneumoniae</i>	1/1 (100%)

The following tables examine efficacy related to various demographic variable to determine if there are intrapopulation variables which would require labelling modifications.

CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
PNEUMONIA N = 221

VARIABLE	BMS	MO CLINICALLY EVAL.	MO STRICTLY EVAL.
	75/92 (82%)	20/48 (42%)	1/3 (33%)
WOMEN	13/15 (87%)	6/11 (55%)	0/0 (0%)
MEN	62/77 (81%)	14/37 (38%)	1/3 (33%)
WHITE	56/68 (82%)	16/39 (41%)	1/2 (50%)
BLACK	17/22 (77%)	4/9 (44%)	0/1 (0%)
OTHER	2/2 (100%)	0/0 (0%)	0/0 (0%)
< 65 YEARS	39/47 (83%)	9/20 (45%)	0/1 (0%)
> 65 YEARS	36/45 (80%)	11/28 (55%)	1/2 (50%)

MEDICAL OFFICER'S COMMENTS:

In the BMS and MO clinically evaluable population, the cure rates for women appear slightly higher than for men. The significance of which cannot be determined, because the sample size is so small. The observation could mean the women received more drug on a mg/kg basis and thus may have experienced a more beneficial outcome. This observation will be followed during the review.

The following table evaluates the effect of underlying lung disease and/or smoking. In the data collection, the information provided included the presence or absence of bronchopulmonary disease. The specific disease process or length of its existence was not usually recorded. Further information was often available in the investigator's note.

EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS
PNEUMONIA N = 221

RESPIRATORY STATUS	BMS	MO CLINICAL EVAL.	MO STRICTLY EVAL.
ALL	75/92 (82%)	20/48 (42%)	1/3 (33%)
SMOKER	14/18 (78%)	2/7 (29%)	0/0 (0%)
LUNG DISEASE	11/12 (92%)	7/12 (58%)	1/1 (100%)
SMOKER & LUNG DISEASE	38/45 (84%)	7/19 (37%)	0/1 (0%)
NONSMOKER	12/17 (71%)	4/10 (40%)	0/1 (0%)

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SAFETY EVALUATION:

Of the 221 patients enrolled with pneumonia and the 48 patients enrolled there were a total of 17 (16 pneumonia deaths.

PNEUMONIA:

A1411061003-029

The patient was a 73 year old white man with a history of chronic obstructive pulmonary disease who was admitted to the hospital with pneumonia. He was initially treated with ceftazidime and followed by a course of Augmentin®. The patient's condition worsened and he was enrolled in the cefepime study. There was initial improvement; however, on the fourth day the patient experienced severe tachypnea and hypoxia. A clinical diagnosis of acute pulmonary embolism was made. The patient expired and an autopsy was denied.

The patient was a 72 year old white man with a history of chronic obstructive pulmonary disease who was admitted to the hospital with a right lower lobe pneumonia. The patient was enrolled and treated with study drug. The patient was treated for 4.5 days and discharged in improved condition. The patient died seven days post-therapy. Minimal clinical information is available for this patient at the time of his death. The investigator states that death was a result of multiple underlying medical conditions including congestive heart failure and chronic renal failure.

The patient was a 34 year old male patient with AIDS who was admitted to the hospital for treatment of pneumonia and bacteremia (*S. pneumoniae*). The patient's sputum was also positive for *M. avium intracellulare*. The patient was treated with cefepime and anti-tuberculosis medications. His respiratory status continued to deteriorate. Therapy with cefepime was discontinued after 17 doses; therapy with trimethoprim-sulfamethoxazole and amikacin was instituted. The patient expired five days after cefepime was discontinued. Death was caused by progressive respiratory failure.

The patient was a 64 year old man debilitated by long-standing cardiac disease who was admitted for surgical repair of a fractured hip. On admission, it was noted that the patient had infiltrates in the right lower lobe and left upper lobe. Surgery was cancelled and the patient was enrolled in the cefepime study. The patient expired after three doses of study drug. Prior to death, it was noted that both lower extremities became mottled and cold. No autopsy was performed.

The patient was a 65 year old man with a history of cancer of the mandible who was admitted with a right upper lobe pneumonia. The patient was enrolled in the cefepime study. After nine days of therapy, the patient did not improve. Cefepime was discontinued and the patient was placed on ceftazidime. According to the investigator, the patient responded satisfactorily to the ceftazidime. The patient expired three weeks after cefepime was discontinued of his underlying malignant disease.

The patient was a 92 year old with a history of heart disease who was admitted for increased dyspnea and sputum production. The admission chest X-ray showed evidence of congestive heart failure and an infiltrate. The patient was started on high dose (2g BID) cefepime, mezlocillin and amikacin. The patient's respiratory status was not improved by day three. Therapy was discontinued and alternative therapy was instituted with ceftazidime and clindamycin. The patient suffered a cardiac arrest seven days after therapy with cefepime was discontinued. An autopsy was not performed.

The patient was a 76 year old black man with a history of multiple sclerosis and a paralyzed left hemidiaphragm. The patient was admitted for an increased non-productive cough and dyspnea. He received intense respiratory therapy and two days of treatment with ampicillin. On the fourth day of admission, the chest X-ray showed an infiltrate; he was started on cefepime therapy. The patient did not do well. He developed atelectasis and required bronchoscopy to help clear some of his secretions. Cefepime was discontinued after ten days. Two days later, the patient was placed on ceftizoxime. The patient died of a respiratory arrest seven days after the cefepime was discontinued.

The patient was an 83 year old man with a history of a neurological deficit who was admitted to the hospital for the treatment of bilateral lower lobe pneumonia. The patient was enrolled in the study and initially responded to treatment. On the sixth day, the patient developed a fungal urinary tract infection. He was treated with amphotericin irrigations. On the ninth day of therapy, the patient was febrile and a repeat X-ray showed bilateral pleural effusions. After 24 doses, cefepime was discontinued and clindamycin and gentamicin was instituted. The patient continued to deteriorate and expired 23 days after cefepime therapy was discontinued.

The patient was a 49 year old man with a history of AIDS and previous *P. carinii* pneumonia. The patient was admitted to the hospital for respiratory distress and a right middle lobe infiltrate on chest X-ray. He was started on cefepime therapy for one dose. He refused aggressive measures and was treated empirically with pentamidine. The patient expired five days after the cefepime was discontinued.

The patient was a 69 year old man with a history of multiple medical problems including chronic obstructive lung disease who was admitted to the hospital for treatment of bilateral lower lobe pneumonia. He was started on cefepime after a gram stain suggested infection with the pneumococcus. The patient received two doses. Acutely, he became dyspneic and succumbed. No autopsy was performed.

The patient was a 66 year old white man with a history of severe bronchopulmonary disease who was admitted for treatment of a bilateral pneumonia. The patient was treated with cefepime for 2 weeks and initially responded. Because of a positive blood culture, he was also suspected of having

staphylococcal endocarditis. Following cefepime therapy, he was treated with oxacillin for the presumed endocarditis. He expired ten days after cefepime was discontinued. No autopsy was done.

The patient was a 71 year old man who suffered a cardiopulmonary arrest as a complication of definitive surgery for transitional cell carcinoma of the bladder. He developed a bilateral infiltrates and was started on cefepime for a nosocomially acquired pneumonia. The patient continued to be febrile and developed hypotension. Diagnostic imagery determined that the patient's kidney was obstructed. Pseudomonas was cultured from the ureter when a nephrostomy tube was placed. Cefepime was discontinued; vancomycin, ceftazidime and gentamicin was started. The patient continued to deteriorate. At the family's request, no aggressive measures were taken. The patient expired four days after the discontinuation of cefepime.

The patient was a 41 year old man with a history of metastatic colon cancer who was admitted to the hospital for treatment of dyspnea and pain. The patient was started cefepime for his pneumonic process and metronidazole for persistent diarrhea. After an initial improvement, the patient deteriorated and died on the sixteenth day of cefepime therapy.

The patient was an 81 year old man originally admitted to the hospital for anemia secondary to a bleeding, gastrointestinal ulcer. The patient was responding well to therapy, when he suffered a cerebrovascular accident in his left cerebellum. Two days later, the patient became febrile and developed infiltrates in the right upper and lower lobes of his lung. Cefepime was initiated for treatment of the nosocomially acquired pneumonia. Fever and leukocytosis persisted. The chest X-ray showed consolidation of the lung. Because the patient also vomited and aspirated, clindamycin was added to the treatment regimen. No aggressive measures were undertaken and the patient expired on the seventh day of treatment.

The patient was an 88 year old man with multiple medical problems who was admitted to the hospital for an acute abdomen. An exploratory laparotomy was negative except for gallstones. Post-operatively, the patient developed a nosocomial pneumonia and wound dehiscence. He was started on cefepime therapy. He was treated with cefepime for two weeks and did well. Four days post therapy, he became bacteremic with *S. aureus* and was treated with ticarcillin, tobramycin, netilmicin and cloxacillin. Aggressive medical measures were withdrawn and the patient died thirty-five days after the cefepime therapy was discontinued.

The patient was a 28 year old white woman who was admitted to the hospital for injuries related to a motor vehicle accident. On the fourth day of admission, the patient's chest X-ray demonstrated a right lower lobe infiltrate. The patient received nine doses of cefepime for this condition. On the sixth day of hospitalization, the patient became increasingly unresponsive secondary to cerebral edema and infarction. The patient died the day after cefepime was discontinued.

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ADVERSE EVENTS:

According to the applicant: Of the 594 patients enrolled in the multicenter, multi-indication study (A1411-061), a total of 78 patients experienced 117 adverse clinical events. Four events (headache, diarrhea, rash and nausea) affected more than 1% of all patients. Seventy-one (13%) of the 553 patients who were treated with cefepime/NaCl experienced ACE, compared to 7 (17%) of the 41 patients who were treated with cefepime/arginine. There was no statistically significant difference ($p = 0.595$) between the two formulations with respect to incidence of ACE. Of the 15 cases of diarrhea, colitis, and pseudomembranous colitis reported by patients in this study, 4 (27%) were reported to be associated with C. difficile.

MEDICAL OFFICER'S COMMENTS:

Unfortunately, the applicant did not subset the adverse events with respect to the indication studied such as urinary tract infection, skin and skin structure infection, infection and so forth.

In addition, laboratory pretreatment values were compared to during and post-treatment values. However, the tables presented by the applicant in the study report were prepared for the entire enrolled population and were not subdivided by indication.

Therefore, the medical officer requested that the applicant present this information for all patients with the infections. The applicant submitted this information in an amendment to the NDA, number 71. However, information per study and information per indication (i.e. pneumonia) were not itemized by the applicant. Tables of ADR and laboratory safety data from all patients diagnosed with infections were adapted from the applicant's submission and are presented in the summary section of this report.

INFUSION TOLERANCE:

Some information with regard to the tolerability of the infusion was listed in the following table from the applicant's study summary (volume 154, page 154)

Local Tolerance to Cefepime Infusion
All Patients
Study 411-061

	Number (%) Patients	
	≤ 2000 mg/day N = 561	> 2000 mg/day N = 33
Intolerance*		
Tolerated Drug Well	545 (97)	33 (100)
Local Intolerance	16 (3)	0
Infiltration	9 (2)	0
Phlebitis	11 (2)	0

* Patients may experience more than one type of intolerance.

MEDICAL OFFICER'S COMMENTS:

Virtually all patients received cefepime 1g BID. The above table does not subset those patients with the types of infection studied, nor does it indicate whether the patients with the infiltration and/or phlebitis received the sodium chloride or arginine formulation.

SUSCEPTIBILITY
Baseline Sensitivity to Cefepime
Pneumonia Patients
(per Applicant)

Infection Type/ Pathogen	Number (%) of Pathogens			Total
	----- Type of Sensitivity -----			
	Susceptible	Intermediate	Resistant	
<i>Corynebacterium</i> sp.	1 (100)			1
<i>S. faecalis</i>			1 (100)	1
Strep. (Group A)	2 (100)			2
Strep. (alpha hemo.)	3 (100)			3
<i>S. viridans</i>	2 (100)			2
Strep. (beta hemo.)	1 (100)			1
Strep. (Group D)	1 (100)			1
Strep. (Group C)	1 (100)			1
<i>S. salivarius</i>	1 (100)			1
Strep. (Group B)	3 (100)			3
<i>S. constellatus</i>	1 (100)			1
<i>S. sanguis</i>	1 (100)			1
<i>S. aureus</i>	15 (75)	1 (5)	4 (20)	20
<i>S. aureus</i> (MR)	1 (100)			1
<i>S. epidermidis</i>	1 (100)			1
<i>S. pneumoniae</i>	47 (100)			47
<i>P. aeruginosa</i>	25 (78)	4 (13)	3 (9)	32
<i>P. maltophilia</i>			3 (100)	3
<i>P. fluorescens</i>	1 (100)			1
<i>E. coli</i>	12 (100)			12
<i>Citrobacter</i> sp.	1 (100)			1
<i>K. pneumoniae</i>	9 (100)			9
<i>K. ozaenae</i>	2 (100)			2
<i>K. oxytoca</i>	1 (100)			1
<i>E. cloacae</i>	11 (100)			11
<i>E. aerogenes</i>	5 (100)			5
<i>S. marcescens</i>	5 (100)			5
<i>P. mirabilis</i>	4 (100)			4
<i>M. morgani</i>	2 (100)			2
<i>P. rettgeri</i>	1 (100)			1
<i>E. agglomerans</i>	1 (100)			1
<i>Haemophilus</i> sp.	1 (100)			1
<i>Haemophilus</i> sp. (p-)	1 (100)			1
<i>H. influenzae</i>	31 (100)			31
<i>H. influenzae</i> (p+)	2 (100)			2
<i>H. influenzae</i> (p-)	8 (100)			8
<i>H. parainfluenzae</i>	4 (100)			4
<i>H. parainfluenzae</i> (p-)	1 (100)			1
<i>P. multocida</i>	1 (100)			1

SUSCEPTIBILITY
Baseline Sensitivity to Cefepime
Pneumonia Patients
(per Applicant)

Infection Type/ Pathogen	Number (%) of Pathogens			Total
	----- Type of Sensitivity -----			
	Susceptible	Intermediate	Resistant	
Neisseria sp.	2 (100)			2
N. sicca	2 (100)			2
A. anitratus	1 (100)			1
Branhamella sp.	1 (100)			1
M. catarrhalis	10 (100)			10
M. catarrhalis (p-)	<u>1</u> (50)	-	<u>1</u> (50)	<u>2</u>
Total	227 (93)	5 (2)	12 (5)	244

**CONCLUSIONS FOR
STUDY A411-061****INFECTIONS**

1. Study 411-061 was a multicenter, multi-indication non-comparative study that enrolled 269 patients with _____ infections. The protocol originally intended to examine _____ infections as a whole. Therefore, the protocol design did not specifically address features unique to _____ pneumonia. Patients were classified subsequently according to the investigator's assessment and the presence or absence of an infiltrate on the chest radiograph. Therefore, there were 221 patients who were diagnosed with pneumonia and 48 patients who were diagnosed with _____. _____ is a term used loosely; further differentiation with regard to an acute exacerbation of chronic obstructive pulmonary disease versus an acute bacterial bronchitis superimposed on a viral infection was not made.
2. This was one of the early Phase II studies which examined largely the efficacy of cefepime to treat mild to severe infections of the urinary tract, skin and skin structures
3. The applicant differed with regard to evaluability based on the required follow-up period and the adequacy of the microbiological specimen. The applicant was advised at the end of Phase II meeting that the minimum follow-up period was 5-14 days. The reviewer extended that follow-up to 21 days. However, follow-up less than five days was not considered acceptable. Secondly, there was no emphasis placed on the gram stain or the characterization of the sputum. The recovery of an organism has no meaning unless it is examined within the appropriate context. Therefore, to assess the effectiveness of the drug, the medical reviewer conducted two analyses - a clinical, modified intent to treat analysis and an analysis of a strictly evaluable population which included patients with bacteremia and/or an appropriate gram stain.
4. The efficacy results were not encouraging. The satisfactory results in the clinically evaluable population were (20/48) 42% and (5/10) 50% for pneumonia _____. The number of strictly evaluable patients were too small to draw a meaningful conclusion.
5. With regard to safety, the deaths did not appear to be related to the drug substance itself. However, some of the deaths were the result of clinical failures. On the whole, there were few discontinuations related to an adverse clinical event or laboratory abnormality. Because the adverse events were not listed individually for the respective indication, the data were not listed above. Therefore, no conclusions are drawn. The study drug appears to be well tolerated locally.

PNEUMONIAPROTOCOL AI411-067 All European Investigators (NDA volumes 1.170 - 1.181)

TITLE: A Phase II Multi-Investigator Non-Comparative Study of Cefepime in the Treatment of Infections of the Urinary Tract, and Skin and Skin Structures

MEDICAL OFFICER'S COMMENTS:

Two dosages were examined in this protocol. The low dosage treatment group refers to those patients who received 1 g BID of cefepime and the high dosage group refers to those patients who received 2 g BID as their treatment regimen.

The following protocol description was excerpted from the applicant's study report (volume 1.170); the reviewer has made minor editorial changes. This study was initiated with the use of cefepime lyophilized in a mixture with sodium chloride. As the study was underway, a dry blend of cefepime dihydrochloride with L-arginine replaced the formulation of the The protocol was designed to study patients with many infections; however, the discussion that follows will be limited to the infections included patients with pneumonia and occasionally other infections such as For this review, pneumonia and were analyzed separately for safety and efficacy; patients with other respiratory diagnoses were analyzed for safety only. It should also be noted that the protocol did not make any separate provisions to distinguish patients versus patients with pneumonia.

STUDY DESIGN:

This trial was a Phase II, Multi-Investigator, Non-Comparative Study of Cefepime in the Treatment of Infections of the Urinary Tract, and Skin and Skin Structures. There were a total of thirteen centers who enrolled patients in Europe. (There were 8 amendments.)

Inclusion Criteria

1. Be male or female, 18 years of age or older.

Note: Women of childbearing potential had to have a negative pregnancy test result immediately before enrollment in this study AND had to use a reliable method of birth control (oral contraceptive, diaphragm, I.U.D., or condom by consort) in the prescribed manner.

2. Had symptoms consistent with:

For low dose: Acute uncomplicated lower respiratory tract infection such as pneumonia.

For high dose: A serious infection including, but not limited to, multilobar pneumonia, hospital-acquired pneumonia occurring in the intensive care setting particularly if infection is the cause of ICU admission, or patients with parenchymal *Pseudomonas* infections

3. Had a proven or suspected infection caused by a pathogen(s) which was susceptible to the study drug
4. Provided informed consent.

Exclusion Criteria

1. Had a history of a serious reaction to a cephalosporin or penicillin compound.
2. Had baseline serum creatinine levels of 1.7 mg/dL or greater or were on renal dialysis.
3. Had impaired hepatic function.
4. Had a presumptive infection, i.e. the initial management of extensive physical trauma.
5. Were likely to receive other antimicrobial drugs concomitant with the study medication.
6. Had been previously enrolled in the study.
7. Had a medically significant disease or disorder that could have endangered the patient, or influenced the results of the study.
8. In the opinion of the principal investigator, required long-term antimicrobial therapy.
9. Presence of underlying chronic obstructive pulmonary disease (e.g. cystic fibrosis) which would negate a valid evaluation of the response to short-term therapy.
10. Patients for which long-term (more than 14 days) therapy was expected, e.g. empyema, aspiration pneumonia, or pneumonia distal to obstructive carcinoma.

Additional exclusions for the high dose protocol:

1. Be pregnant or nursing.
2. Be anuric or on hemo or peritoneal dialysis.
3. Have a granulocyte count of less than $500/\text{mm}^3$ as a result of underlying disease or cytotoxic therapy.
4. Have signs and symptoms of CNS infection.
5. Have a medically significant disease or disorder which may have bearing on the outcome of the study (e.g. (1) a HIV-positive patient with suspected because of possibility of pneumocystis; (2) AIDS or HIV-positive patient with perirectal ulcer, because of possibility of herpes, etc.; (3) for patients, HIV-positive because of pneumocystis, documented AIDS because of herpes infection, etc.).
6. Have a very severe, life-threatening infection including symptoms and signs of septic shock, granulocytopenia secondary to infection rather than underlying disease, or chemotherapy, or organ failure of more than one organ system.
7. Have been placed on "do not resuscitate" (DNR) or "No Code" status (includes patients for whom ventilator support will not be administered).

Procedures and Observations

The table below lists the procedures and observations that were specified in the Protocol and the Amendments for

Study Schedule
Study 411-067

Procedure	Pre-treatment	During-treatment ¹	Post-treatment
	Within 48 hrs Preceding to Day 1	Day 2 to last day of Therapy	Day 1-14 After Therapy
Informed Consent	X	-	-
Medical History	X	-	-
Physical Examination	X	X	X
Laboratory Testing: ²			
Hematology	X	X	X
Serum Chemistry	X	X	X
Urinalysis	X	X	X
Chest X-ray*	X*	-	X*
Bacteriologic Testing			
Culture**	X	X	X
Susceptibility	X	X	X
Evaluation of Clinical Signs & Symptoms of Infection	X	X	X

* Pre-treatment chest X-rays for patients with lower respiratory tract infections were obtained within 3 days preceding or within 2 days after beginning the study drug. Post-treatment X-rays were obtained on all patients with a diagnosis of pneumonia (confirmed by pre-treatment X-ray). The post-treatment X-ray could be waived if an X-ray taken during-treatment was negative.

** Cultures during-treatment and post-treatment were obtained if there was a source to culture. If there was no source to culture due to healing of the infected site, the date of the attempted culture was documented in the CRF with the notation "No Source to Culture".

MEDICAL OFFICER'S COMMENTS:

The study schedule above was identical for the low and high dose groups; however, the applicant added the two footnotes below to the schedule of the high dose group.

¹ In the high dose study, during treatment procedures had to be conducted between Days 3 to 5 of therapy. patients without any during treatment evaluation were considered evaluable.

² In the high dose study, laboratory studies including X-ray during treatment were not required.

Pre-therapy Procedures

1. Within 48 hours before treatment began, a medical history was recorded and a physical examination was completed.
2. The presence of clinical signs and symptoms of infection were evaluated within 48 hours of beginning therapy to Day 1 of treatment and after stopping any previous antimicrobial.
3. Bacteriologic confirmation of the infection was obtained by culturing the infected site(s) or blood within 48 hours prior to treatment to Day 1 of treatment and after any previous antimicrobial. For lower respiratory tract infections, an aspirated sputum specimen or a deep-cough, purulent expectorated sputum sample was obtained.

MEDICAL OFFICER'S COMMENTS:

The protocol did request deep expectorated sputum, transtacheal aspirates, endotracheal and bronchoscopy specimens. It also stated that, in general, "the etiology of the infection is confirmed by gram stain and positive culture(s) of the infected site." However, there was not an emphasis on documentation of the validity of the specimen or how the specimen was collected. As a result, the investigators did not provide much, if any, information with regard to the quality and quantity of the bacteriological specimen.

4. Each pathogen(s) was identified and tested for susceptibility to cefepime by disc or Minimum Inhibitory Concentration methods.
5. A chest X-ray was done on each patient with symptoms of _____ infection within 72 hours before or 48 hours after the beginning of cefepime treatment to confirm diagnosis of pneumonia.
6. Blood cultures were obtained at the discretion of the investigator.
7. Laboratory evaluations were requested within 48 hours prior to treatment to Day 1 of therapy. Additional laboratory tests were done at the discretion of the investigator. The requested assessments were:

HEMATOLOGY

Hemoglobin
Hematocrit
Leukocyte count, total and differential
Platelet count or estimate from smear
Erythrocyte sedimentation rate
Prothrombin time (PT)
Partial thromboplastin time (PTT)

SERUM CHEMISTRY

Aspartate aminotransferase (AST, SGOT)
Alanine aminotransferase (ALT, SGPT)
Total bilirubin
Alkaline phosphatase
Blood urea nitrogen (BUN) or blood urea
Creatinine
Glucose
Electrolytes (Sodium, Potassium, Calcium, and Phosphorus)

URINALYSIS

Specific gravity
 pH
 Albumin
 Glucose
 Microscopic Examination (WBC, RBC, Casts, Bacteria,
 Epithelial cells, Crystals)

During-Treatment Procedures

Investigators were requested to observe their patients at least once during therapy.

1. An abbreviated physical examination was conducted during treatment.
2. Clinical signs and symptoms of infection were assessed during treatment within windows as specified in the table above.
3. A culture was prepared from an appropriate specimen during treatment.
 - a. All pathogens from a positive culture were to be isolated and identified and tested for susceptibility. At that time, the investigator was to determine whether a patient still having a positive culture should be discontinued and placed on other therapy.
 - b. The occurrence of a negative culture was to be recorded.
 - c. If a specimen could not be obtained for culture because sputum could not be obtained, the attempt and date were to be noted on the CRF with the statement "NO SOURCE TO CULTURE".
4. Pathogens from concurrent infections that developed were to be appropriately cultured and tested for susceptibility.
5. Chest X-ray : were to be repeated as needed to assess patients with pneumonia.
6. Laboratory evaluations were to be performed.

Post-Treatment Procedures

The procedures listed below were completed before any other antimicrobial was given and within Days 1 to 14 for patients with

MEDICAL OFFICER'S COMMENTS:

At the end of Phase II meeting which took place on February 14, 1989, both the Division and the Applicant agreed that the appropriate follow-up period for infections was 5-14 days post treatment. (The low dose protocol was conducted from 9/19/87 to 1/17/90. The high dose study was conducted from 7/31/89 to 4/35/91.) The reviewer believes that patients who were not followed for at least five days post-therapy cannot be adequately assessed.

1. A physical examination was to be performed.
2. Clinical signs and symptoms of infection were to be evaluated.

3. For patients with a culture was to be taken if the specimen source remained. Any pathogen cultured was identified and tested for susceptibility. The lack of a suitable specimen source was recorded with the statement "NO SOURCE TO CULTURE".
4. At least one post-treatment chest X-ray was to be done on any patient with a confirmed diagnosis of pneumonia. However, retroactively it was agreed that this post-treatment X-ray could be waived if an X-ray taken during therapy was negative.

MEDICAL OFFICER'S COMMENTS:

A follow-up chest X-ray was required. The protocol stated as follows: "Subsequent X-ray examination should be repeated as deemed appropriate for during treatment assessments of all patients with a confirmed diagnosis of pneumonia after completion of drug therapy." The reviewer and the IDSA in their guideline concur that a post-therapy chest X-ray is essential for evaluation of new drug therapy in the treatment of infections.

2. Laboratory evaluations were to be performed, and repeated as appropriate when results were abnormal.

Drug Information and Dose Selection

Cefepime was supplied by Bristol-Myers Squibb Company in vials containing 1 gram of either a lyophilized mixture of cefepime and NaCl or a dry-powder blend of cefepime dihydrochloride and L-arginine. Conditions for storage were specified on the label of each vial. The NaCl mixture required storage under refrigeration, whereas the L-arginine blend provided long-term stability at room temperature.

Investigators prepared cefepime of either formulation for infusion and administered the resulting solution intravenously over 30 minutes. Patients received doses of 1 g or 2g every 12 hours for up to 14 days. Amendment 5 of the low dose group (approved on 02/26/88) allowed for treatment up to 30 days. All patients were treated with only one formulation of the drug.

In the high dose protocol, a dosage adjustment for renal impairment was permitted. Patients with a creatinine clearance between 11-30 mL/min received 2g every 24 hours.

Concomitant Therapy

The Protocol allowed medications, except for systemic antimicrobial agents, to be administered as indicated to enrolled patients. Use of any non-study medication was to be recorded on the CRF.

Applicant Criteria for Evaluability

A patient was considered evaluable for efficacy only if the following criteria were met. Any additional or altered requirements from the original Protocol are indicated.

1. An infection of the lower respiratory tract was diagnosed on clinical grounds and confirmed by a positive pre-treatment culture.
2. Any pathogen isolated in the pretreatment culture was identified and shown to be susceptible to cefepime.

3. During-treatment clinical and bacteriologic assessments were requested between Day 2 and the last day of treatment. Post treatment clinical assessments were to be conducted on Days 1-14 post-treatment.
4. Patients diagnosed as having pneumonia or bronchopneumonia had pre-treatment and during- or post-treatment X-ray examinations that confirmed the diagnosis and response, respectively. The initial chest X-ray confirmed the diagnosis of pneumonia or bronchopneumonia within 72 hours before or 48 hours after treatment began.
5. No other systemic antimicrobial agent that had activity against the pathogen being treated was taken during the time between the pre-treatment and post-treatment cultures and clinical evaluations.
6. Cefepime was administered intramuscularly or intravenously at the dose, frequency, and duration specified in the appropriate protocol or amendment. Within 96 hours each patient received a minimum of 7 doses. For patients with renal impairment whose treatment regimen was changed to one dose daily, a minimum of 4 days of treatment was needed.

MEDICAL OFFICER'S COMMENTS:

The reviewer disagrees with the applicant's selection of a minimum number of seven doses of cefepime to be supportive of an efficacy claim for infections. In general, a parenteral product is targeted primarily at the more severely ill patients. Therefore, a minimum number of five days of therapy should be required; this concurs with the IDSA guideline of treatment for an evaluable patient with pneumonia.

Applicant Efficacy Criteria Definitions

Patients were to be examined and assigned a Clinical Response category at their final acceptable visit. Cultures obtained both during and after therapy were used to determine Bacteriologic Response.

Clinical Response

After treatment was completed, each patient was to be assessed by the investigator and assigned to a Clinical Response category:

Satisfactory: All signs and symptoms of the infection that were present prior to therapy were improved or resolved, and no new signs or symptoms of the infection were present at the post-treatment follow-up, and, for patients the post-therapy chest X-ray did not demonstrate new or increased production or presence of infiltrate.

Unsatisfactory: One or more signs or symptoms of the infection persisted or worsened, or one or more new signs or symptoms of the infection were evident at the post-treatment follow-up or, for patients the post-therapy chest X-ray demonstrates new or increased production or presence of infiltrate.

Undetermined: All cases where a response could not be determined:

- Other antimicrobial given between pre- and post-treatment evaluation of the study drug;
- Pre-treatment or follow-up chest x-ray not done if pneumonia was diagnosed;
- Patient lost to follow-up, no post-treatment evaluation of the study drug.

Bacteriologic Response

Cultures obtained both during and post-treatment were to be used to assess Bacteriologic Response. Each pathogen was assigned a response as follows:

Eradicated: The pathogen was not present in the post-treatment culture or there was no source to culture.

Persisted: The continued presence of the pathogen in the post-treatment culture.

Undetermined: The response could not be evaluated (e.g., no follow-up evaluation).

MEDICAL OFFICER'S COMMENTS:

To be strictly evaluable by the reviewer, a patient had to have:

1. *met the inclusion and exclusion criteria established by the applicant.*
2. *at least two signs and/or symptoms consistent with a _____ infection. Pneumonia was differentiated from _____ by the presence of an infiltrate on chest X-ray.*

NOTE:

a. To support the observed diagnosis, the investigator could document the presence of signs and symptoms from a list of pre-selected terms. They were as follows:

<i>Fever</i>	<i>Chills</i>
<i>Chest Pain</i>	<i>Cough</i>
<i>Sputum</i>	<i>Circumoral Cyanosis</i>
<i>Rales</i>	<i>Pleural Effusion</i>
<i>Chest Retractions</i>	<i>Tachypnea</i>
<i>Diminished Breath Sounds</i>	<i>Dyspnea</i>

b. Respiratory rates were not recorded for any patient. Sputum production was not characterized with regard to quantity, quality or relationship to baseline. In patients with chronic respiratory disease, a change in sputum production and/or cough was also not noted.

c. The IDSA states that leukocytosis and pyrexia should be present to support the diagnosis of a _____ infection. In this indication, many patients were afebrile and without a significant elevation of the white count. The study was not designed to capture information with respect to chronic administration of steroids and/or the use of acetaminophen or aspirin products. Therefore, this information could not be used as diagnostic criteria.

d. For a reviewer to validate the diagnosis of a specific respiratory illness, certain minimal clinical and laboratory information is necessary. In some instances, this includes baseline respiratory conditions and/or relevant medications. Other helpful supporting data are respiratory rates or arterial oxygen content. This study as others in this indication had limited information to precisely characterize the _____ condition; however, there was sufficient data to determine that a pulmonary process was present. To the reviewer, the minimum clinical observations required to support the diagnosis of pneumonia _____ were cough, sputum production, and/or abnormal auscultatory sounds.

3. *a culture documented pathogen susceptible to cefepime.*

NOTE:

a. A gram stain was requested by the applicant. However, a written description was provided at the discretion of the investigator.

b. For the most part, the type of specimen was not identified, e.g. transtracheal aspirate, deep expectorated sputum, etc., nor was the quality described e.g. mucoid, voluminous, blood tinged, etc.

c. Those patients with a documented, valid gram stain and/or positive blood culture constituted the "strictly evaluable" reviewer population.

4. received 24 hours or less of pre-study antimicrobial drug with activity against the identified pathogen or a demonstration of a pathogen resistant to the pre-study antimicrobial drug.

NOTE:

The reviewer believes that this criterion is critical in this study; because treatment by applicant definition could be short (i.e. 3.5 days) and the influence of the pre-study antibiotic is unknown. Second, because validated gram stains were not a study requirement, sputum samples could not always differentiate between a colonizing organism and a true pathogen. The applicant did not address the issue of pre-study antimicrobials in their protocol or study report. The reviewer refers the reader to the published IDSA general guideline which states that: "Patients may be enrolled if they have received < 24 hours of treatment with a presumably effective anti-infective drug for an infectious process thought (on the basis of published reference material) to require a standard duration of therapy of ≥ 7 days." The only extenuating circumstances where a patient may exceed the suggested 24 hour limit of pre-study therapy are illnesses which require lengthy therapy e.g. osteomyelitis and endocarditis or patients infected with a pathogen resistant to the initial anti-infective drug and sensitive to the study drug. (pp. S17-18)

Exceptions to this requirement were those patients who had an acceptable interval (five half-lives) between the administration of alternative systemic antimicrobials and study drug.

5. received a minimum of 4.5 days of therapy (i.e. 9 doses of cefepime) for success. This requirement is consistent with the general IDSA guidelines which recommends a minimum 5 days of therapy for pneumonia (However, a patient could be classified as a failure after only five cefepime doses.)
6. received a maximum of 18 days therapy. (Amendments to the protocol specified 14 days of therapy with cefepime/arginine and 30 days for cefepime/NaCl.)
7. had neither concomitant nor post-study antimicrobial therapy with activity against the identified pathogen in excess of a single dose.
8. had the minimum of three clinical evaluations: pre-therapy visit, during therapy visit and the follow-up visit (5-21 days).

NOTE:

In instances when an in-person test-of cure visit was not possible: The reviewer accepted telephone follow-up information provided by the patient (not a third party, e.g. relative), because this mechanism was mutually accepted during the development program. However, the reviewer would like to state her opinion that this information is of dubious value. There was no standard questionnaire to provide consistent data collection and documentation of these telephone conversations. Therefore, each investigator could ask a different battery of questions.

9. had evidence of bacterial clearance ("sputum production resolved") or a statement with regard to "No source to culture" at the follow-up visit (5-21 days).
10. had a pre-treatment chest X-ray and a post-treatment (either end of treatment or follow-up) chest x-ray. The IDSA guideline recommends that: "A chest radiograph will be obtained 3 days after the initiation of therapy, within 72 hours of completion of therapy, and at any other time the investigator deems necessary." (p. S85) It should be noted that the post-treatment X-ray was a requirement in the original protocol.

Clinical Response:

Satisfactory: Improvement and/or resolution of all pre-treatment signs and symptoms diagnostic of pneumonia/ at the test of cure visit (5-21 days). The end of treatment/follow-up chest X-ray had to show either improvement or lack of progression of the pneumonic process.

Unsatisfactory: Persistence or worsening of any clinical signs or symptoms associated with pneumonia. during treatment or at the time of the follow-up evaluation (5-21 days). The end of treatment/follow-up chest X-ray showed no improvement or worsening.

Unevaluable: Assessment of the clinical outcome could not be determined e.g. the patient did not return for follow-up evaluation.

Bacteriologic Response:

Eradication - Either the causative pathogen(s) was not isolated from the follow-up culture or there was a presumptive eradication because there was no material available for culture.

Persistence - The original pathogen(s) was isolated from the follow-up culture or the patient was a clinical failure with a presumed pathogen persistence.

Unevaluable - It was not possible to determine a bacteriological response, e.g. because the patient did not return for follow-up.

The reviewer conducted an assessment of the "strictly evaluable" population based on the criteria described above. However, the reviewer feels that the design of this study was severely deficient. Problematic areas were as follows:

- a. Inadequate gram stain assessments/documentation
- b. The lack of description with respect to quality and quantity of sputum samples
- c. The lack of description of the method in which a sputum sample was collected
- d. The absence of characterization of "change" of described signs and symptoms from baseline (especially in the patient with chronic lung disease)
- e. The lack of a gradation system with respect to the improvement of signs and symptoms
- f. The lack of assessments with respect to pre-treatment antibiotics on selected patients
- g. The absence of correlation with white blood cell counts (elevations and/or bandemia) and temperature
- h. The absence of definition and attempts to clarify the setting of the pneumonic processes for either pneumonia (i.e. not all pneumonias infections are alike.)
- i. The absence of pre-determined format or questionnaire to gather telephone follow-up data

Not unexpectedly, there were few "strictly evaluable" patients. However, a secondary analysis of a "clinically evaluable" patient population was conducted. The "clinically evaluable" population met all the criteria described above with the exception of the valid pathogen requirement. These patients fell into four categories: a) those patients with an inadequate gram stain, b) those patients whose organism did not have sensitivities done, c) those patients with an inadequate gram stain and a resistant organism and d) those patients in which no organism was isolated. Obviously, this population subset contained patients whose respiratory illness was viral/other and not necessarily bacterial in origin. The reviewer believes that the outcome results of this population are more reflective of the "real world" clinical situation and are more consistent with how the drug will perform when used empirically.

New Infections

A new infection occurred if (1) a different pathogen was cultured from the original infection site and clinical signs of infection were observed, or (2) either the original pathogen or a new organism caused an infection at a body site unrelated to the original site.

Safety Assessments

All patients who received one dose of cefepime were evaluable for safety. All adverse clinical events were reported on the CRF along with the investigator's judgement of the relationship of the reaction to cefepime. Also recorded were the date of onset, duration, and severity of each ACE, and any change in a patient's treatment. If serious or alarming adverse experience(s) occurred that seemed related to cefepime investigators were to stop administering cefepime and notify Bristol-Myers Squibb Company.

Investigators recorded on the CRF whether cefepime was well or poorly tolerated at the infusion site. The occurrence of phlebitis, hematoma, infiltration or other conditions was noted.

Laboratory assessments were required before, during, and after treatment. In addition, a patient with

abnormal laboratory results was to be retested until the values returned to approximately the baseline levels for that patient. These assessments were not always done. However, all available laboratory test results were evaluated with respect to normal ranges by the investigators, who recorded on the CRF the relationship of any abnormal or unusual result to cefepime. Data from all study sites were reviewed and analyzed at Bristol-Myers Squibb.

For safety analyses, the laboratory tests listed below were selected as the most appropriate indicators of toxicity. To identify clinical abnormalities, "direction of toxicity" was defined for each of the selected tests as follows (clinically relevant levels are also provided for each unit) :

Decrease below the lower limit of normal:

Increase above the upper limit of normal:

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Hematocrit :	< 24 vol%
Neutrophil :	≤ 500/cmm
WBC :	≤ 2000/cmm
Platelet :	≤ 50,000/cmm
Prothrombin Ratio :	< 50%

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Alkaline phosphatase :	≥ 3 x UNL
AST, ALT :	≥ 3 x UNL
Total Bilirubin :	≥ 3.0 mg/dL
BUN :	≥ 50.0 mg/dL
BUR :	≥ 100.0 mg/dL
Creatinine :	≥ 3.0 mg/dL
Prothrombin Time :	> 25 sec.
PTT :	> 90 sec.
Eosinophil :	≥ 1000/cmm

Outside normal limits :

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Sodium :	≤ 119 or ≥ 160 mEq/dL
Potassium :	≤ 2.4 or ≥ 6.5 mEq/dL
Calcium :	≤ 7.0 or ≥ 12.0 mg/dL
Phosphorus :	≤ 1.7 or ≥ 6.1 mg/dL

Additional criteria were implemented in testing for neutropenia and eosinophilia.

The following definitions apply to laboratory values :

Abnormal : Outside the normal range limit in the direction of toxicity.

Normal : All other laboratory values were defined to be normal.

Standard conversion factors were applied as needed to both test results and normal range values in order to express data in units as in the table above so that the data could be grouped and analyzed by a minimal number of algorithms.

Discontinuations

The protocol stated that any of the following conditions could justify the early discontinuation of a patient from cefepime treatment. However, investigators sometimes continued cefepime therapy for patients who improved clinically.

1. No pathogen isolated from the pre-treatment culture.
2. *In vitro* susceptibility testing indicated that the pathogen had a MIC (or correlated disc diffusion zone size) defined as resistant to cefepime (MIC $\geq$ 32 mg/ml; zone size $\leq$ 14 mm for 30 mg disc).
3. A poor clinical response was evident after 72 hours of therapy.
4. A serious or alarming adverse event, including an adverse clinical event, abnormal laboratory result, or severe reaction at the infusion site.
5. Intercurrent illness.
6. Patient's decision not to participate further.
7. Investigator's decision that it was in the best interest of the patient to discontinue cefepime treatment.
8. Administrative reasons.

Deaths and discontinuations are summarized at the end of this report.

RESULTS:**Low dose:**

There were 239 patients enrolled in this study. Of this number, 85 patients were designated as having pneumonia and 23 designated as having bronchitis. There were ten (of thirteen) investigators who enrolled patients with respiratory infections.

High dose:

There were 156 patients enrolled in this study. Of this number, 83 patients were designated as having pneumonia and 8 designated as having bronchitis. There were eight (of eight) investigators who enrolled patients with respiratory infections.

STUDY 007 - PNEUMONIA PATIENTS

LOW DOSE N = 85					
CENTER	INVESTIG./ COUNTRY	CEFEPIME ENROLLED	BMS EVALUABLE	NO CLIN ¹ EVALUABLE	NO STRICT ² EVALUABLE
001	V. LANDUYT/BELG	1	1	0	0
003	GLAUSER/SWITZ	31	9	14	2
004	GJAMARELLOU/GR	16	8	4	0
007	HOEPELMAN/HOLL	13	3	7	0
008	BERGER/SWITZ	4	0	1	0
009	MOUTON/FRA	7	1	2	0
011	VEYSSTER/FR.	9	4	8	0
014	VANDENBERGH/BEL	3	0	1	0
016	MATTIE/HOLL	1	1	0	0
TOTALS		85	27	37	2
HIGH DOSE N = 83					
009	MOUTON/FRA	11	4	4	0
010	HUMBERT/FRA	17	1	4	0
011	VEYSSTER/FRA	5	2	4	0
012	MODAI/FRA	6	1	2	0
018	BERTRAND/FRA	11	1	1	0
020	DELLAMONICA/FRA	6	0	2	1
021	NICOLD/FRA	26	0	13	2
022	JOURDAN/FRA	1	0	0	0
TOTALS		83	9	30	3

¹Clinically evaluable patients were those patients who were enrolled with a infection, who did not have a valid pathogen, but who met all other reviewer evaluability criteria.

²The strictly evaluable population included those patients who were followed clinically and whose identified pathogen was microbiologically evaluable. These patients had either a good gram stain recorded (i.e. ≥ 25 PMNs and ≤ 10 epithelial cells under low power magnification) or had a positive blood culture.

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REASONS PATIENTS COULD BE CONSIDERED NON-EVALUABLE BY THE REVIEWER:

1. The patient did not have the minimally required three clinical evaluations: a) pre-therapy, b) during/end of therapy and c) post-therapy.
2. The isolated pathogen was resistant to study drug.
3. No pathogen was isolated.
4. There were antimicrobials administered for greater than twenty-four hours prior to study start. Usually there was insufficient information to determine whether the antimicrobial administered did not impact on the clinical and/or microbiological outcome of the infection.
5. Additional antimicrobial therapy was prescribed between the end of treatment and follow-up assessments.
6. The patient received concomitant antimicrobial therapy.
7. There was no follow-up assessment made at the test of cure visit (5-21 days post-therapy).
8. The patient did not receive the minimum number of doses required for an assessment of cure (9 doses) or failure (5 doses).
9. Therapy exceeded 18 days.
10. The patient did not have either pneumonia or bronchitis. Or, an initial chest X-ray was indicated and it was not performed.
11. A pathogen was isolated and identified. However, no sensitivity testing (no zone sizes or MICs) was completed.
12. The dosage of the study drug administered was other than that indicated in the Protocol.
13. The patient was also receiving another investigational drug.
14. No end-of treatment or follow-up chest X-ray was performed. Radiological assessments were acceptable after end of treatment ($\pm$ 1 day).
15. There was either no gram stain available, an inadequate gram stain was recorded and/or a blood culture was negative.

The above lists the possible reasons a patient could be classified as non-evaluable. The tabulation below serves only an indicator of the reasons patients were excluded from the efficacy analysis. Many patients had more than one reason; however, only one reason per patient was listed.

HOW TO READ THE FOLLOWING TABLE:

The table below is a composite of two tables (reasons patients were not clinically evaluable and reasons patients were not strictly evaluable). The gray shaded area labelled "subtotal" is the number of patients who were not clinically evaluable. The gray shaded area labelled "total" is the number of patients who were excluded from the strictly evaluable population. The patients in the parentheses are those patients whose only reason for being excluded from the strictly evaluable population was an inappropriate pathogen (i.e. no gram stain documentation, a resistant organism identified, no sensitivities done or no pathogen at all was isolated). For example, listed under no pathogen/pneumonia patients, what does "29 + (19)" mean? This means that 48 patients had no pathogen identified and were excluded from the strictly evaluable population. Of these 48, there were 19 patients who met all other evaluability save for an appropriate pathogen. The other 29 patients were not eligible for the clinically evaluable population, because they had a second reason (not identified here) that made them non-evaluable. For example: Often, when an investigator determined that a patient's culture was negative; the patient was removed from the study. Because the patient was not followed to study completion, the patient could not be considered clinically evaluable.

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CLINICAL EFFICACY

PNEUMONIA (N = 85): LOW DOSE

CLINICAL RESPONSE	BMS	MO CLINICALLY EVAL	MO STRICTLY EVAL
SATISFACTORY	25 (93%)	26 (70%)	2 (100%)
UNSATISFACTORY	2 (7%)	11 (30%)	0 (0%)
UNEVALUABLE	58	48	83
TOTALS (N)	85	85	85

The BACTERIOLOGICAL responses for pneumonia based on patients that were strictly evaluable are as follows:

S. pneumoniae

2/2 (100%)

PNEUMONIA (N = 83): HIGH DOSE

CLINICAL RESPONSE	BMS	MO CLINICALLY EVAL	MO STRICTLY EVAL
SATISFACTORY	0 (100%)	18 (60%)	2 (67%)
UNSATISFACTORY	0 (0%)	12 (40%)	1 (33%)
UNEVALUABLE	74	53	80
TOTALS (N)	83	83	83

The BACTERIOLOGICAL responses for pneumonia based on patients that were strictly evaluable are as follows:

S. pneumoniae

2/3 (67%)

The following tables examine efficacy related to various demographic variables to determine if there are intrapopulation variables which would require labelling modifications.

CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
PNEUMONIA N = 85
LOW DOSE

VARIABLE	BMS	MO CLINICALLY EVAL.	MO STRICTLY EVAL
ALL	25/27 (93%)	26/37 (70%)	2/2 (100%)
WOMEN	6/7 (86%)	12/16 (75%)	2/2 (100%)
MEN	19/20 (95%)	14/21 (67%)	-
WHITE	25/27 (93%)	26/37 (70%)	2/2 (100%)
BLACK	-	-	-
OTHER	-	-	-
< 65 YEARS	11/12 (92%)	10/15 (67%)	-
> 65 YEARS	14/15 (93%)	16/22 (73%)	2/2 (100%)

The following table evaluates the effect of underlying lung disease and/or smoking. In the data collection, the information provided included the presence or absence of disease. The specific disease process or length of its existence was not usually recorded. Further information was sometimes available in the investigator's note.

EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS
PNEUMONIA N = 85
LOW DOSE

RESPIRATORY STATUS	BMS	MO CLINICAL EVAL.	MO STRICTLY EVAL.
ALL	25/27 (93%)	26/37 (70%)	2/2 (100%)
SMOKER	5/5 (100%)	3/4 (75%)	-
LUNG DISEASE	3/3 (100%)	6/9 (67%)	1/1 (100%)
SMOKER & LUNG DISEASE	11/12 (92%)	8/12 (67%)	-
NONSMOKER	6/7 (86%)	9/12 (75%)	1/1 (100%)

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The following tables examine efficacy related to various demographic variable to determine if there are intrapopulation variables which would require labelling modifications.

CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
PNEUMONIA N = 83
HIGH DOSE

VARIABLE	BMS	MO CLINICALLY EVAL.	MO STRICTLY EVAL.
ALL	9/9 (100%)	18/30 (60%)	2/3 (67%)
WOMEN	4/4 (100%)	9/14 (64%)	1/1 (100%)
MEN	5/5 (100%)	9/16 (56%)	1/2 (50%)
WHITE	7/9 (100%)	16/27 (59%)	2/3 (67%)
BLACK	-	1/2 (50%)	-
OTHER	-	1/1 (100%)	-
< 65 YEARS	3/3 (100%)	9/15 (60%)	1/2 (50%)
> 65 YEARS	6/6 (100%)	9/15 (60%)	1/1 (100%)

The following table evaluates the effect of underlying lung disease and/or smoking. In the data collection, the information provided included the presence or absence of disease. The specific disease process or length of its existence was not usually recorded. Further information was sometimes available in the investigator's note.

EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS
PNEUMONIA N = 93
HIGH DOSE

RESPIRATORY STATUS	BMS	MO CLINICAL EVAL.	MO STRICTLY EVAL.
ALL	9/9 (100%)	18/30 (60%)	2/3 (67%)
SMOKER	-	1/3 (33%)	0/1 (0%)
LUNG DISEASE	2/2 (100%)	5/9 (56%)	1/1 (100%)
SMOKER & LUNG DISEASE	1/1 (100%)	1/3 (33%)	-
NONSMOKER	6/6 (100%)	12/15 (80%)	1/1 (100%)

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SAFETY EVALUATION:

Of the LOW DOSE group, 85 patients enrolled with pneumonia and the 23 patients enrolled with there were a total of 6 (5 pneumonia and 1) deaths.

LOW DOSE PNEUMONIA:

The patient was a 90 year old man with multiple medical problems who was admitted for treatment of right lower lobe pneumonia. Sputum and blood cultures were positive for *S pneumoniae*. The was treated for eight days and appeared to improve clinically. On the eighth day of therapy, the patient became acutely dyspneic and he expired. The investigator believed the patient died either of pulmonary embolism or a cardiorespiratory arrest.

The patient was a 78 year old white man with a history of atrial fibrillation and other medical problems. He was admitted to the hospital for treatment of right upper lobe pneumonia and bacteremia. The patient was treated with cefepime for ten days and responded well. Three days after cefepime was discontinued, the patient suffered a cerebrovascular accident. Days after the treatment with cefepime was discontinued, the patient began to have fever and respiratory symptoms. The investigator believed that the patient aspirated due to neurological compromise. The patient expired nine days post cefepime therapy.

The patient was a 71 year old man with multiple medical problems who was admitted for treatment of pneumonia. Therapy with cefepime was instituted and continued 11 days. The patient's infection improved. However, the patient was cachectic and continued to deteriorate; he expired fourteen days after cefepime therapy was discontinued.

The patient was an 82 year old woman with multiple medical problems who was admitted to the hospital for treatment of heart failure and right lower lobe pneumonia. The patient was treated with cefepime for five days with some improvement. Because the patient had difficulty with delivering the therapy intravenously, the patient was switched to an alternative oral therapy. The patient was discharged. The patient died four weeks after discharge of unknown causes.

The patient was a 73 year old man with a history of chronic obstructive lung disease who was admitted to the hospital for treatment of a right lower lobe pneumonia. Treatment with cefepime lasted nine days with some improvement. The patient's cardiac status deteriorated and the patient died. The investigator listed the cause of death as cardiac decompensation. No autopsy was performed.

HIGH DOSE PNEUMONIA:

The patient was a 31 year old man with a history of oligodendroglioma who was admitted to the hospital with bilateral pneumonia. Cefepime therapy was instituted, but discontinued after 4 days when no pathogen was isolated. The patient then received amoxicillin clavulanate. One day later, the patient was given vancomycin and amikacin for the isolation of a multi-resistant *S. aureus*. The patient died five days after cefepime was discontinued. The investigator thought the cause of death was cerebral herniation.

The patient was a 74 year old woman with a history of end-stage respiratory disease who was admitted to the hospital for treatment of pneumonia. No pathogen was isolated. She was treated for five days with cefepime with no essential improvement. Blood cultures became positive for enterococcus (intermediate sensitivity to cefepime). The clinician diagnosed the patient also with tuberculosis and anti-tuberculous treatment was instituted. The patient expired 64 days after cefepime was discontinued of progressive respiratory failure.

The patient was a 77 year old man with a history of bronchopulmonary disease who was admitted for treatment of bronchopneumonia. The patient was treated with cefepime and improved significantly. The patient died of his underlying respiratory condition 24 days after the cefepime was discontinued.

The patient was a 52 year old man with a history of alcoholism who was admitted for treatment of his bronchopneumonia. He received two doses of cefepime and was discontinued when no pathogen was isolated. The patient died of a cardiorespiratory arrest (no further details given) nine days after the study drug was discontinued.

The patient was a 72 year old man who was admitted for treatment of bronchopneumonia. One of the pathogens isolated was resistant to cefepime; therefore, the patient was treated with only three

doses before receiving alternative antibiotics. Blood cultures became positive for cytomegalovirus. The investigator listed the cause of death as pulmonary embolus. Death occurred 9 days after cefepime was terminated.

The patient was a 69 year old white man with a history of metastatic renal carcinoma who was hospitalized for treatment of a left lobar pneumonia. No pathogen was isolated, but the patient was treated with cefepime for 10 days. During therapy, the roentgenogram showed improvement. Six days post-treatment, pleural effusions were again present. These were though not to be infectious. The patient expired 26 days after cefepime therapy was discontinued. The investigator believed that death was related to the underlying malignancy.

The patient was an 87 year old woman with multiple medical problems admitted to the hospital in a debilitated state for treatment of pneumonia. No pathogen was isolated, but the patient received treatment for 11 days with cefepime. The patient demonstrated improvement; however at the end of treatment, the patient received imipenem for a persistence of a moderate fever and a pleural effusion. Seventeen days after cefepime was discontinued, the patient had a recurrence of respiratory symptoms. The patient expired 25 days post-treatment. No autopsy was performed.

The patient was a 78 year old white man with multiple medical problems who was admitted for pneumonia. No pathogen was isolated. Cefepime was instituted and continued for 13 days. The patient clinically deteriorated. The patient died of respiratory causes two days after cefepime therapy was discontinued. No autopsy was performed.

Discontinuations:

LOW DOSE:

Discontinuations due to an adverse event:

There were three (three patients with pneumonia patients who discontinued therapy due to an adverse experience.

PATIENTS WHO DISCONTINUED DUE TO ADVERSE CLINICAL EVENTS
VOLUME 170 p. 145
LOW DOSE

PATIENT	ACE	SEVERITY	TOTAL DOSE (in G)	RELATION TO DRUG	OUTCOME
	RASH	MODERATE	12	PROBABLY	RECOVERED
	DISORIENTATION	MODERATE	3	UNRELATED	RECOVERED
	FLUSH HEADACHE	MODERATE MODERATE	7	PROBABLY PROBABLY	RECOVERED RECOVERED

LOW DOSE:

One low dose patient discontinued therapy due to a laboratory test abnormality:

Discontinuation on day 4 of therapy due to eosinophilia (47%).

HIGH DOSE:

Discontinuations due to an adverse event:

There were three (two patients with pneumonia) patients who discontinued therapy due to an adverse experience.

**PATIENTS WHO DISCONTINUED DUE TO ADVERSE CLINICAL EVENTS
VOLUME 177 p. 133
HIGH DOSE**

PATIENT	ACE	SEVERITY	TOTAL DOSE (in G)	RELATION TO DRUG	OUTCOME
	DIARRHEA	SEVERE	22	PROBABLY	RECOVERED
	URTICARIA PAPULE	MILD	20	PROBABLY	RECOVERED
	RASH	MODERATE	38	PROBABLY	RECOVERED

LOCAL TOLERANCE:

There were also three low dose patients with pneumonia and one high dose patient with another infection who had to discontinue treated due to local intolerance of the infusion. They were as follows:

low dose	pneumonia
low dose	pneumonia
low dose	pneumonia
high dose	other respiratory infection

MEDICAL OFFICER'S COMMENTS:

It is interesting to note that the only patients who were discontinued due to local intolerance at the infusion site originated from the same center. However, local intolerance was fairly evenly distributed as evidenced by the applicant's table below.

Frequency of Local Intolerance,
by Center
Study 411-067 - Low Dose

Center	Intolerance
I-001	2/15 (13%)
I-002	0/22 (0%)
I-003	11/34 (32%)
I-004	5/41 (12%)
I-006	0/2 (0%)
I-007	5/20 (25%)
I-008	2/5 (40%)
I-009	7/25 (28%)
I-010	0/17 (0%)
I-011	4/26 (15%)
I-012	1/8 (13%)
I-014	3/8 (38%)
I-016	1/16 (6%)

The following is a summary of tolerance provided by the applicant. In addition, the applicant reported that local tolerance to the infusions was not a function of the formulation (i.e. NaCl or arginine).

Frequency of Local Tolerance
All Patients
Study 411-067 High Dose
N = 156

<u>Well Tolerated</u> :	142	(91)
<u>Poorly Tolerated</u> :	14	(9)
- Infiltration	8	(5)
- Phlebitis	5	(3)
- Inflammation	1	(1)

ADVERSE EVENTS:

According to the applicant, six (4%) of the 156 high dose patients experienced 8 adverse clinical events. In the low dose group, twenty-five (10%) of the enrolled 239 patients experienced 32 adverse clinical events. The most commonly reported events were diarrhea, rash and nausea. Of the twenty-five, seventeen (17/134 = 13%) received cefepime/NaCl and eight (8/105 = 8%) received treatment with cefepime/l-arginine.

MEDICAL OFFICER'S COMMENTS:

Unfortunately, the applicant did not subset the adverse events with respect to the indication studied such as urinary tract infection, skin and skin structure infection, and so forth.

In addition, laboratory pretreatment values were compared to during and post-treatment values. However, the tables presented by the applicant in the study report were prepared for the entire enrolled population and were not subdivided by indication.

Therefore, the medical officer requested that the applicant present this information for all patients with the . The applicant submitted this information in an amendment to the NDA, number 71. However, information per study and information per indication (i.e. pneumonia) were not itemized by the applicant. Tables of ADR and laboratory safety data from all patients diagnosed with were adapted from the applicant's submission and are presented in the summary section of this report.

Susceptibility of Causative Organisms Isolated
Pre-Treatment
All Patients
Study 411-067 - Low Dose

Organism	Number (%) of Isolates*				Total
	Susceptible	Inter- mediate	Resistant	Not Done	
<i>S. faecalis</i>	1 (50)	1 (50)			2
Strep (α-hemolytic)	1 (100)			1	2
<i>S. viridans</i>				2	2
<i>S. agalactiae</i>	1 (100)				1
Strep. (Group G)	1 (100)				1
<i>S. mitis</i>	1 (100)				1
<i>S. milleri</i>	1 (100)				1
<i>S. aureus</i>	5 (100)				5
<i>S. epidermidis</i>	4 (100)				4
<i>S. saprophyticus</i>	1 (100)				1
<i>S. pneumoniae</i>	26 (100)			2	28
<i>Pseudomonas</i> sp.			1 (100)	1	2
<i>P. aeruginosa</i>	16 (84)	1 (5)	2 (11)	1	20
<i>E. coli</i>	90 (100)			6	96
<i>C. freundii</i>	1 (100)				1
<i>K. pneumoniae</i>	10 (100)				10
<i>K. oxytoca</i>	3 (100)				3
<i>Enterobacter</i> sp.	1 (100)				1
<i>E. cloacae</i>	4 (100)				4
<i>P. mirabilis</i>	15 (100)			1	16
<i>P. vulgaris</i>	2 (100)				2
<i>M. morgani</i>	1 (100)			1	2
<i>H. influenzae</i>	12 (100)			4	16
<i>H. parainfluenzae</i>	5 (100)				5
<i>Neisseria</i> sp.	1 (100)				1
<i>M. catarrhalis</i>	2 (100)				2
<i>C. albicans</i>				1	1
<i>A. anitratus</i>	1 (100)				1
<i>B. fragilis</i>			1 (100)		1
Total	206 (97)	2 (1)	4 (2)	20	232

* Pathogens not tested are not included in the percentages.

Susceptibility of Initial Pathogen
All Patients
Study 411-067 (High Dose) Europe

Organism	NUMBER (%) OF TESTED ISOLATES*				TOTAL
	Susceptible	Inter mediate	Resistant	Not Done	
A. calcoaceticus	1 (100)				1
Acinetobacter sp.	1 (33)		2 (67)		3
7usobacterium sp.	1 (100)				1
Strep. (Group D)	1 (100)				1
Strep. (Group A)	1 (100)				1
S. marcescens	2 (100)				2
S. enteritidis	1 (100)				1
S. aureus	4 (80)		1 (20)		5
S. pneumoniae	15 (100)			2	17
Serratia sp.	1 (100)				1
P. aeruginosa	6 (100)			1	7
E. coli	42 (100)				42
Klebsiella sp.	1 (100)				1
Peptostreptococcus sp.	1 (100)				1
P. mirabilis	2 (100)				2
P. maltophilia	1 (50)		1 (50)		2
M. morgani	1 (100)				1
H. influenzae	4 (100)				4
H. influenzae (beta-)	2 (100)				2
Haemophilus sp.	1 (100)				1
H. parainfluenzae	1 (100)				1
M. catarrhalis	3 (100)			1	4
E. cloacae	1 (100)				1
TOTAL	94 (96)	0	4 (4)	4	102

* Pathogens not tested are not included in the percentage.

PNEUMONIAPROTOCOL AI411-070All North American Investigators (NDA volumes 1.129 - 1.137)North American Blinded Study (NDA volumes 1.143 - 146)All European Investigators (NDA volumes 1.138-142)

TITLE: A Comparative Study of Cefepime and Ceftazidime in the Treatment of Patients with Infections

MEDICAL OFFICER'S COMMENTS:

The following protocol description was excerpted from the applicant's study reports (volumes 1.129, 1.138 and 1.143); the reviewer has made minor editorial changes. This study was designed to investigate "infections." Infections included patients with pneumonia and occasionally other infections. For this portion of the review, pneumonia were analyzed separately for safety and efficacy; patients with other respiratory infections were analyzed with the safety review. It should be noted that the protocol did not make any separate provisions to distinguish patients versus patients with pneumonia.

STUDY DESIGN:

This trial was a Phase III, open, randomized (2:1, cefepime:ceftazidime), comparative clinical study conducted in nine centers in Europe and in thirty centers in the United States. Three of the US centers conducted blinded studies using this protocol. There were a total of 5 amendments; their issues are presented in BOLD type.)

Inclusion Criteria:

1. Male or female patients at least 18 years old of any race.
2. If female, had a negative pregnancy test immediately prior to enrollment, was taking oral contraceptives in the prescribed manner, was surgically sterilized, or was post menopausal. (Originally women of childbearing potential were excluded, amendment 2 allowed for their inclusion.)
3. Had clinical symptoms consistent with infection. (The original Protocol limited the study to patients with infection but Amendment 1 allowed inclusion of patients with infection and advanced pulmonary disease.)
4. Had an infection suspected to be caused by a pathogen(s) susceptible to both cefepime and ceftazidime.
5. Provided Informed Consent.

Exclusion Criteria

1. History of a serious reaction to a penicillin or a cephalosporin. Patients with Type 1 hypersensitivity reaction to penicillin could have been given study drug with caution.
2. Impaired renal function (serum creatinine of ≥ 1.7 mg/dL), or on renal dialysis.
3. Impaired hepatic function.
4. Infection not yet established (e.g., antibiotic therapy for the initial management of extensive physical trauma).
5. Likelihood of receiving other antimicrobials concomitantly.
6. Previous enrollment in the study.
7. Medically significant disease or disorder that in the opinion of the investigator could influence the results of the study.
8. Pregnant or lactating.
9. Presence of cystic fibrosis (The original Protocol excluded all patients with advanced pulmonary disease; Protocol Amendment 1 allowed inclusion of all except patients with cystic fibrosis).
10. Infection requiring long-term (more than 14 days) therapy (e.g. empyema, aspiration pneumonia, etc.).
11. Granulocyte count of < 500 .

Procedures and Observations Outlined in the Protocol and Amendments

The table below lists the procedures and observations that were specified in the Protocol and Amendments.

Study Schedule
Study 411-070

Procedure	Within 48 hrs Pretreatment	Days 2-6 During Treatment	Days 1-14 Post-Treatment
Eligibility	X	-	-
Informed Consent	X	-	-
Medical History	X	-	-
Physical Examination	X	X	X
Clinical Evaluation	X	X	X ^a
Bacteriologic Tests ^b	X	X	X
Laboratory Tests ^c	X	X	X
Chest X-ray ^d	X	-	X

a For patients with a satisfactory during-treatment response, the investigator must confirm that the response remains satisfactory on post-treatment Day 5-14 (The applicant allowed Day 1-4 for patients enrolled on or before June 1, 1988).

b Bacteriologic Tests include culture, subculture, and susceptibility tests. During- and post-treatment cultures and subcultures were to be obtained only if there was a source to culture. If there is no source to culture due to diminished or absent sputum production the date of the attempted

culture should be documented in the CRF as "NO SOURCE TO CULTURE."

c Laboratory tests are listed below.

d Pre-treatment chest X-ray for patients with suspected pneumonia was to be taken within 72 hours before, or 24 hours after beginning the study drug. Post-treatment X-ray was to be taken for all patients with a diagnosis of pneumonia (confirmed by pre-treatment X-ray).

Pre-therapy Procedures

1. Within 48 hours before treatment began a medical history was to be recorded and a physical examination was to be completed.
2. The presence of clinical signs and symptoms of infection was to be evaluated within 48 hours before beginning therapy.
3. Bacteriologic confirmation of the infection was to be obtained by culturing the infected site(s) (a suctioned sputum specimen or a deep-cough, purulent, expectorated sputum sample and/or blood sample) within 48 hours before beginning treatment. If the blood culture was positive, a subsequent during- or post-treatment blood culture was required.

MEDICAL OFFICER'S COMMENTS:

The protocol stated the following: "Sputum specimens for gram stain and culture will be obtained by sterile suctioning (transtracheal, endotracheal, or bronchoscopy) or deep-coughed purulent expectorated sputum. A pre-treatment specimen (sputum or aspirate) will be gram-stained to determine if a predominant morphologic form of identifiable pathogen is present which will be subsequently cultured. The specimen must be purulent as demonstrated by the presence of leukocytes. A second pre-treatment sample will be obtained if large numbers of squamous epithelial cells are present suggesting contamination with oral secretions. The quantitative microscopic data will be integrated with the qualitative data derived from subsequent cultures of sputum or aspirate specimens." The applicant did not provide definitions (e.g. ≤ 10 squamous epithelial cells with ≥ 25 PMNs per low power magnification field) with regard to the adequacy of a particular sputum sample. The case report allotted a space in the CRF in which the investigator could document a gram stain; he/she was requested to assess whether the gram stain supported the primary diagnosis. However, quantitative or qualitative sputa descriptions were not requested.

4. Each pathogen was to be identified and tested for susceptibility to both drugs by disc or Minimum Inhibitory Concentration methods.
5. In most cases, subcultures of pathogens were to be prepared and shipped to Bristol-Myers Squibb Company.
6. A chest X-ray was to be done on each patient within the period 72 hours before treatment or within 24 hours after beginning treatment.
7. Laboratory studies were requested within 48 hours before treatment. Additional laboratory tests were done at the discretion of the investigator. The requested assessments were:

HEMATOLOGY

Hemoglobin
 Hematocrit
 Leukocyte count, total and differential
 Platelet count or estimate from smear
 Erythrocyte Sedimentation Rate
 Prothrombin Time (PT)
 Partial Thromboplastin Time (PTT)

SERUM CHEMISTRY

Aspartate aminotransferase (AST, SGOT)
 Alanine aminotransferase (ALT, SGPT)
 Total bilirubin
 Alkaline phosphatase
 Blood Urea Nitrogen (BUN)
 Creatinine
 Glucose
 Electrolytes (sodium, potassium, calcium,* and phosphorus*)
 (* Added by Protocol Amendment 1.)

URINALYSIS

Specific gravity
pH
Albumin
Glucose
Microscopic Examination (WBC, RBC, casts, crystals, epithelial cells)

During-Treatment Procedures

Investigators were requested to observe their patients at least once during treatment:

1. A physical examination was to be repeated on Day 2-5 of treatment.
2. The Protocol requested that clinical signs and symptoms of infection be assessed on Day 2-6.
3. The Protocol requested a culture be prepared from an appropriate specimen obtained on Day 2-6.
 - a. All pathogens from a positive culture were to be isolated and identified. After testing each pathogen's susceptibility, the investigator was to subculture it for shipment to Bristol-Myers Squibb, and at the same time, determine whether a patient with a positive culture should be discontinued and placed on other therapy.
 - b. The occurrence of a negative culture was to be recorded.
 - c. If a specimen could not be obtained for culturing because sputum could not be produced, the attempt and date were to be noted on the CRF with the statement "NO SOURCE TO CULTURE."
 - d. If a pre-treatment blood culture was positive, a subsequent blood culture was requested.
4. Chest X-rays were to be repeated as deemed appropriate. A chest X-ray was not required during treatment
5. Laboratory tests required as pretreatment evaluations were to be repeated on Day 2-6 of treatment (values determined from Day 2 to the end of treatment were accepted) and as appropriate when results were abnormal.

Post-Treatment Procedures

The procedures listed below were to be completed within 1-14 days after completion of study therapy.

1. A physical examination was requested.
2. The Protocol requested clinical signs and symptoms of infection be evaluated on post-treatment Day 1-14. Amendment 3 to the original Protocol requested that for patients with a satisfactory during-treatment response, the investigator had to confirm that the response remained satisfactory on post-treatment Day 5-14, either by observation or by telephone (The applicant noted in their report that patients enrolled on or before June 1, 1988 could have a follow-up visit on Day 1-4, according to an agreement with the Food and Drug Administration (FDA) reviewer.

MEDICAL OFFICER'S COMMENTS:

At the end of Phase II meeting which took place on February 14, 1989, the applicant presented a time-table of proposed follow-up examinations for all indications. The follow-up period suggested for infections was 5-14 days post-treatment. From the minutes of the meeting submitted to the Division on April 13, 1989, this time frame was considered acceptable by both the applicant and the Division. There was no indication that the aforementioned 1-4 day post-therapy visit would be acceptable for pre-amendment patients. To date, the applicant cannot locate the minutes of a discussion with the FDA which addresses the 1-4 day follow-up exemption.

3. The Protocol requested a post-treatment culture be obtained from the sputum (or aspirate) of each patient on post-treatment Day 1-14 if the specimen source remained. If a pretreatment blood culture was positive, a subsequent (either during or post-treatment) blood culture was requested. Any pathogen cultured was to be identified and tested for susceptibility, then subcultured and sent to Bristol-Myers Squibb Company. If a specimen could not be obtained for culturing because sputum could not be produced, the attempt and date were to be noted on the C.F with the statement "NO SOURCE TO CULTURE."
4. The Protocol required at least one post-treatment chest X-ray in any patient with a diagnosis of pneumonia.
5. Laboratory studies requested as pretreatment evaluations were to be repeated on post-treatment Day 1-14 and as appropriate when results were abnormal.

Treatment-Group Assignment

This study was designed as an open, randomized, comparative study. At each study center, patients were randomly assigned to receive one of the two treatments in a 2:1 (cefepime:ceftazidime) ratio.

Dosage and Administration

Cefepime was supplied in vials containing 500 mg or 1 g of either a lyophilized mixture of cefepime and NaCl or a dry-powder blend of cefepime dihydrochloride and L-arginine. Ceftazidime was supplied in vials containing 500 mg or 1 g ceftazidime in a dry powder.

Investigators were to administer cefepime and ceftazidime by intravenous infusion over a 30-minute period or by intramuscular injection (IM injection allowed by Replacement Protocol Amendment 1), with repeat dosing of cefepime every 12 hours (1 g BID) or of ceftazidime every 8 hours (1 g TID).

For the double-blinded portion of the study: Centers 012 and 066 were to administer study drug or placebo (normal saline) by intravenous infusion over a period of 30 minutes. The first dose was to be active drug. Cefepime patients were to receive two 1 g doses of active drug and two doses of placebo in each 24 hour period. The placebo was administered 8 and 16 hours after the first dose of drug. Ceftazidime patients were to receive three 1 g doses of active drug and one dose of placebo in each 24 hour period. The placebo was administered 12 hours after the first dose of ceftazidime.

Center 039 allowed dosing every four hours; the first dose was active drug. Cefepime patients were to receive two 1g doses of active drug and four doses of placebo in each 24 hour period. The placebo was to be administered 4, 8, 16 and 20 hours after the first dose of cefepime. Ceftazidime patients were to receive three 1g doses of active drug and three doses of placebo in the 24 hour period; the first dose was to be active drug. The placebo was administered 4, 12 and 20 hours after the first dose of ceftazidime.

Length of therapy

The length of therapy was a maximum of 14 days. (After results of toxicity studies became available for cefepime/NaCl, Protocol Amendment 2 extended the duration of treatment to 30 days. When Protocol Amendment 5 allowed the use of cefepime/arginine, the duration of treatment for patients receiving cefepime/arginine was to be 14 days.)

Each patient had to receive seven doses of cefepime or 11 doses of ceftazidime in 96 hours to be evaluable for efficacy (minimum number of doses established by Protocol Amendment 1).

MEDICAL OFFICER'S COMMENTS:

The reviewer disagrees with the Protocol's request for a minimum number of doses (7 - cefepime; 11 - ceftazidime) required for efficacy. In general, a parenteral product is targeted primarily at the more severely ill patient. Therefore, a minimum of five days of therapy should be required; this concurs with the IDSA guideline of treatment for an evaluable patient with pneumonia.

Concomitant Therapy

The Protocol allowed medications, except for antimicrobial agents, to be administered as indicated to enrolled patients. Use of any non-study medication was to be recorded on the CRF. Antimicrobial therapy other than study drug was not allowed during the study or in the post-treatment follow-up period. In addition, topical antibiotics could be used only if they would not influence the treatment of the original infection.

MEDICAL OFFICER'S COMMENTS:

The applicant in practice and in their analysis allowed patients to have concomitant antimicrobial medications if the "agent had no known activity (as defined in the official labelling in the 1990 PDRI)" against the genus of organism involved in the original infection. Because it was difficult to differentiate which pathogens were colonizers and which were true pathogens, the assessment for anti-infective activity in a study patient would be difficult, at best.

Microbiology Assessments

Based on the disc sensitivity method, isolates were defined as susceptible if the zone diameter was 18 mm or greater, resistant if the zone diameter was 14 mm or less, and intermediate if the zone diameter was 15 mm to 17 mm in diameter. Based on results of MIC testing, isolates were defined as susceptible if the MIC was 8 mcg/ml or less, resistant if the MIC was 32 mcg/ml or greater, and intermediate if the MIC was 16 mcg/ml.

New Infections

According to the Protocol, a new infection occurred if a different pathogen was cultured from the original infection site after the pretreatment culture. Patients were also considered to have a new infection if either the original pathogen or a new pathogen caused an infection at a body site unrelated to the original site of infection. New infections were diagnosed based on the culture results; associated clinical signs and symptoms were not necessarily present. However, patients also could have a new infection diagnosed solely on the basis of clinical signs and symptoms.

Applicant Criteria for Evaluability:

A patient was considered evaluable for efficacy only if the following criteria were met. Any additional or altered requirements from the original Protocol are indicated.

1. An infection of the _____ was diagnosed clinically and confirmed by a positive pretreatment culture within 48 hours before study medication was administered and after any previous antimicrobial therapy.
2. Any causative pathogen isolated in the pretreatment culture was identified and shown to be susceptible to cefepime and ceftazidime.
3. A culture was obtained post-treatment Day 1-14. A clinical assessment was done post-treatment Day 5-14. Clinical assessments done post-treatment Day 1-4 were accepted for patients who enrolled on or before June 1, 1988 (according to the original Protocol).

MEDICAL OFFICER'S COMMENTS:

With regard to the proposed follow-up period, the reader is referred above.

4. A pre-treatment chest X-ray was done within the period 72 hours before treatment began (after any previous antimicrobial therapy) up to Day 2 of treatment. (This X-ray did not have to support the diagnosis of pneumonia, but it should not have confirmed pneumonia in patients diagnosed with _____. The original Protocol required at least one post-treatment (Day + 1 or after) chest X-ray for any patient with a diagnosis of pneumonia. However, retroactively, it was decided that this post-treatment X-ray could be omitted if an X-ray was taken during therapy (Day 3 to last day of treatment). Post-treatment X-ray was not required for patients with _____

MEDICAL OFFICER'S COMMENTS:

This statement is a significant modification of the protocol. The reviewer does not agree with the proposal to validate pneumonia patients without a positive infiltrate on chest X-ray or an appropriate gram stain. The applicant's definitions were originally very liberal; excluding the X-ray requirement makes it difficult, if not impossible, to confirm the specified diagnosis.

5. According to the Protocol, no other systemic antimicrobial agent was to be taken during the time between the pretreatment clinical assessment and culture and the post-treatment clinical and bacteriologic assessments (Amendment 3). In fact, concomitant systemic antimicrobials were allowed as long as they had no activity (according to official labeling) against the genus of pathogen being treated.
6. Cefepime or ceftazidime was administered intramuscularly or by intravenous infusion at the dose, frequency, and duration specified in the Protocol. A minimum of seven doses of cefepime or 11 doses of ceftazidime was received within a 96-hour period.

Applicant Efficacy Criteria Definitions:Clinical Response

Satisfactory: All signs and symptoms of the infection that were present before therapy were improved or resolved, the post-treatment chest X-ray did not show new or increased production or presence of infiltrate, and no new signs or symptoms of the infection were present at the post-treatment follow-up.

Unsatisfactory: One or more signs or symptoms of the infection persisted or worsened; or one or more new signs or symptoms of the infection were evident at the post-treatment follow-up; or post-treatment chest X-ray showed new or increased production or presence of infiltrate.

Undetermined: All cases where a response could not be determined (e.g., no follow-up evaluation).

Bacteriologic Response

Eradicated: The causative pathogen was not present in the post-treatment sputum culture; or, there was no source of sputum for the during- and/or post-treatment cultures.

Persisted: The continued presence of the causative pathogen in the post-treatment sputum culture.

Undetermined: The response could not be determined (e.g., no follow-up evaluation).

NOTE: For evaluable patients only, if the investigator's assessment of Clinical Response or Bacteriologic Response did not conform to the Protocol definitions, the applicant corrected the response to the Protocol specifications.

MEDICAL OFFICER'S COMMENTS:

To be strictly evaluable by the reviewer, a patient had to have:

1. met the inclusion and exclusion criteria defined by the applicant.
2. at least two signs and/or symptoms consistent with a *infection. Pneumonia was* differentiated from *by the presence of an infiltrate on chest X-ray.*

NOTE:

a. To support the observed diagnosis, the investigator could document the presence of signs and symptoms from a list of pre-selected terms. They were as follows:

Fever	Diminished Breath Sounds
Chills	Wheezes
Cough	Restlessness
Sputum Production	Tachypnea
Rales, Rattles	Dyspnea
Percussion Dullness	Chest Retractions
Tactile Fremitus	Chest Pain
Increased Breath Sounds	Circumoral Cyanosis
Facial Flush	Increased Breath Sounds

b. Respiratory rates were not recorded for any patient. Sputum production was not characterized with regard to quantity, quality or relationship to baseline. In patients with chronic respiratory disease, a change in sputum production and/or cough was also not noted.

c. The IDSA states that leukocytosis and pyrexia should be present to support the diagnosis of *a* *infection. In this indication, many patients were afebrile and without*

a significant elevation of the white count. The study was not designed to capture information with respect to chronic administration of steroids and/or the use of acetaminophen or aspirin products. Therefore, this information could not be used as diagnostic criteria.

d. For a reviewer to validate the diagnosis of a specific respiratory illness, certain minimal clinical and laboratory information is necessary. In some instances, this includes baseline respiratory conditions and/or recent medications. Other helpful supporting data are respiratory rates or arterial oxygen content. This study as others in this indication had limited information to precisely characterize the respiratory condition; however, there was sufficient data to determine that a pulmonary process was present. To the reviewer, the minimum clinical observations required to support the diagnosis of pneumonia were cough, sputum production, and/or abnormal auscultatory sounds.

3. a culture documented pathogen susceptible to cefepime and ceftazidime.

NOTE:

a. A gram stain was requested by the applicant. However, a written description was provided at the discretion of the investigator.

b. For the most part, the type of specimen was not identified, e.g. transtracheal aspirate, deep expectorated sputum, etc., nor was the quality described e.g. mucoid, voluminous, blood tinged, etc.

c. Those patients with a documented, valid gram stain and/or positive blood culture constituted the "strictly available" reviewer population.

4. received 24 hours or less of pre-study antimicrobial drug with activity against the identified pathogen or a demonstration of a pathogen resistant to the pre-study antimicrobial drug.

NOTE:

The reviewer believes that this criterion is critical in this study; because treatment by applicant definition could be short (i.e. 3.5 days) and the influence of the pre-study antibiotic is unknown. Second, because validated gram stains were not a study requirement, sputum samples could not always differentiate between a colonizing organism and a true pathogen. The applicant did not address the issue of pre-study antimicrobials in their protocol or study report. The reviewer refers the reader to the published IDSA general guideline which states that: "Patients may be enrolled if they have received < 24 hours of treatment with a presumably effective anti-infective drug for an infectious process thought (on the basis of published reference material) to require a standard duration of therapy of ≥ 7 days." The only extenuating circumstances where a patient may exceed the suggested 24 hour limit of pre-study therapy are illnesses which require lengthy therapy e.g. osteomyelitis and endocarditis or patients infected with a pathogen resistant to the initial anti-infective drug and sensitive to the study drug. (pp. S17-18)

Exceptions to this requirement were those patients who had an acceptable interval (five half-lives) between the administration of alternative systemic antimicrobials and study drug.

5. received a minimum of 4.5 days of therapy (i.e. 9 doses of cefepime or 13 doses of ceftazidime) for success. This requirement is consistent with the general IDSA guidelines which recommends a minimum 5 days of therapy for pneumonia (However, a patient could be classified as a failure after only five cefepime doses.)
6. received a maximum of 18 days therapy. (Amendments to the protocol specified 14 days of therapy with cefepime/arginine and 30 days for cefepime)
7. had neither concomitant nor post-study antimicrobial therapy with activity against the identified pathogen in excess of a single dose.
8. had the minimum of three clinical evaluations: pre-therapy visit, during therapy visit and the follow-up visit (5-21 days).

NOTE:

In instances when an in-person test-of cure visit was not possible: The reviewer accepted telephone follow-up information provided by the patient (not a third party, e.g. relative), because this mechanism was mutually accepted during the development program. However, the

reviewer would like to state her opinion that this information is of dubious value. There was no standard questionnaire to provide consistent data collection and documentation of these telephone conversations. Therefore, each investigator could ask a different battery of questions.

9. had evidence of bacterial clearance ("sputum production resolved") or a statement with regard to "No source to culture" at the follow-up visit (5-21 days).
10. had a pre-treatment chest X-ray and a post-treatment (either end of treatment or follow-up) chest x-ray. The IDSA guideline recommends that: "A chest radiograph will be obtained 3 days after the initiation of therapy, within 72 hours of completion of therapy, and at any other time the investigator deems necessary." (p. S85) It should be noted that the post-treatment X-ray was a requirement in the original protocol.

Clinical Response:

Satisfactory: Improvement and/or resolution of all pre-treatment signs and symptoms diagnostic of pneumonia/ at the test of cure visit (5-21 days). The end of treatment/follow-up chest X-ray had to show either improvement or lack of progression of the pneumonic process.

Unsatisfactory: Persistence or worsening of any clinical signs or symptoms associated with pneumonia during treatment or at the time of the follow-up evaluation (5-21 days). The end of treatment/follow-up chest X-ray showed no improvement or worsening.

Unevaluable: Assessment of the clinical outcome could not be determined e.g. the patient did not return for follow-up evaluation.

Bacteriologic Response:

Eradication - Either the causative pathogen(s) was not isolated from the follow-up culture or there was a presumptive eradication because there was no material available for culture.

Persistence - The original pathogen(s) was isolated from the follow-up culture or the patient was a clinical failure with a presumed pathogen persistence.

Unevaluable - It was not possible to determine a bacteriological response, e.g. because the patient did not return for follow-up.

The reviewer conducted an assessment of the "strictly evaluable" population based on the criteria described above. However, the reviewer feels that the design of this study was severely deficient. Problematic areas were as follows:

- a. Inadequate gram stain assessments/documentation
- b. The lack of description with respect to quality and quantity of sputum samples
- c. The lack of description of the method in which a sputum sample was collected
- d. The absence of characterization of "change" of described signs and symptoms from baseline (especially in the patient with chronic lung disease)
- e. The lack of a gradation system with respect to the improvement of signs and symptoms
- f. The lack of assessments with respect to pre-treatment antibiotics on selected patients
- g. The absence of correlation with white blood cell counts (elevations and/or bandemia) and temperature
- h. The absence of definition and attempts to clarify the setting of the pneumonic processes for either pneumonia (i.e. not all pneumonias infections are alike.)
- i. The absence of pre-determined format or questionnaire to gather telephone follow-up data

Not unexpectedly, there were few "strictly evaluable" patients. However, a secondary analysis of a "clinically evaluable" patient population was conducted. The "clinically evaluable" population met all the criteria described above with the exception of the valid pathogen requirement. These patients fell into four categories: a) those patients with an inadequate gram stain, b) those patients whose organism did not have sensitivities done, c) those patients with an inadequate gram stain and a resistant organism and d) those patients in which no organism was isolated. Obviously, this population subset contained patients whose respiratory illness was viral/other and not necessarily bacterial in origin. The reviewer believes that the outcome results of this population are more reflective of the "real world" clinical situation and are more consistent with how the drug will perform when used empirically.

Safety Assessments

All patients who received one dose of cefepime or ceftazidime were evaluable for safety. All adverse clinical events were reported on the CRF along with the investigator's judgement of the relationship of the reaction to cefepime or ceftazidime. Also recorded were the date of onset, duration, and severity of each Adverse clinical event, and any change in a patient's treatment. If serious or alarming adverse experience(s) occurred, investigators were to stop administering the drug and notify Bristol-Myers Squibb Company.

Investigators recorded on the CRF whether cefepime or ceftazidime was well or poorly tolerated at the infusion site. The occurrence of phlebitis, hematoma, infiltration or other conditions was noted.

Laboratory assessments were required before, during, and after treatment. In addition, a patient with abnormal laboratory results was to be retested until the values returned to approximately the baseline levels for that patient. Data from all study sites were reviewed and analyzed at Bristol-Myers Squibb.

For safety analyses, the laboratory tests listed below were selected as the most appropriate indicators of toxicity. To identify clinical abnormalities, "direction of toxicity" was defined for each of the selected tests as follows (clinically relevant levels are also provided for each unit):

Decrease below the lower limit of normal:

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Hematocrit :	< 24 vol%
Neutrophil :	≤ 500/cmm
WBC :	≤ 2000/cmm
Platelet :	≤ 50,000/cmm
Prothrombin Ratio :	< 50%

Increase above the upper limit of normal:

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Alkaline phosphatase :	≥ 3 x UNL
AST, ALT :	≥ 3 x UNL
Total Bilirubin :	≥ 3.0 mg/dL
BUN :	≥ 50.0 mg/dL
BUR :	≥ 100.0 mg/d
Creatinine :	≥ 3.0 mg/dL
Prothrombin Time :	> 25 sec.
PTT :	> 90 sec.
Eosinophil :	≥ 1000/cmm

Outside normal limits :

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Sodium :	≤ 119 or ≥ 160 mEq/dL
Potassium :	≤ 2.4 or ≥ 6.5 mEq/dL
Calcium :	≤ 7.0 or ≥ 12.0 mg/dL
Phosphorus :	≤ 1.7 or ≥ 6.1 mg/dL

Additional criteria were implemented in testing for neutropenia and eosinophilia.

The following definitions apply to laboratory values :

Abnormal : Outside the normal range limit in the direction of toxicity.

Normal : All other laboratory values were defined to be normal.

Standard conversion factors were applied as needed to both test results and normal range values in order to express data in units as in the table above so that the data could be grouped and analyzed by a minimal number of algorithms.

Discontinuations

The Protocol stated that any of the following conditions could justify the early discontinuation of a patient from treatment. However, investigators sometimes continued treatment for patients who improved clinically.

1. No pathogen isolated from the pretreatment culture.
2. *In vitro* susceptibility testing indicated that the pathogen had an MIC (or correlated disc diffusion zone size) defined as resistant to cefepime or ceftazidime.
3. A poor Clinical Response was evident within 72 hours of therapy.
4. A serious or alarming adverse event.
5. Intercurrent illness.
6. Patient decision not to participate further.
7. Investigator decision that it was in the best interest of the patient to discontinue treatment.
8. Administrative reasons.

Deaths and discontinuations are summarized at the end of this report.

RESULTS:

This study was designed to include those patients with _____ infections. The following discussion will be divided into three segments: a) non-blinded North American investigators, b) blinded North American investigators, and c) non-blinded European investigators. The enrollment is summarized as follows:

NON-BLIND - North America**Pneumonia**

treated with cefepime	180
treated with ceftazidime	89

BLIND - North America**Pneumonia**

treated with cefepime	39
treated with ceftazidime	21

NON-BLIND - Europe**Pneumonia**

treated with cefepime	83
treated with ceftazidime	39

In summary, there were 451 patients with pneumonia and 121 patients with _____ in this study. The open North American study was conducted from April 5, 1988 to May 9, 1991; the open European study was conducted from November 14, 1988 to April 29, 1991; and the blinded North American study was conducted from June 9, 1988 to June 10, 1991.

STUDY 070 PNEUMONIA PATIENTS^{1,2}
N = 269
NON-BLINDED - NORTH AMERICA

CTR	INVESTIG STATE	CEFEPIME				CEFTAZIDIME			
		ENROLLED	BMS EVALUABLE	MO CLIN EVALUABLE	MO STRICT EVALUABLE	ENROLLED	BMS EVALUABLE	MO CLIN EVALUABLE	MO STRICT EVALUABLE
002	McCABE/CA	44	19	19	16	23	11	10	8
003	FARKAS/OH	21	11	5	2	11	6	4	1
005	PELLETIER/KS	11	5	6	5	5	2	4	4
006	GECKLER/MD	2	0	0	0	2	1	1	0
007	PLOTKIN/PA	1	1	1	0	0	0	0	0
008	LEVISON/PA	6	3	0	0	4	0	0	0
009	ZELLNER/FL	1	0	0	0	1	0	0	0
010	LANE/NC	4	0	1	1	2	1	1	0
011	YANGCO/FL	16	6	9	1	8	0	3	0
015	CRAIG/MI	6	1	2	0	1	0	0	0
016	MOGABGAB/LA	1	0	0	0	0	0	0	0
018	MALOW/IL	2	0	0	0	2	0	1	0
019	ERNST/NY	12	1	1	0	4	0	0	0
028	RAMIREZ/PR	12	8	5	0	6	2	4	1
030	JEMSEK/NC	0	0	0	0	1	1	0	0
031	SORG/OH	3	0	0	0	1	1	1	1
038	GREENBERG/MO	3	0	1	0	0	0	0	0
040	SIEGER/FL	16	6	5	2	8	0	1	1
045	FORLENZA/NY	2	0	1	0	1	0	0	0
050	HANDWERGR/NY	1	0	0	0	0	0	0	0
052	LERNER/TX	1	1	0	0	0	0	0	0
058	MARKOWITZ/MI	4	2	0	0	4	2	2	0
062	BUTLER/TX	4	2	0	0	2	0	0	0
063	GAINER/WV	4	3	3	1	2	1	1	0
065	McCABE/CA	3	2	2	2	1	1	0	0
TOT		180	68	61	30	89	29	33	16

¹Clinically evaluable patients were those patients who were enrolled with a _____ infection, who did not have a valid pathogen, but who met all other reviewer evaluability criteria.

²The strictly evaluable population included those patients who were followed clinically and whose identified pathogen was microbiologically evaluable. These patients had either a good gram stain recorded (i.e. ≥ 25 PMNs and ≤ 10 epithelial cells under low power magnification) or had a positive blood culture.

STUDY 070 PNEUMONIA PATIENTS^{1,2}
 N = 60
 BLIND - NORTH AMERICA

CTR	INVESTIG STATE	CEFEPIME				CEFTAZIDIME			
		ENROLLED	BMS EVALUABLE	NO CLIN EVALUABLE	NO STRICT EVALUABLE	ENROLLED	BMS EVALUABLE	NO CLIN EVALUABLE	NO STRICT EVALUABLE
012	HADDOW/MO	20	11	7	0	9	4	4	0
039	LEVINE/MI	16	2	3	1	10	2	2	1
066	FARKAS/OH	3	2	0	0	2	2	2	2
TOT		39	15	10	1	21	8	8	3

¹Clinically evaluable patients were those patients who were enrolled with a _____ infection, who did not have a valid pathogen, but who met all other reviewer evaluability criteria.

²The strictly evaluable population included those patients who were followed clinically and whose identified pathogen was microbiologically evaluable. These patients had either a good gram stain recorded (i.e. ≥ 25 PMNs and ≤ 10 epithelial cells under low power magnification) or had a positive blood culture.

STUDY 070 PNEUMONIA PATIENTS^{1,2}

N = 122

NON-BLIND - EUROPE

CTR	INVESTIG STATE	CEFEPIME				CEFTAZIDIME			
		ENROLLED	BMS EVALUABLE	NO CLIN EVALUABLE	NO STRICT EVALUABLE	ENROLLED	BMS EVALUABLE	NO CLIN EVALUABLE	NO STRICT EVALUABLE
036	LEOPHPO/FR	8	0	5	0	4	4	4	1
037	BERTRAND/FR	7	0	3	1	1	0	0	0
043	NOUVET/FR	37	9	16	0	16	6	10	0
044	LUCHT/FR	4	0	1	1	2	1	1	0
046	DELAVAL/FR	4	0	1	0	0	0	0	0
047	DEPIERRE/FR	6	1	2	0	3	1	2	1
048	HUGUES/FR	5	1	2	1	4	0	4	1
059	ULMER/GER	3	0	2	0	4	2	1	0
060	SUNDELHOF/SW	9	1	8	1	5	2	5	0
		83	12	40	4	39	16	27	3

¹Clinically evaluable patients were those patients who were enrolled with a infection, who did not have a valid pathogen, but who met all other reviewer evaluability criteria.

²The strictly evaluable population included those patients who were followed clinically and whose identified pathogen was microbiologically evaluable. These patients had either a good gram stain recorded (i.e. ≥ 25 PMNs and ≤ 10 epithelial cells under low power magnification) or had a positive blood culture.

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Finally, it should be recognized that the bulk of patients studied under this indication are in the clinically evaluable population. Because investigators did not anticipate a clinically evaluable population; they often elected to prematurely terminate patients, who did not have a valid pathogen, from the study. Since fewer days of observation are required to detect a failure, there were potentially more patients with negative outcomes that were evaluable.

REASONS PATIENTS COULD BE CONSIDERED NON-EVALUABLE BY THE REVIEWER:

1. The patient did not have the minimally required three clinical evaluations: a) pre-therapy, b) during/end of therapy and c) post-therapy.
2. The isolated pathogen was resistant to study drug.
3. No pathogen was isolated. There was always an additional reason why a patient in this category was unevaluable or he/she is listed in parentheses as a patient considered for the clinically evaluable category.
4. There were antimicrobials administered for greater than twenty-four hours prior to study start. Usually there was insufficient information to determine whether the antimicrobial administered did not impact on the clinical and/or microbiological outcome of the infection.
5. Additional antimicrobial therapy was prescribed between the end of treatment and follow-up assessments.
6. The patient received concomitant antimicrobial therapy.
7. There was no follow-up assessment made at the test of cure visit (5-21 days post-therapy).
8. The patient did not receive the minimum number of doses required for an assessment of cure (9 doses) or failure (5 doses) for cefepime or cure (13 doses) or failure (8 doses).
9. Therapy exceeded 18 days.
10. The patient did not have either pneumonia Or, an initial chest X-ray was indicated and it was not performed.
11. A pathogen was isolated and identified. However, no sensitivity testing (no zone sizes or MICs) was completed.
12. The dosage of the study drug administered was other than 2g BID or renal equivalent dosing.
13. The patient was also receiving another investigational drug.
14. No end-of treatment or follow-up chest X-ray was performed. Radiological assessments were acceptable after end of treatment ($\pm$ 1 day).
15. There was either no gram stain available, an inadequate gram stain was recorded and/or a blood culture was negative.

The above lists the possible reasons a patient could be classified as non-evaluable. The tabulation below serves only an indicator of the reasons patients were excluded from the efficacy analysis. Many patients had more than one reason; however, only one reason per patient was listed.

HOW TO READ THE FOLLOWING TABLE:

The tables below are composites of two tables (reasons patients were not clinically evaluable and reasons patients were not strictly evaluable). The gray shaded area labelled "sub-total" is the number of patients who were not clinically evaluable. The gray shaded area labelled "total" is the number of patients who were excluded from the strictly evaluable population. The patients in the parentheses are those patients whose only reason for being excluded from the strictly evaluable population was an inappropriate pathogen (i.e. no gram stain documentation, a resistant organism identified, no sensitivities done or no pathogen at all was isolated). For example, listed under no pathogen/pneumonia patients, what does "39 + (5)" mean? This means that 44 patients had no pathogen identified and were excluded from the strictly evaluable population. Of these 44, there were 5 patients who met all other evaluability save for an appropriate pathogen. The other 39 patients were not eligible for the clinically evaluable population, because they had a second reason (not identified here) that made them non-evaluable. For example: Often, when an investigator determined that a patient's culture was negative; the patient was removed from the study. Because the patient was not followed to study completion, the patient could not be considered clinically evaluable.

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CLINICAL EFFICACY
NON-BLIND NORTH AMERICA

PNEUMONIA (N = 289)

CLINICAL RESPONSE	BNS		NO CLINICALLY EVAL		NO STRICTLY EVAL	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
SATISFACTORY	58 (85%)	21 (72%)	48 (79%)	26 (79%)	22 (73%)	15 (94%)
UNSATISFACTORY	10 (15%)	8 (28%)	13 (21%)	7 (21%)	8 (27%)	1 (6%)
UNEVALUABLE	112	60	119	56	150	73
TOTALS (N)	180	89	180	89	180	89

The BACTERIOLOGICAL responses for pneumonia based on patients that were strictly evaluable are as follows:

	CEFEPIME:	CEFTAZIDIME:
<u>E. coli</u>	0/1 (0%)	
<u>H. influenzae</u>	0/1 (0%)	1/1 (100%)
<u>H. influenzae (P+)</u>	1/1 (100%)	1/1 (100%)
<u>H. influenzae (P-)</u>	3/3 (100%)	3/4 (75%)
<u>H. parahaemolyticus</u>	1/1 (100%)	
<u>H. parainfluenzae (P-)</u>	1/1 (100%)	2/2 (100%)
<u>K. oxytoca</u>	1/1 (100%)	
<u>K. pneumoniae</u>	1/1 (100%)	
<u>M. catarrhalis</u>		1/1 (100%)
<u>M. catarrhalis (P+)</u>	2/2 (100%)	
<u>M. catarrhalis (P-)</u>		1/1 (100%)
<u>N meningitidis</u>		1/1 (100%)
<u>Neisseria sp.</u>	0/1 (0%)	
<u>P. aeruginosa</u>	1/1 (100%)	
<u>P. mirabilis</u>	1/2 (50%)	
<u>P. putida</u>	1/1 (100%)	
<u>S. aureus</u>	0/1 (0%)	
<u>S. aureus</u>	1/1 (100%)	
<u>S. marcescens</u>	1/1 (100%)	
<u>S. mitis</u>	1/1 (100%)	1/1 (100%)
<u>S. pneumoniae</u>	0/1 (0%)	4/4 (100%)
<u>S. pneumoniae</u>	12/14 (86%)	4/4 (100%)
<u>S. viridans</u>		1/1 (100%)

CLINICAL EFFICACY
BLIND

PNEUMONIA (N = 60)

CLINICAL RESPONSE	BMS		NO CLINICALLY EVAL		NO STRICTLY EVAL	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
SATISFACTORY	12 (80%)	7 (88%)	6 (60%)	7 (88%)	0 (0%)	2 (67%)
UNSATISFACTORY	3 (20%)	1 (13%)	4 (40%)	1 (12%)	1 (100%)	1 (33%)
UNEVALUABLE	24	13	29	13	38	18
TOTALS (N)	39	21	39	21	39	21

The BACTERIOLOGICAL responses for pneumonia based on patients that were strictly evaluable are as follows:

<u>M. catarrhalis</u> (P+)	CEFEPIME:	CEFTAZIDIME:
<u>P. aeruginosa</u>	0/1 (0%)	1/1 (100%)
<u>S. aureus</u>		0/1 (0%)
<u>S. pneumoniae</u>		2/3 (67%)

CLINICAL EFFICACY
NON-BLIND EUROPE

PNEUMONIA (N = 122)

CLINICAL RESPONSE	BMS		NO CLINICALLY EVAL		NO STRICTLY EVAL	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
DRUG						
SATISFACTORY	8 (67%)	15 (94%)	30 (75%)	18 (67%)	4 (100%)	2 (67%)
UNSATISFACTORY	4 (33%)	1 (6%)	10 (25%)	9 (33%)	0 (0%)	1 (33%)
UNEVALUABLE	71	23	43	12	79	36
TOTALS (N)	83	39	83	39	83	39

The BACTERIOLOGICAL responses for pneumonia based on patients that were strictly evaluable are as follows:

S. pneumoniae
S. sanquis

CEFEPIME:
 3/3 (100%)
 1/1 (100%)

CEFTAZIDIME:
 2/3 (67%)

The tables combine the subgroups of this study pneumonia. First, all North American studies (blind and unblind) are combined and then all North American and European studies.

CLINICAL EFFICACY
ALL NORTH AMERICAN

PNEUMONIA (N = 329)

CLINICAL RESPONSE	BNS		NO CLINICALLY EVAL		NO STRICTLY EVAL	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
SATISFACTORY	70 (84%)	28 (76%)	54 (76%)	33 (80%)	22 (71%)	17 (89%)
UNSATISFACTORY	13 (16%)	9 (24%)	17 (24%)	8 (20%)	9 (29%)	2 (11%)
UNEVALUABLE	133	73	148	69	189	91
TOTALS (N)	219	110	219	110	219	110

CLINICAL EFFICACY
ALL NORTH AMERICAN AND EUROPEAN PATIENTS
AI411-070

PNEUMONIA (N = 451)

CLINICAL RESPONSE	BMS		NO CLINICALLY EVAL		NO STRICTLY EVAL	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
SATISFACTORY	78 (82%)	43 (81%)	84 (76%)	51 (75%)	26 (76%)	19 (86%)
UNSATISFACTORY	17 (17%)	10 (19%)	27 (24%)	17 (25%)	9 (26%)	3 (14%)
UNEVALUABLE	204	96	191	81	267	88
TOTALS (N)	302	110	302	110	302	110

The following tables examine efficacy related to various demographic variables to determine if there is any intrapopulation variation which would require labelling modifications.

CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
PNEUMONIA N = 269
NON-BLIND NORTH AMERICA

VARIABLE	BMS		NO CLINICALLY EVAL.		NO STRICTLY EVAL.	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
ALL	58/68 (85%)	21/29 (72%)	48/61 (79%)	26/33 (79%)	22/30 (73%)	15/16 (94%)
WOMEN	11/11 (100%)	1/3 (33%)	10/11 (91%)	2/2 (100%)	6/6 (100%)	1/1 (100%)
MEN	47/57 (82%)	20/26 (77%)	38/50 (76%)	24/31 (77%)	16/24 (67%)	14/15 (93%)
WHITE	47/56 (84%)	19/24 (79%)	36/47 (77%)	21/26 (81%)	17/23 (74%)	13/13 (100%)
BLACK	7/7 (100%)	2/4 (50%)	10/11 (91%)	5/6 (83%)	4/5 (80%)	2/2 (100%)
OTHER	4/5 (80%)	0/1 (0%)	2/3 (67%)	0/1 (0%)	1/2 (50%)	0/1 (0%)
< 65 YEARS	34/38 (89%)	10/10 (100%)	26/32 (81%)	12/13 (92%)	13/16 (81%)	8/8 (100%)
> 65 YEARS	24/30 (80%)	11/19 (58%)	22/29 (76%)	14/20 (70%)	9/14 (64%)	7/8 (88%)

CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
 PNEUMONIA N = 60
 BLIND NORTH AMERICA

VARIABLE	BMS		NO CLINICALLY EVAL.		NO STRICTLY EVAL	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
ALL	12/15 (80%)	7/8 (88%)	6/10 (60%)	7/8 (88%)	0/1 (0%)	2/3 (67%)
WOMEN	7/8 (88%)	3/4 (75%)	3/4 (75%)	3/4 (75%)	-	1/2 (50%)
MEN	5/7 (71%)	4/4 (100%)	3/6 (50%)	4/4 (100%)	0/1 (0%)	1/1 (100%)
WHITE	11/13 (85%)	6/6 (100%)	6/7 (86%)	6/6 (100%)	-	2/2 (100%)
BLACK	1/2 (50%)	1/2 (50%)	0/2 (0%)	1/2 (50%)	0/1 (0%)	0/1 (0%)
OTHER	-	-	0/1 (0%)	-	-	-
< 65 YEARS	4/5 (80%)	2/3 (67%)	2/5 (40%)	2/3 (67%)	0/1 (0%)	1/2 (50%)
> 65 YEARS	8/10 (80%)	5/5 (100%)	4/5 (80%)	5/5 (100%)	-	1/1 (100%)

CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
 PNEUMONIA N = 122
 NON-BLIND EUROPE

VARIABLE	BMS		NO CLINICALLY EVAL.		NO STRICTLY EVAL	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
ALL	8/12 (67%)	15/16 (94%)	30/47 (75%)	18/27 (67%)	4/4 (100%)	2/3 (67%)
WOMEN	2/3 (67%)	2/2 (100%)	6/7 (86%)	3/5 (60%)	1/1 (100%)	1/1 (100%)
MEN	6/9 (67%)	13/14 (93%)	24/33 (73%)	15/22 (68%)	3/3 (100%)	1/2 (50%)
WHITE	7/11 (64%)	15/16 (94%)	29/39 (74%)	18/27 (67%)	4/4 (100%)	2/3 (67%)
BLACK	-	-	-	-	-	-
OTHER	1/1 (100%)	-	1/1 (100%)	-	-	-
< 65 YEARS	4/5 (80%)	6/7 (86%)	13/18 (72%)	7/11 (64%)	2/2 (100%)	0/1 (0%)
> 65 YEARS	4/7 (57%)	9/9 (100%)	17/22 (77%)	11/16 (69%)	2/2 (100%)	2/2 (100%)

The following table evaluates the effect of underlying lung disease and/or smoking. In the data collection, the information provided included the presence or absence of disease. The specific disease process or length of its existence was not usually recorded. Further information was sometimes available in the investigator's note.

EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS
 PNEUMONIA N = 269
 NON-BLIND NORTH AMERICA

RESPIRATORY STATUS	BMS		NO CLINICAL EVAL.		NO STRICTLY EVAL.	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
ALL	58/68 (85%)	21/29 (72%)	48/61 (79%)	26/33 (79%)	22/30 (73%)	15/16 (94%)
SMOKER	7/8 (88%)	4/4 (100%)	9/10 (90%)	6/6 (100%)	4/5 (80%)	4/4 (100%)
LUNG DISEASE	23/25 (92%)	4/10 (40%)	17/19 (89%)	4/8 (50%)	5/7 (71%)	1/1 (100%)
SMOKER & LUNG DISEASE	24/30 (80%)	12/14 (86%)	17/26 (65%)	12/15 (80%)	12/17 (71%)	8/9 (88%)
NONSMOKER	4/5 (80%)	1/1 (100%)	5/6 (83%)	4/4 (100%)	1/1 (100%)	2/2 (100%)

The following table evaluates the effect of underlying lung disease and/or smoking. In the data collection, the information provided included the presence or absence of disease. The specific disease process or length of its existence was not usually recorded. Further information was sometimes available in the investigator's note.

EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS
PNEUMONIA N = 60
BLIND NORTH AMERICA

RESPIRATORY STATUS	BMS		NO CLINICAL EVAL.		NO STRICTLY EVAL.	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
ALL	12/15 (80%)	7/8 (88%)	6/10 (60%)	7/8 (88%)	0/1 (0%)	2/3 (67%)
SMOKER	1/1 (100%)	0/1 (0%)	1/2 (50%)	0/1 (0%)	-	0/1 (0%)
LUNG DISEASE	1/3 (33%)	4/4 (100%)	0/2 (0%)	4/4 (100%)	(0%)	-
SMOKER & LUNG DISEASE	9/10 (90%)	1/1 (100%)	4/5 (80%)	1/1 (100%)	-	1/1 (100%)
NONSMOKER	1/1 (100%)	2/2 (100%)	1/1 (100%)	2/2 (100%)	-	1/1 (100%)

The following table evaluates the effect of underlying lung disease and/or smoking. In the data collection, the information provided included the presence or absence of disease. The specific disease process or length of its existence was not usually recorded. Further information was sometimes available in the investigator's note.

EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS
PNEUMONIA N = 122
NON-BLIND EUROPE

RESPIRATORY STATUS	BMS		NO CLINICAL EVAL.		NO STRICTLY EVAL.	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
ALL	8/12 (67%)	15/16 (94%)	30/40 (75%)	18/27 (67%)	4/4 (100%)	2/3 (67%)
SMOKER	1/1 (100%)	1/1 (100%)	6/8 (75%)	3/6 (50%)	1/1 (100%)	-
LUNG DISEASE	1/3 (33%)	6/6 (100%)	7/9 (78%)	6/7 (86%)	1/1 (100%)	-
SMOKER & LUNG DISEASE	6/7 (86%)	4/4 (100%)	13/17 (76%)	6/8 (75%)	1/1 (100%)	1/1 (100%)
NONSMOKER	0/1 (0%)	4/5 (80%)	4/6 (67%)	3/6 (50%)	1/1 (100%)	1/2 (50%)

SAFETY EVALUATION

Of the 572 patients with _____ who were enrolled in Study 411-070, there were 47 (47/572 = 8%) deaths. There were 29 (29/381 = 8%) cefepime deaths and 18 (18/191 = 9%) ceftazidime deaths. This was further subdivided as follows:

Non-Blinded - North America:

PNEUMONIA (N = 269)

treated with cefepime	16/180 = 9%
treated with ceftazidime	8/89 = 9%

Blinded:

PNEUMONIA (N = 60)

treated with cefepime	3/39 = 8%
treated with ceftazidime	3/21 = 14%

Non-Blinded - Europe:

PNEUMONIA (N = 122)

treated with cefepime	7/83 = 8%
treated with ceftazidime	3/39 = 8%

PNEUMONIA - CEFEPIME - NORTH AMERICA - NONBLIND

The patient was a 74 year old man with a history of multiple medical problems including panhypopituitarism and a seizure disorder who was admitted for treatment of a probable pneumonia. The patient received treatment with cefepime for five days with resultant clinical improvement. Six days after discontinuation of therapy, the patient became confused and combative. He also developed leukocytosis. All cultures were negative, but an infusion site was noted to be infected. The patient was placed on alternative antimicrobial agents, but did not improve. Further investigation did not clarify the clinical situation. The patient was given morphine and suffered a cardiorespiratory arrest. He expired seven days after the cefepime was discontinued. Blood cultures taken before death were subsequently positive for coagulase negative staphylococcus and enterococcus.

The patient was an 82 year old hispanic man with multiple medical problems including old tuberculosis and chronic pulmonary disease who was admitted for treatment of gastric outlet obstruction. During the hospitalization, the patient developed symptoms of pneumonia. It was suspected that the pneumonia was caused by aspiration as related to his gastrointestinal obstruction. He was placed on therapy and improved slightly. It was thought that the patient may have aspirated again when a new infiltrate appeared in the contralateral lung. Therapy with study drug was discontinued and alternative antibiotic therapy was begun. The patient continued to deteriorate; the patient requested withdrawal of heroic measures and died six days after removal from the study drug.

The patient was a 61 year old man with many medical problems included long standing obstructive pulmonary disease and metastatic lung carcinoma. He was admitted for treatment of new infiltrate on chest X-ray. He was placed on therapy with cefepime and received five doses. However, it was decided that the patient did not have pneumonia and the study drug was discontinued. Six days after discontinuation of therapy, the patient was bacteremic; *S. pneumoniae* was isolated. He received alternate antimicrobial therapy. He died the day after therapy was instituted and seven days after study drug was discontinued.

The patient was a 59 year old man who was admitted to the hospital for treatment of anaemia. During the work-up on admission, it was noted that the patient had a right lower lobe pneumonia. The patient improved after six days of cefepime therapy. A large mucous plug was also aspirated from the bronchus. However, three days after study drug discontinuation, the patient became confused and disoriented. Atelectasis was present; a sputum culture was negative. The patient continued to decline and died of a respiratory arrest seven days after the study drug was discontinued. Further information was not available except that investigator noted new evidence of lung cancer.

The patient was a 78 year old white woman who was recently treated for bronchitis was admitted to the hospital for the surgical repair of a ventral hernia. Post-operatively, the patient developed pneumonia and was treated with study drug and responded well. She was weaned from the respirator and transferred to a medical floor. She was then found pulseless and breathless. Autopsy determined that the cause of death was a pulmonary embolism.

The patient was a 76 year old man who was admitted for a surgical repair of small bowel obstruction. During the hospitalization, he developed symptoms consistent with pneumonia. The patient was placed on cefepime therapy. He received only two doses of the drug when he developed chest pain and arrhythmia. He died of a cardiopulmonary arrest.

The patient was a 77 year old woman with a history of pulmonary disease and recent discharge from the hospital after treatment of pneumonia. It was unclear the time interval between the last admission and the current admission for respiratory failure secondary to pneumonia. The patient was treated with study drug for eight days with clinical improvement. Ventilatory assistance was thought no longer necessary and was removed. The patient subsequently developed respiratory distress thought by the investigator to be due to cardiac disease. The patient requested no heroic measures and died nineteen days after discontinuation of study drug.

The patient was a debilitated 77 year old white woman who was admitted for treatment of bilateral pneumonia. She was entered into the study and received therapy with cefepime. Early in the study, the patient developed acute respiratory distress and required mechanical ventilation. The patient

received treatment for 6 days with improvement; however, therapy was discontinued. The patient received alternate antibiotics five days post-therapy for a prophylaxis for a minor surgical procedure. Four days post-cefepime treatment, the patient was found to have a positive blood culture with enterococcus. Vancomycin was instituted. Her condition continued to decline. She died 35 days after the discontinuation of cefepime.

The patient was a 66 year old man with a history of severe oxygen-dependent chronic obstructive pulmonary disease who was admitted to the hospital for treatment of pneumonia. The patient received treatment with cefepime, but requested that he not be placed on a ventilator. The investigator noted a brief initial improvement, but the patient became tired and could not clear secretions. His condition worsened and he died of respiratory failure after the fifth dose of treatment.

The patient was a 74 year old man with steroid dependent chronic pulmonary disease who was admitted for treatment of pneumonia. He received 10 days of therapy with some improvement. On the last day of treatment, the patient was noted to be confused. His sputum was still purulent and alternative antimicrobial therapy was prescribed. Twenty-nine days after study drug was discontinued, the patient was readmitted to the hospital with "sepsis," recurrent pneumonia and gastrointestinal bleeding. He died at this time.

The patient was a 46 year old who was admitted for pneumococcal pneumonia and bacteremia. The patient was enrolled in the study and received four doses of cefepime. He had a rapid decline and respiratory distress. The investigator decided to switch the patient to alternative antimicrobial therapy. The patient died on the same day of septic shock.

The patient was a 74 year old white man with a history of chronic pulmonary disease who was with tachypnea and increased sputum production. The patient was enrolled and randomized to receive treatment with cefepime. The admitting chest X-ray had a questionable infiltrate; the chest X-ray on the second day was suggestive of congestive heart failure. The patient was admitted to the intensive care unit, but refused ventilatory support and extraordinary measures. The patient received treatment for seven days without improvement. He had an acute respiratory arrest on the eighth day. The autopsy demonstrated chronic obstructive pulmonary disease and bronchopneumonia.

The patient was a 69 year old man with a history of chronic pulmonary disease and cor pulmonale. He was admitted to the hospital for treatment of pneumonia and theophylline toxicity. He received two doses of cefepime. Seven hours after the second dose, the patient suffered a myocardial infarction and died.

The patient was a 78 year old woman with a history of cardiac disease and lymphoma who was

admitted to the hospital for treatment of pneumonia. One of the patient's cardiac anti-arrhythmic drugs was discontinued. The patient was found dead the following day. The investigator believed the cause of death was probably related to an arrhythmia. The patient had received only three doses of study drug.

The patient was a 72 year old man with a history of a recent abdominal aortic aneurysm repair. During hospitalization, the patient developed abnormal respiratory symptoms. A chest X-ray showed atelectasis and effusion. A diagnosis of pneumonia was made and the patient was enrolled in the study. The patient failed to improve. After three doses, the patient was switched to alternative therapy. He died 66 days after receiving his last dose of study drug. The causes of death were listed as vascular collapse secondary to pulmonary insufficiency, congestive heart failure, renal failure and possible "sepsis."

MEDICAL OFFICER'S COMMENTS:

The investigator, in his note, questions the possibility of neurotoxicity related to the drug. However, this phenomenon is not further explained and is not listed as an adverse reaction.

The patient was a 71 year old man with a history of many medical problems including interstitial lung disease who was admitted to the hospital for an unknown reason. During his admission, he developed symptoms of pneumonia. The patient was randomized to receive treatment with cefepime. The patient received a single dose of study drug, before the investigator chose alternative therapy. The patient died 14 days after the study drug was discontinued. The cause of death was respiratory failure related to the patient's underlying lung disease.

PNEUMONIA - CEFTAZIDIME- NORTH AMERICA - NONBLIND

The patient was an 83 year old woman with a history of multiple medical problems who had received erythromycin for her respiratory illness. She was admitted to the hospital with bilateral pulmonary infiltrated on chest X-ray. She was randomized to receive treatment with ceftazidime. Three days after treatment was started, the patient deteriorated and required mechanical ventilation. A blood culture was positive for *Bacteroides* species. Study drug was discontinued and the patient was placed on alternative therapy. The patient developed further pulmonary congestion, hypotension, bradycardia and expired. She died of "sepsis" six days after study drug was discontinued.

The patient was a 58 year old man with chronic pulmonary disease who underwent a thoracotomy for an unknown reason and was treated perioperatively with ampicillin-clavulanate. He developed symptoms of a lower respiratory tract infection six days post-operatively. The patient was placed on study drug and treated for eight days. Improvement was seen. The patient developed a gastrointestinal bleeding site. The patient had a biopsy of the chest for an unknown reason. Later that afternoon, he became hypotensive and died. The cause of death was unknown. No autopsy was

performed.

The patient was a 72 year old man with multiple medical problems who was admitted for treatment of bilateral pneumonia. Therapy was started with ampicillin-clavulanate and erythromycin. The patient was switched to study drug. The patient remained tachypneic; but, sputum production was reduced. The patient developed bradycardia and died on the seventh day of therapy. The investigator believed that the cause of death was underlying pulmonary disease.

The patient was a 76 year old man with a history of progressive pulmonary fibrosis who was admitted for treatment of a right lower lobe pneumonia and a urinary tract infection. The patient was enrolled in the study and received treatment with ceftazidime. The patient responded well and was discharged from the hospital. The patient was readmitted and died shortly thereafter of respiratory failure secondary to his underlying disease. The patient died eight days after therapy was discontinued.

The patient was a 69 year old man who was admitted for chest pain and vomiting. An infiltrate was seen on the admission chest X-ray and thought to be an aspiration of blood. The patient was enrolled and received two doses of study drug. He developed increasing respiratory distress which required mechanical ventilation. At the time of intubation, bright red blood appeared. The patient deteriorated and died of cardiogenic shock. No autopsy was performed.

The patient was a 74 year old black women who was admitted for treatment of aspiration pneumonia. She received multiple antibiotics during her hospitalization. During the hospitalization, a gram negative pneumonia was diagnosed and the patient was enrolled in the study. The patient appeared to have some improvement. However, she developed an ileus and the investigator chose to discontinue the patient from the study. The ileus was thought to be due to the patient's ischemic bowel disease. Alternative anti-microbial therapy was given. The patient died 31 days after study drug was discontinued. The cause of death was listed as pneumonia and renal failure.

The patient was a 50 year old black man with a history of a recent cerebrovascular accident that was admitted to the hospital for the treatment of an acute pneumonia. He was enrolled in the study and received three doses of study drug; the following day he was found pulseless and unresponsive.

The patient was a 56 year old man with a history metastatic large cell carcinoma was admitted for treatment of an upper intestinal bleeding mass. The gastric mucosa was perforated and communicated with a large abdominal mass. During the treatment for this condition, the patient developed signs and symptoms consistent with pneumonia. He was placed on study drug and treated for eight days. The patient was thought to have a positive response. Therapy was discontinued. Subsequently, the patient received radiation therapy for the abdominal mass. One week after the study drug was

discontinued, the patient became tachypneic and died.

PNEUMONIA - CEFEPIME - NORTH AMERICA - BLIND

The patient was a 86 year old diabetic white man with a history of significant heart disease who was admitted for treatment of pneumonia. The patient was receiving treatment with an oral cephalosporin. He was enrolled in the trial and cefepime was administered. In addition, the treatment with the oral antimicrobial drug continued. On the second day of treatment, the patient had a cardiac arrest and was successfully resuscitated. The study drug was discontinued and the patient received therapy with cefuroxime and ceftazidime. The patient deteriorated due to the fractured ribs and poor inspiratory

effort. Extraordinary measures were withdrawn; the patient died of respiratory failure 14 days after study drug was discontinued.

The patient was a 39 year old man with a history of nasopharyngeal carcinoma who was admitted to the hospital with intractable pain, malnutrition and a pulmonary infiltrate. Although the patient was afebrile and the cultures negative, the patient was enrolled in the clinical trial. A bronchoscopy was performed and tumor was demonstrated in the left bronchus. The patient became febrile that evening. Study drug was discontinued and alternative antibiotic drugs were selected. Heroic medical measures were withdrawn. The patient continued to have episodes of dyspnea. He expired of his underlying condition five days after study drug was discontinued.

The patient was a 63 year old woman who was admitted with bilateral upper lobe pneumonia. The patient was enrolled in the study. One day after enrollment, the patient's condition deteriorated such that she required mechanical intervention. The chest X-ray had worsened as well. The investigator decided to terminate the study drug and placed the patient on conventional antibiotic therapy. The patient died of respiratory failure three days after study drug was discontinued.

PNEUMONIA - CEFTAZIDIME- NORTH AMERICA - BLIND

The patient was a 76 year old white woman with chronic lung disease who was admitted for intractable vomiting and dehydration. She underwent a surgical correction of a small bowel obstruction. Perioperatively, the patient developed signs and symptoms consistent with pneumonia. The patient was enrolled on the study drug. She suffered a middle cerebral infarct the day following study entry. Her study medication was discontinued by the investigator the following day. The patient expired two days after the stroke.

The patient was a 62 year old man who was admitted to the hospital for treatment of pneumonia. He was entered into the study. Two days after entry, the patient had a sudden cardiac arrest. The investigator believed the death was the result of a pulmonary embolism.

The patient was a 51 year old white man with multiple medical problems including alcoholism, laryngeal carcinoma and renal failure who was admitted to the hospital for treatment of pneumonia. The patient had received treatment for 10 days prior to admission with penicillin. The patient was enrolled in the study. *Legionella pneumophila* was identified after the second day of therapy. The study drug was discontinued and treatment with erythromycin was instituted. However, the patient's condition had deteriorated and required mechanical ventilatory assistance. Further investigation of the patient revealed cells consistent with squamous cell carcinoma in the pleural fluid. The patient continued to deteriorate and died 13 days after study drug was discontinued.

PNEUMONIA - CEFEPIME - EUROPE - NON-BLIND

The patient was a 36 year old man who was admitted for treatment of pneumonia. He was randomized to receive treatment with cefepime. He received two doses of study drug. The patient deteriorated rapidly. The investigator chose to switch to conventional antibiotic therapy. The patient died two days after therapy was discontinued.

The patient was a 76 year white man who was admitted to the hospital for an unknown reason. During the hospitalization, the patient developed pneumonia. The patient received treatment with cefepime for ten days and had clinical improvement. However, eleven days after treatment the patient again developed respiratory symptoms. He was subsequently treated with ceftazidime and tobramycin. The patient died 136 days after the study drug was discontinued.

The patient was a 64 year old woman with a history of tuberculosis who was admitted for treatment of pneumonia. She was initially treated with amoxicillin. After six days, the patient was enrolled in study and received an additional six days of treatment with cefepime. The patient did not improve. Antituberculous therapy was instituted. During the hospitalization, a diagnosis of thyroid carcinoma with pulmonary metastases was made. The patient died two days after study drug was discontinued.

The patient was an 82 year old white man with multiple medical problems who was admitted for treatment of pneumonia. The patient received treatment for 8 days with cefepime. Clinical improvement was noted. Therapy was discontinued, because the patient required alternative prophylactic antibiotics for surgical treatment of an aortic aneurysm. Post-surgery, the patient again developed signs and symptoms of pneumonia. She died 13 days after study drug was discontinued.

The patient was a 71 year old man who was admitted for treatment of pneumonia and bacteremia. He was enrolled in the study and received treatment with cefepime. Because the blood isolates were resistant to study drug and there was no clinical improvement, the patient was removed from the study. Alternative antibiotics were instituted; the patient continued to deteriorate clinically. He died 10 days after cefepime was discontinued.

The patient was a 62 year old man with a history of squamous cell carcinoma of the lung who was admitted with signs and symptoms consistent with pneumonia. He was randomized to receive treatment with cefepime. He received a course of study drug for thirteen days; therapy was discontinued due to a lack of clinical improvement. The patient died the day following discontinuation of study drug.

The patient was a 76 year old white man who was admitted for treatment of bronchopneumonia. The patient was randomized to receive treatment with cefepime. Therapy was discontinued after five days, because of the lack of clinical or radiological improvement. Alternative triple antibiotic therapy was instituted. The patient died eight days after study drug was discontinued. The investigator believed death was related to the patient's underlying malignancy.

PNEUMONIA - CEFTAZIDIME- EUROPE- NON-BLIND

The patient was a 79 year old white man with a history of multiple medical problems who was admitted for treatment of pneumonia. Treatment was instituted with ceftazidime. The patient did not clinically improve. An emergency bronchoscopy demonstrated an obstructing tumorous lesion. The patient died after three doses of study drug therapy, the result of the underlying malignancy.

The patient was an 88 year old man with multiple medical problems who was admitted for treatment of acute respiratory distress. The patient was diagnosed with pneumococcal pneumonia and bacteremia. Treatment with ceftazidime was instituted. The patient responded well. However, the patient's discharge was delayed due to a pathological fracture, a result of newly diagnosed multiple myeloma. He expired 32 days after study drug was discontinued from his underlying medical conditions.

The patient was an 81 year old white woman with pulmonary disease who was admitted for treatment of pneumonia. He was randomized to receive treatment with ceftazidime. She received nine doses of ceftazidime without clinical improvement. Sudden death occurred on the fourth day of therapy. An autopsy demonstrated that death was due to bronchopneumonia.

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Discontinuations due to an Adverse Event:**MEDICAL OFFICER'S COMMENTS:**

Much of the data that follows is derived directly from the applicant's study reports.

Of the 572 patients in study A1411-070 diagnosed with either pneumonia there were fourteen patients who discontinued therapy due to an adverse clinical event. Eleven (11/381 = 3%) of these patients were treated with cefepime and three (3/191 = 2%) were treated with ceftazidime as follows:

Non-Blinded - North America:**PNEUMONIA (N = 269)**

treated with cefepime	6/180 = 3%
treated with ceftazidime	1/89 = 1%

Blinded:**PNEUMONIA (N = 60)**

treated with cefepime	1/39 = 1%
treated with ceftazidime	1/21 = 1%

Non-Blinded - Europe:**PNEUMONIA (N = 122)**

treated with cefepime	3/83 = 4%
treated with ceftazidime	0/39 = 0%

Patients Who Discontinued Due to Adverse Clinical Events
All Patients Non-Blind North America
Study 411-070

Patient	Adverse Event ^a	Severity	Dose ^b (g)	Rel ^c	Outcome ^d
CEFEPIME					
	Delirium tremens*		5	Unk	
	Hypertension	Moderate	5	Not	T/R
	Congestive heart failure	Severe	9	Not	T/R
	Hypotension	Mild	10	Not	NT/R
	Headache	Moderate	5	Unk	T/R
	Nasal congestion	Mild	9	Unk	T/R
	Itching, extremities	Moderate	12	Not	NT/R
	Wheezing	Severe	1	Unk	NT/R
	Nausea	Moderate	3	Prob	T/S/R
	Vomiting	Moderate	3	Prob	T/S/R
	Flush	Mild	29	Unk	NT/R
	Urticaria	Mild	4	Prob	T/R
	Seizure(s)	Moderate	10	Not	T/H
CEFTAZIDIME					
	Fibrillation, atrial	Severe	2	Not	T/R
	Wheezing	Moderate	17	Unk	NT/R
	Shortness of breath	Moderate	17	Unk	NT/R

a Investigator's term.

b Total dose at onset.

c Rel = Relationship to study drug; Prob = probably related; Unk = of unknown relationship; Not = not related.

d Indicates outcome of adverse event, whether it was treated (T), not treated (NT), whether patient recovered (R), sequelae occurred (S), or patient experienced prolonged hospitalization (H).

e Severity and outcome were not recorded.

Patients Who Discontinued Due to Adverse Clinical Events
All Patients - North American Blinded
Study 411-070

Patient	Adverse Event ^a	Severity	Dose ^b	Rel ^c	Outcome ^d
CEFEPIME					
	Headache	Severe	5	Prob	T/R
CEFTAZIDIME					
	Lesions	Moderate	3	Prob	T/R
	Rash, maculo- papular	Moderate	3	Prob	T/R

a Investigator's term.

b Total number of doses at onset (includes both active and placebo).

c Rel = Relationship to study drug; Prob = probably related; Unk = of unknown relationship; Not = not related.

d Indicates outcome of adverse event, whether it was treated (T), not treated (NT), whether patient recovered (R), sequelae occurred (S), or patient experienced prolonged hospitalization (H).

Patients Who Discontinued Due to Adverse Clinical Events
All Patients
Study 411-070 Europe

Patient	Adverse Event ^a	Severity	Dose ^b	Rel ^c	Outcome ^d
CEFEPIME					
	Cutaneous Rash	Severe	5	Prob	R
	Cutaneous Intol.	Mild	8	Prob	R
	Headache	Severe	7	Prob	R

a Investigator's term.

b Total number of doses at onset (includes both active)

c Rel = Relationship to study drug; Prob = probably related; Unk = of unknown relationship; Not = not related.

d Indicates outcome of adverse event, whether it was treated (T), not treated (NT), whether patient recovered (R), sequelae occurred (S), or patient experienced prolonged hospitalization (H).

Discontinuation due to a Laboratory Event:

There were only two discontinuations due to an adverse laboratory event. Both patients were treated with cefepime (2/269 = 1%) in the open North American trial. They were as follows:

Treatment with cefepime was discontinued for Patient _____ when the investigator noted that the patient's pre-treatment liver function tests were elevated.

Treatment with cefepime was discontinued for Patient _____ when the investigator noted elevations in the patient's AST, alkaline phosphatase and creatinine. The patient's potassium was noted to have decreased. The investigator decided that the changes in potassium, alkaline phosphatase and creatinine were possibly related to cefepime administration.

Patients treated with ceftazidime in the open North American portion of the study did not have any patients who were discontinued due to abnormal laboratory results. This was also true for ALL patients in the blinded, North American and the non-blinded European portions of the study.

Discontinuations due to Local Tolerance of the infusion:

There was a single patient in the entire trial who discontinued treatment due to infusion intolerance. This patient, _____ was treated with cefepime. The infusion was discontinued due to tingling at the infusion site. The tingling disappeared after the infusion was stopped.

Local Tolerance:MEDICAL OFFICER'S COMMENTS:

Below is summary safety information with regard to the tolerance of study drug infusions and with regard to the appearance of adverse clinical events after treatment with study drug. The information on the following pages has been taken directly from the safety summaries of the APPLICANT's final study reports. The denominators in the safety data differ slightly from those given in the reviewer's text thusfar. The explanation may lie with the fact that the applicant enrolled patients with all types of _____ infections. Several of these patients had respiratory infections that were "other" than pneumonia. These patients were entered in the safety database, but were excluded from the pneumonia efficacy database.

In the North American, non-blinded portion of the study, tolerance at the infusion site was reported for 216 (216/225 = 96%) of the cefepime group. There were four reports of phlebitis, four reports of infiltration and one report of tingling (see above). Three patients had at least part of their therapy with cefepime administered intramuscularly and all tolerated the injection well. One hundred five of the ceftazidime (105/110 = 95%) of the patients tolerated the infusion well. There were three reports of infiltration, one of ecchymosis and one report of irritation in this group. Ceftazidime was not administered intramuscularly to any patient.

In the North American, blinded portion of the study, favorable tolerance at the infusion site was reported for 50 (50/65 = 77%) of the cefepime group. However, there were thirteen reports of infiltration, one report of phlebitis, one report of collapsed veins and two reports of knot/hematoma also reported in this group. In the ceftazidime group, twenty-eight (28/34 = 82%) patients tolerated the infusion well. Six patients had local intolerance at the infusion site; four had phlebitis and two had infiltration. No patients were treated intramuscularly.

In the European non-blinded portion of the study, ninety-two (92/97 = 95%) tolerated treatment with cefepime well. There were also three reports of phlebitis, two reports of infiltration and one report of lymphangitis in this group. Of the 49 patients who received ceftazidime 48 (48/49 = 98%) tolerated the infusion well. One patient developed phlebitis. No patients were treated intramuscularly.

ADVERSE CLINICAL EVENTS

MEDICAL OFFICER'S COMMENTS:

The next few pages catalogue the adverse clinical events reported by the patients in this study. They are tabulated by the applicant and grouped as follows: nonblinded, North American; blinded, North American; and non-blinded Europe.

North America - nonblind

Fifty-two (23%) of the 225 patients treated with cefepime experienced ACE compared to 25 (23%) of the 111 patients treated with ceftazidime.

Adverse Clinical Event Rates, by Body System
and Relationship to Study Drugs
All Patients North America - nonblind
Study 411-070

Body System/ Primary Term	----- Cefepime ----- N = 225 ^a				----- Ceftazidime ----- N = 111 ^b			
	<u>Relationship</u>				<u>Relationship</u>			
	Prob.	Unk.	Not	Total	Prob.	Unk.	Not	Total
Body as a Whole								
Accidental injury		1		1				
Asthenia		3		3				
Edema		1		1				
Drainage							1	1
Fever	1			1				
Headache		3	1	4		1	2	3
Lesion			1	1				
Pain		1		1				
Pain, arms		1		1				
Pain, arthritic		1		1				
Pain, facial		1		1				
Pain, foot (feet)			1	1				
Pain, shoulder(s)		1		1				
Pain, stump		1		1				
Sensation of heat			1	1				
Toxic reaction							1	1
CV System								
Atrial fibrillation							1	1
Bradycardia		1		1				
Cardiorespiratory arrest							1	1

Adverse Clinical Event Rates, by Body System
and Relationship to Study Drugs
All Patients North America - nonblind
Study 411-070

Body System/ Primary Term	----- Cefepime ----- N = 225 ^a				----- Ceftazidime ----- N = 111 ^b			
	<u>Relationship</u>				<u>Relationship</u>			
	Prob.	Unk.	Not	Total	Prob.	Unk.	Not	Total
CV System cont.								
Congestive heart failure			1	1				
Hypertension			1	1				
Hypotension			1	1				
Pain, chest			1	1			3	3
Shock							1	1
Supraventricular tachycardia							1	1
Tachycardia		1		1				
Vasodilation		1		1				
Digestive System								
Bowel movement disorder			1	1				
Constipation	1			1		3	1	4
Diarrhea	2	4	1	7	1	1		2
Duodenal ulcer hemorrhage							1	1
Dyspepsia						1		1
Facal incontinence		1		1				
Flatulence			1	1				
Hematemesis			1	1				
Hemorrhage			1	1			1	1
Ileus							1	1
Jaundice							1	1
Melena		1		1				
Moniliasis, oral	1			1	1	1		2
Nausea	2	5	1	9 ^c		2	1	3
Pain, abdomen		2	2	5 ^c		1	3	4
Pain, mouth		1		1				
Rectal disorder		1		1				
Vomiting	1	4		5		2		2
Hemic and Lymphatic System								
Thrombocytopenia						1		1

Adverse Clinical Event Rates, by Body System
and Relationship to Study Drugs
All Patients North America - nonblind
Study 411-070

Body System/ Primary Term	----- Cefepime ----- N = 225 ^a				----- Ceftazidime ----- N = 111 ^b			
	<u>Relationship</u>				<u>Relationship</u>			
	Prob.	Unk.	Not	Total	Prob.	Unk.	Not	Total
Metabolic and Nutrition Disorders								
Edema		1		1			1	1
Musculoskeletal System								
Myalgia			1	1				
Nervous System								
Agitation			2	2			1	1
Anxiety		1	3	4			2	2
Confusion	1	1		2			2	2
Convulsion			1	1				
Delirium		1	1	2				
Depression			1	1				
Dizziness		1		1			1	1
Insomnia		1	1	2			1	1
Nervousness						1		1
Paresthesia	2			2				
Respiratory System								
Apnea			3	3			2	2
Aspiration			1	1				
Asthma		1		1		1		1
Dyspnea		1		1		1		1
Edema						1		1
Epistaxis							1	1
Pain, throat		1	1	2				
Rhinitis		1		1				
Skin & Appendages								
Blister(s)							1	1
Pruritus			2	2	1			1
Rash	1	1		2				
Urticaria	1			1				
Special Senses								
Blurred Vision		1		1				

Adverse Clinical Event Rates, by Body System
and Relationship to Study Drugs
All Patients North America - nonblind
Study 411-070

Body System/ Primary Term	----- Cefepime ----- N = 225 ^a				----- Ceftazidime ----- N = 111 ^b			
	<u>Relationship</u>				<u>Relationship</u>			
	Prob.	Unk.	Not	Total	Prob.	Unk.	Not	Total
Urogenital System								
Hematuria		1		1				
Urinary incontinence		1		1				
Urinary obstruction		1		1				
Total	13	51	33	99	4	16	32	52

- a Fifty-two (23%) cefepime patients reported ACE.
 - b Twenty-five (23%) ceftazidime patients reported ACE.
 - c The relationship of ACE to study drug was not recorded for 1 patient.
- NOTE: Prob. = Probably related to study drug; Not = Not related;
Unk. = Unknown relationship.

North America - blind

Thirty-two (49%) of the 65 patients treated with cefepime experienced adverse clinical events compared to 18 (53%) of the 34 patients treated with ceftazidime.

Adverse Clinical Events, by Body System
and Relationship to Study Drugs
All Patients
Study 411-070 North America - blind

Body System ACE	----- Cefepime ----- N = 65 ^a				----- Ceftazidime ----- N = 34 ^b			
	<u>Relationship</u>				<u>Relationship</u>			
	Prob.	Unk.	Not	Total	Prob.	Unk.	Not	Total
Body as a Whole								
Asthenia		4		4			1	1
Chest pain						1		1
Headache	1	2	2	5		1	1	2
Lesion					1			1
Malaise						1		1
Pain		2		2				
Pain, back		1	1	2				
Pain, hip(s)		1		1				

Adverse Clinical Events, by Body System
and Relationship to Study Drugs
All Patients
Study 411-070 North America - blind

Body System ACE	----- Cefepime ----- N = 65 ^a				----- Ceftazidime ----- N = 34 ^a			
	<u>Relationship</u>				<u>Relationship</u>			
	Prob.	Unk.	Not	Total	Prob.	Unk.	Not	Total
Body as a Whole cont.								
Pain, joints							1	1
Pain, neck					1			1
CV System								
Arrhythmia	1		1	2		1		1
Atrial fibrillation			1	1				
Cardiovascular disorder			1	1				
Cerebrovascular accident							1	1
Chest pressure	1			1				
Heart arrest			1	1				
Hypotension			1	1				
Pain, chest	2		1	3				
Pulmonary embolus							1	1
Syncope	1			1				
Tachycardia	1			1				
Digestive System								
Anorexia	2			2				
Constipation	3		1	4		1		1
Diarrhea						2	1	3
Dyspepsia			1	1		1		1
Flatulence							1	1
Hemorrhage			2	2				
Ileus			1	1				
Lesion			1	1				
Nausea	5		2	7			1	1
Pain, abdomen	1		1	2		2		2
Pain, mouth			1	1				
Pseudomembranous colitis						1		1
Vomiting	2		1	3			1	1
Hemic and Lymphatic System								
Contusion							1	1
Ecchymosis	1			1				

Adverse Clinical Events, by Body System
and Relationship to Study Drugs
All Patients
Study 411-070 North America - blind

Body System ACE	----- Cefepime ----- N = 65 ^a				----- Ceftazidime ----- N = 34 ^a			
	<u>Relationship</u>				<u>Relationship</u>			
	Prob.	Unk.	Not	Total	Prob.	Unk.	Not	Total
Metabolic and Nutrition Disorders								
Edema		1		1			1	1
Musculoskeletal System								
Fracture			1	1				
Myalgia							1	1
Nervous System								
Anxiety	1	5		6	1			1
Confusion		1	1	2	1	1		2
Depersonalization			1	1				
Dizziness		1	1	2				
Drowsiness			1	1				
Emotional lability		1		1				
Hallucinations			1	1				
Insomnia		1		1				
Somnolence			1	1				
Speech disorder		1		1				
Respiratory System								
Apnea			1	1				
Dyspnea			1	1				
Epistaxis			1	1				
Hyperventilation		1		1				
Pneumonia						1		1
Skin and Appendages								
Blisther(s)						1		1
Erythema						1		1
Rash	1	2		3	1			1
Saborrhea			1	1				
Sweating			1	1				
Urogenital System								
Breast Pain			1	1				
Pain, genitourinary	—	—	1	1	—	—	—	—
Total	3	44	34	81	3	16	13	32

a Thirty-two (49%) cefepime patients and 18 (53%) ceftazidime patients reported ACE.

NOTE: Prob. = Probably related to study drug; Not = Not related;
Unk. = Unknown relationship.

Europe - nonblind

Six (6%) of the 97 European patients who were treated with cefepime experienced 8 adverse events and two (4%) of the 49 ceftazidime patients experienced 2 adverse events.

Adverse Clinical Events, by Body System,
Relationship to Study Drug and Treatment Group
All Patients Europe - nonblind
Study 411-070

Body System/	Relationship to Cefepime				Relationship to Ceftazidime			
	Prob.	No	Unk.	Total	Prob.	No	Unk.	Total
<u>Body as a whole</u>								
Headache	1	0	0	1	0	0	0	0
Cutaneous Intolerance	1	0	0	1	0	0	0	0
<u>Digestive System</u>								
Diarrhea	0	0	0	0	1	0	0	1
Hepatic Disorder	1	0	0	1	0	0	0	0
Nausea	1	0	0	1	0	0	0	0
Vomiting	1	0	0	1	0	0	0	0
<u>Skin & Appendages</u>								
Rash, Cutaneous	2	0	0	2	0	0	0	0
Eruption	0	1	0	1	0	0	0	0
Toxicoderma	0	0	0	0	1	0	0	1
TOTAL	7	1	0	8	2	0	0	2

NOTE: Prob. = Probably related to Study Drug ; No = Not related ;
Unk. = Unknown relationship.

LABORATORY INFORMATIONMEDICAL OFFICER'S COMMENTS:

The following laboratory safety information was provided by the applicant. It is again divided into the three subgroups.

During- or Post-Treatment Laboratory Test Abnormalities
for Patients with A Normal Pretreatment Value
Study 411-070 North America - Non-blind

Laboratory Test	Number (%) Patients					
	Cefepime			Ceftazidime		
	N ^a	Abnormal ^b	Cl. Rel. ^c	N ^a	Abnormal ^b	Cl. Rel. ^c
HEMATOLOGY						
Hematocrit	100	53 (53)	1 (1)	52	24 (46)	2 (4)
Platelet ct.	178	2 (1)	0	96	6 (6)	0
WBC	191	7 (4)	0	100	4 (4)	0
Neutrophil ct.	171	6 (4)	0	89	3 (3)	0
Eosinophil ct.	164	19 (11)	2 (1)	87	10 (11)	0
COAGULATION						
Prothrombin	139	10 (7)	4 (3)	66	2 (3)	0
PTT	137	11 (8)	3 (2)	65	4 (7)	1 (2)
LIVER FUNCTION						
Alkaline phosphatase	118	22 (19)	0	51	9 (18)	1 (2)
AST (SGOT)	133	29 (22)	3 (2)	57	11 (20)	2 (4)
ALT (SGPT)	134	28 (21)	5 (4)	52	8 (15)	0
Total bilirubin	144	5 (4)	1 (1)	71	1 (1)	1 (1)
RENAL FUNCTION						
BUN	165	29 (18)	0	76	9 (12)	1 (1)
Creatinine	167	6 (4)	0	85	3 (4)	0
ELECTROLYTES						
Na ⁺	124			64		
Decrease		20 (16)	0		16 (25)	0
Increase		5 (4)	0		4 (6)	0
K ⁺	161			78		
Decrease		18 (11)	0		10 (13)	0
Increase		20 (13)	1 (1)		12 (15)	0
Ca ⁺⁺	91			44		
Decrease		28 (31)	0		16 (36)	0
Increase		1 (1)	0		0	0
PO ₄ ⁻³	105			45		
Decrease		21 (20)	6 (6)		6 (13)	0
Increase		10 (10)	0		5 (11)	0

a N indicates number of patients tested.

b During- or post-treatment results outside the investigator's normal range limit in the direction of toxicity.

c Patients Clinically Relevant values are included in the "Abnormal" column

During or Post-Treatment Laboratory Test Abnormalities
for Patients with An Abnormal Pretreatment Value
Study 411-070 North America - Non-blind

Laboratory Test	Number (%) Patients					
	Cefepime			Ceftazidime		
	N ^a	Worsened ^b	Cl. Rel. ^c	N ^a	Worsened ^b	Cl. Rel. ^c
HEMATOLOGY						
Hematocrit	96	9 (9)	2 (2)	49	11 (22)	2 (4)
Platelet ct.	13	2 (15)	0	5	1 (20)	0
WBC	5	1 (20)	0	1	0	0
Neutrophil ct.	4	0	0	2	0	0
Eosinophil ct.	10	0	0	4	1 (25)	1 (25)
COAGULATION						
Prothrombin	21	1 (5)	1 (5)	12	0	0
PTT	21	2 (10)	2 (10)	10	0	0
LIVER FUNCTION						
Alkaline phosphatase	42	3 (7)	1 (2)	22	1 (5)	1 (5)
AST (SGOT)	34	4 (12)	2 (6)	21	4 (19)	2 (10)
ALT (SGPT)	19	3 (16)	0	9	3 (33)	2 (22)
Total bilirubin	20	1 (5)	0	7	2 (29)	1 (14)
RENAL FUNCTION						
BUN	26	2 (8)	1 (4)	18	4 (22)	3 (17)
Creatinine	23	0	0	9	0	0
ELECTROLYTES						
Na ⁺	67			33		
Decrease		1 (1)	0		0	0
Increase		1 (1)	1 (1)		0	0
K ⁺	29			18		
Decrease		1 (3)	0		0	0
Increase		1 (3)	0		1 (6)	0
Ca ⁺⁺	57			27		
Decrease		4 (7)	1 (2)		4 (15)	1 (4)
Increase		0	0		0	0
PO ₄ ⁻³	38			21		
Decrease		1 (3)	1 (3)		0	0
Increase		1 (3)	0		0	0

a N indicates the number of patients tested.

b During- or post-treatment as compared with pretreatment. Worsened indicates that the value changed to a worse class not simply that the absolute value changed.

c Clinically Relevant values are included in the "Worsened" column.

During- or Post-Treatment Laboratory Test Abnormalities
for Patients with A Normal Pretreatment Value
Study 411-070 North America - Blind

Laboratory Test	Number (%) Patients					
	Cefepime			Ceftazidime		
	N ^a	Abnormal ^b	Cl. Rel. ^c	N ^a	Abnormal ^b	Cl. Rel. ^c
HEMATOLOGY						
Hematocrit	32	16 (50)	0	19	9 (47)	0
Platelet ct.	53	0	0	27	0	0
WBC	57	3 (5)	0	28	2 (7)	0
Neutrophil ct.	51	1 (2)	0	28	3 (11)	0
Eosinophil ct.	51	5 (10)	1 (2)	28	4 (14)	0
COAGULATION						
Prothrombin	45	3 (7)	0	22	1 (5)	0
PTT	48	2 (4)	2 (4)	23	1 (4)	1 (4)
LIVER FUNCTION						
Alkaline phosphatase	46	1 (2)	0	22	0	0
AST (SGOT)	39	6 (15)	2 (5)	17	2 (12)	0
ALT (SGPT)	22	4 (18)	1 (5)	12	2 (17)	0
Total bilirubin	50	3 (6)	1 (2)	27	0	0
RENAL FUNCTION						
BUN	44	9 (20)	0	22	0	0
Creatinine	51	0	0	21	2 (10)	0
ELECTROLYTES						
Na ⁺	44					
Decrease		6 (14)	0	20	2 (10)	0
Increase		0	0	20	0	0
K ⁺	53					
Decrease		6 (11)	0	21	2 (10)	0
Increase		3 (6)	0	21	1 (5)	0
Ca ⁺⁺	29					
Decrease		11 (38)	0	16	3 (19)	0
Increase		0	0	16	0	0
PO ₄ ⁻³	33					
Decrease		4 (12)	0	16	2 (12)	1 (6)
Increase		1 (3)	0	16	3 (19)	0

a N indicates number of patients tested.

b During- or post-treatment results outside the investigator's normal range limit in the direction of toxicity.

c Patients with Clinically Relevant values are included in the "Abnormal" column.

During or Post-Treatment Laboratory Test Abnormalities
for Patients with An Abnormal Pretreatment Value
That Worsened in the Direction of Toxicity
Study 411-070 North America - Blind

Laboratory Test	----- Number (%) Patients -----					
	Cefepime			Ceftazidime		
	N ^a	Worsened ^b	Cl. Rel. ^c	N ^a	Worsened ^b	Cl. Rel. ^c
HEMATOLOGY						
Hematocrit	26	7 (27)	0	10	2 (20)	1 (10)
Platelet ct.	5	1 (20)	1 (20)	2	0	0
WBC	1	0	0	1	0	0
Neutrophil ct.	1	0	0			
Eosinophil ct.		0	0			
COAGULATION						
Prothrombin	9	0	0	4	0	0
PTT	6	0	0	2	0	0
LIVER FUNCTION						
Alkaline phosphatase	8	0	0	5	0	0
AST (SGOT)	16	1 (6)	1 (6)	10	2 (20)	2 (20)
ALT (SGPT)	5	0	0	2	0	0
Total bilirubin	5	0	0			
RENAL FUNCTION						
BUN	14	2 (14)	0	8	1 (13)	0
Creatinine	7	0	0	9	0	0
ELECTROLYTES						
Na ⁺	14					
Decrease		0	0	9	1 (11)	0
Increase		0	0	9	0	0
K ⁺	5					
Decrease		0	0	8	1 (13)	0
Increase		0	0	8	0	0
Ca ⁺⁺	13					
Decrease		0	0	8	3 (38)	1 (13)
Increase		0	0	8	0	0
PO ₄ ⁻³	9					
Decrease		1 (11)	1 (11)	7	1 (14)	0
Increase		0	0	7	0	0

a N indicates the number of patients tested.

b During- or post-treatment as compared with pretreatment. Worsened indicates that the value changed to a worse class

c Clinically Relevant values are included in the "Worsened" column.

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During or Post-treatment Laboratory Test Abnormalities
of Clinical Relevance,
for Patients with Normal Pre-treatment Values, by Treatment Group
All Patients
Study 411-070 Europe - Non-blind

Laboratory Test	----- Number (%) of Patients -----					
	Cefepime			Ceftazidime		
	N ^a	Abnormal Values	Clinically Relevant Abnormalities	N ^a	Abnormal Values	Clinically Relevant Abnormalities
<u>Hematology</u>						
Hematocrit	49	17 (34.7)	0	26	8 (30.8)	0
Platelet count	71	1 (1.4)	0	34	1 (2.9)	0
Leukocyte count	86	4 (4.7)	0	43	0	0
Neutrophil count ^b	67	6 (9.0)	0	38	4 (10.5)	0
Eosinophil count ^b	67	6 (9.0)	0	37	4 (10.8)	0
<u>Coagulation</u>						
Prothrombin ratio	73	0	0	31	2 (6.5)	0
PTT	59	3 (5.1)	0	25	4 (16.0)	0
Prothrombin time	2	0	0	0	0	0
<u>Renal Function</u>						
Creatinine	67	5 (7.5)	0	34	1 (2.9)	0
BUN	60	11 (18.3)	1 (1.7)	24	3 (12.5)	0
<u>Liver Function</u>						
ALT (SGPT)	63	15 (23.8)	2 (3.2)	29	6 (20.7)	0
AST (SGOT)	67	14 (20.9)	0	28	7 (25.0)	0
Alkaline phosphatase	67	5 (7.5)	0	33	4 (12.1)	0
Total bilirubin	62	2 (3.2)	0	25	2 (8.0)	0
<u>Electrolytes</u>						
Sodium	60	9 (15.0)	1 (1.7)	31	4 (12.9)	0
Potassium	57	21 (36.8)	0	37	9 (24.3)	1 (2.7)
Calcium	31	12 (38.7)	0	21	8 (38.1)	0
Phosphorus	44	8 (18.2)	1 (2.3)	26	6 (23.1)	1 (3.8)

^a Includes all patients with pre-treatment values within investigator's normal range limits and with at least one additional value obtained.

^b Calculated: WBC x (% neutrophils/100) or WBC x (eosinophils/100).

Overall Changes in Laboratory Test Values
for Patients with Abnormal Pre-treatment Values, by Treatment Group
All Patients
Study 411-070 Europe - Nonblind

Laboratory	----- Number (%) of Patients -----					
	Cefepime			Ceftazidime		
	N ^a	Results Improved or Same	Results Worsened	N ^a	Results Improved or Same	Results Worsened
<u>Hematology</u>						
Hematocrit	40	35 (88)	5 (13)	17	15 (88)	2 (12)
Leukocyte count	3	3 (100)	0	0	0	0
Neutrophil count ^b	1	1 (100)	0	0	0	0
Eosinophil count ^b	1	1 (100)	0	1	0	1 (100)
Platelet count	18	17 (94)	1 (6)	7	7 (100)	0
<u>Coagulation</u>						
Prothrombin ratio	11	11 (100)	0	5	5 (100)	0
PTT	20	20 (100)	0	12	12 (100)	0
<u>Renal Function</u>						
Creatinine	17	17 (100)	0	8	8 (100)	0
BUN	25	22 (88)	3 (12)	19	18 (95)	1 (5)
<u>Liver Function</u>						
ALT (SGPT)	19	11 (58)	8 (42)	10	4 (40)	6 (60)
AST (SGOT)	15	9 (60)	6 (40)	11	8 (73)	3 (27)
Alkaline phosphatase	10	8 (80)	2 (20)	5	5 (100)	0
Total bilirubin	12	10 (83)	2 (17)	12	11 (92)	1 (8)
<u>Electrolytes</u>						
Sodium	23	23 (100)	0	12	12 (100)	0
Potassium	26	25 (96)	1 (4)	6	6 (100)	0
Calcium	43	39 (91)	4 (9)	17	16 (94)	1 (6)
Phosphorus	17	15 (88)	2 (12)	7	7 (100)	0

^a Includes all patients with pre-treatment values outside investigator's normal range limits and with at least one additional value obtained.

^b Calculated: WBC x (% neutrophils/100) or WBC x (eosinophils/100).

Sensitivity of Pathogens to Study Drugs
All Patients Study 411-070 North America - Nonblind

Infection Type/ Pathogen	----- Number (%) of Pathogens -----							
	<u>Cefepime Sensitivity</u>				<u>Ceftazidime Sensitivity</u>			
	Susc.	Inter.	Res.	Total	Susc.	Inter.	Res.	Total
Strep. (Group A)	2			2	2			2
S. viridans	1			1	1			1
Strep. (Group F)	2			2	1		1	2
S. salivarius	1			1	1			1
Strep. (Group B)	2			2	2			2
S. mitis	2			2	2			2
S. aureus	9			9	7	2		9
S. pneumoniae	66			66	64	1	1	66
Pseudomonas sp.	1			1	1			1
P. aeruginosa	17	2	1	20	20			20
P. maltophilia			1	1	1			1
P. fluorescens	4			4	4			4
P. putida	2			2	2			2
E. coli	7			7	7			7
C. diversus	1			1	1			1
K. pneumoniae	14			14	14			14
K. ozaenae	1			1	1			1
K. oxytoca	6			6	6			6
E. cloacae	4			4	4			4
E. aerogenes	1			1	1			1
S. marcescens	4			4	4			4
P. mirabilis	5			5	5			5
M. morgani	1			1	1			1
Haemophilus sp. (p-)	1			1	1			1
H. influenzae	26			26	26			26
H. influenzae (p+)	9			9	9			9
H. influenzae (p-)	42			42	42			42
H. parainfluenzae	3		1	4	4			4
H. parainfluenzae (p-)	7			7	7			7
H. parahaemolyticus	2			2	2			2
A. xylosoxidans	1			1	1			1
Neisseria sp.	3			3	3			3
N. meningitidis	8			8	8			8
N. sicca	1			1	1			1
P. multocida	1			1	1			1
Acinetobacter sp.	1			1		1		1
A. anitratus			1	1		1		1
M. catarrhalis	4			4	4			4
M. catarrhalis (p+)	11			11	11			11
M. catarrhalis (p-)	2			2	2			2
B. bronchiseptica	1			1	1			1
Total	276	2	4	282	275	5	2	282
(Percent)	(98)	(<1)	(1)		(98)	(2)	(<1)	

* Pathogens were to be tested for sensitivity to each study drug.
NOTE: Susc. = susceptible; Inter. = intermediate; Res. = resistant.

Sensitivity of Pathogens to Study Drugs
All Patients
Study 411-070 North America - Blind

Infection Type/ Pathogen	----- Number of Pathogens*-----					
	<u>Cefepime Sensitivity</u>			<u>Ceftazidime Sensitivity</u>		
	Susc.	Res.	Total	Susc.	Res.	Total
LRTI						
<i>S. aureus</i>	3		3	3		3
<i>S. pneumoniae</i>	18		18	18		18
<i>Pseudomonas sp.</i>	1		1	1		1
<i>P. aeruginosa</i>	16		16	15	1	16
<i>P. maltophilia</i>	1		1	1		1
<i>P. fluorescens</i>	1		1	1		1
<i>E. coli</i>	4		4	4		4
<i>K. pneumoniae</i>	4		4	4		4
<i>K. oxytoca</i>	1		1	1		1
<i>E. cloacae</i>	3		3	3		3
<i>E. aerogenes</i>	1		1	1		1
<i>S. marcescens</i>	1		1	1		1
<i>M. morgani</i>	1		1	1		1
<i>H. influenzae</i>	9		9	9		9
<i>H. influenzae (p+)</i>	1		1	1		1
<i>H. influenzae (p-)</i>	7		7	7		7
<i>H. parainfluenzae</i>	1		1	1		1
<i>N. sicca</i>	1		1	1		1
<i>A. lwoffii</i>	2		2	2		2
<i>M. catarrhalis</i>	1		1	1		1
<i>M. catarrhalis (p+)</i>	<u>3</u>		<u>3</u>	<u>3</u>		<u>3</u>
Total	80		80	79	1	80
(Percent)	(100)		(100)	(99)	(1)	(100)

* Pathogens from both treatment groups were to be tested for sensitivity to each study drug.

NOTE: Susc. = susceptible; Res. = resistant.

Susceptibility of Initial Pathogen to Cefepime
All Patients
Study 411-070 Europe Non-blind

Organism	NUMBER (%) OF TESTED ISOLATES				
	Suscept.	Intermed	Resist.	ND	TOTAL
<i>C. diversus</i>				1	1
<i>Citrobacter sp.</i>	1 (100)				1
<i>Corynebacterium sp.</i>				1	1
<i>E. cloacae</i>				1	1
<i>E. coli</i>	5 (100)				5
<i>Eikenella sp.</i>	1 (100)				1
<i>H. influenzae</i>	22 (100)			1	23
<i>H. influenzae (beta-)</i>	8 (100)				8
<i>H. parainfluenzae</i>	4 (80)		1 (20)	1	6
<i>Haemophilus sp.</i>				1	1
<i>K. oxytoca</i>	2 (100)				2
<i>K. pneumoniae</i>				1	1
<i>Kluyvera sp.</i>	1 (100)				1
<i>M. catarrhalis</i>	3 (100)				3
<i>M. catarrhalis (beta+)</i>	4 (100)				4
<i>N. meningitidis</i>	2 (100)				2
<i>Neissera sp.</i>				2	2
<i>P. aeruginosa</i>			1 (100)		1
<i>P. mirabilis</i>	4 (100)			1	5
<i>P. rettgeri</i>				1	1
<i>P. vulgaris</i>	1 (100)				1
<i>S. aureus</i>	2 (50)		2 (50)		4
<i>S. pneumoniae</i>	47 (100)			8	55
<i>S. sanguis</i>	1 (100)				1
Strep. (alpha hemo.)				1	1
Strep. (Group B)	3 (100)				3
Strep. (Group D)			1 (100)		1
Strep. (Group F)	1 (100)				1
<i>Streptococcus sp.</i>				1	1
TOTAL	112 (96)	0	5 (4)	21	138

Pages 142-144

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PNEUMONIA

PROTOCOL A1411-097 All North American Investigators (NDA volume 1.182-206; 1.210-215)

TITLE: A Multi-Investigator Comparative Study of Cefepime and Ceftazidime in the Treatment of Serious Bacterial Infections.

MEDICAL OFFICER'S COMMENTS:

The following protocol description was excerpted from the applicant's study report (volumes 1.182, 1.210); the reviewer has made minor editorial changes. The protocol was designed to study patients with many infections; however, the discussion that follows will be limited to the infections included patients with pneumonia and occasionally other infections. For this review, pneumonia were analyzed separately for safety and efficacy; patients with other respiratory diagnoses were analyzed for safety only. It should also be noted that the protocol did not make any separate provisions to distinguish versus patients with pneumonia.

STUDY DESIGN:

This trial was an open, Phase III, Multi-Investigator, randomized Comparative Study of Cefepime and Ceftazidime in the Treatment of Serious Bacterial Infections. There were forty-two investigators that enrolled patients in this study; there were also three centers that conducted a blinded section of this study. There were nine amendments.

Inclusion Criteria:

1. Provide informed consent;
2. 18 years of age or older of any race;

Note: Women of childbearing potential had to have a negative pregnancy test result immediately prior to enrollment with the exception of patients who were taking oral contraceptives in the prescribed manner, patients who were post-menopausal or patients who had been surgically sterilized.

3. Had a proven or suspected infection caused by a pathogen(s) susceptible to both study drugs;
3. Had signs and symptoms consistent with a serious infection including multilobar pneumonias, hospital acquired pneumonia occurring in the intensive care setting, or parenchymal *Pseudomonas* infections.

Exclusion Criteria

1. Previous enrollment in the study;
2. History of a serious hypersensitivity reaction to a cephalosporin or penicillin antibiotic;
3. Pregnant and/or lactating women;
4. Anuric patients or those on hemo or peritoneal dialysis;
5. Granulocyte count of less than 500 mm³ or expected to become less than 500 mm³ as a result of underlying disease or cytotoxic therapy;
6. Treatment regimen likely to include other antimicrobial drugs during therapy with the study medication or during the post-treatment period;
7. Requirement for long-term (greater than 28 days - Amendment 5) antimicrobial therapy for treatment of clinical symptoms or eradication of the causative pathogen(s) (e.g. osteomyelitis, empyema, lung abscess);
8. Infection not yet established (e.g., antibiotic therapy for the initial management of extensive physical trauma);
9. Signs and symptoms of CNS infection;
10. Presence of medically significant disease or disorder which may have a bearing on the outcome on the study (e.g. because of the possibility of *Pneumocystis* infection, a patient who tests positive for HIV);
11. A very severe, life-threatening infection (patients with symptoms and signs of septic shock; patients with granulocytopenia secondary to infection rather than underlying disease or chemotherapy; or patients with organ failure of more than one organ system); or
12. Placed a "do not resuscitate (DNR)" or "No code" status.
13. Cystic fibrosis, empyema, lung abscess or pneumonia distal to obstructive carcinoma

Procedures and Observations

The table below lists the procedures and observations that were specified in the Protocol for infections.

Study Schedule
Study 411-097-ALL

Procedure	Pretreatment Within 48 hrs ^a	During Treatment Day 3-5	End of Treatment Day 0-4	Post- Treatment Day 5-14
Eligibility	X	-	-	-
Informed Consent	X	-	-	-
Medical History	X	-	-	-
Laboratory Tests	X	X ^c	X ^b	-
Physical Examination	X	X ^c	X ^c	-
Clinical Evaluation	X	X	X	X
Bacteriologic Tests	X ^d	X ^e	X ^e	X ^e
Chest X-ray	X ^f	X ^g	X ^h	-

a And after termination of any previous antimicrobial therapy.

b Laboratory tests were requested either at the post-treatment Day 0-4 evaluation or at the post-treatment Day 5-14 evaluation.

c Abbreviated physical examination.

d Two blood cultures were requested for each patient, as well as a culture from the infected site.

e If there is a source to culture.

f Chest X-rays were requested within 48 hours before or 24 hours after beginning treatment.

g During-treatment X-ray was requested if clinically indicated.

h End-of-treatment X-ray within 48 hours of completing treatment or at the end-of-treatment (post-treatment Day 0-4) evaluation was requested only for patients with pneumonia.

Pre-treatment Procedures

1. Within 48 hours before treatment began, a medical history was to be recorded and a physical examination completed.
2. Clinical signs and symptoms of infection were to be evaluated within 48 hours before beginning therapy and after any previous antimicrobial therapy.
3. Bacteriologic confirmation of the infection was to be made by a positive culture from the infected site(s) or blood within 72 hours prior to start of therapy (Day 1) and after the completion of any previous antimicrobial.

- * Two blood cultures were to be performed for all patients, as well as a culture of the infected site.

- a suctioned sputum specimen or a deep-cough, purulent, expectorated sputum sample was to be obtained.
- 4. Each pathogen was to be identified and tested for susceptibility to cefepime and ceftazidime by disc or minimum inhibitory concentration (MIC) methods.
- 5. A chest X-ray was to be done within 48 hours before or 24 hours after the beginning of treatment.
- 6. Laboratory studies were to be performed within 48 hours before treatment. The requested assessments were:

HEMATOLOGY

Hemoglobin
 Hematocrit
 White blood cell (WBC) count, total and differential
 Platelet count or estimate from smear
 Erythrocyte sedimentation rate
 Prothrombin time (PT)
 Partial thromboplastin time (PTT)
 Direct Coombs' test (added by Amendment 1)

SERUM CHEMISTRY

Aspartate aminotransferase (AST/SGOT)
 Alanine aminotransferase (ALT/SGPT)
 Total bilirubin
 Alkaline phosphatase
 Blood urea nitrogen (BUN)
 Creatinine
 Glucose
 Albumin (added by Amendment 1)
 Electrolytes (sodium, potassium, calcium, phosphorus)

URINALYSIS

Specific gravity
 pH
 Albumin
 Glucose
 Microscopic examination (WBC, RBC, casts, crystals, epithelial cells)

During Treatment Procedures

The following procedures were to be performed by investigators at least once during therapy:

1. An abbreviated physical examination was to be conducted on Day 3-5 of treatment.
2. Signs and symptoms of infection were to be assessed on Day 3-5.
3. A culture was to be prepared from an appropriate specimen obtained on Day 3-5. All pathogens from a positive culture were to be isolated and identified. The occurrence of a negative culture was to be recorded. If a specimen could not be obtained for culturing because sputum could not be produced, the attempt and date were to be noted on the case report form (CRF) with the statement "NO SOURCE TO CULTURE."

4. Chest X-rays were to be repeated as needed for patients with LRTI.
5. Laboratory tests were to be repeated on Day 3-5.

Post-Treatment Procedures

The procedures listed below were to be completed after the last dose of study drug and before any disallowed antimicrobial was given.

1. A physical examination was requested.
2. Clinical signs and symptoms of infection were to be evaluated on post-treatment Day 0-4 for all patients and again on Day 5-14.
3. Specimens for culture were to be obtained from all patients (if a suitable specimen source remained) on post-treatment Day 0-4 and again on post-treatment Day 5-14. Any pathogen cultured was to be identified and tested for susceptibility, then subcultured and sent to Bristol-Myers Squibb Company. The lack of a suitable specimen source was to be recorded with the statement "NO SOURCE TO CULTURE."
4. For any patient with a confirmed diagnosis of pneumonia, a chest X-ray was to be done within 48 hours of completing treatment or at the end-of-treatment Day 0-4 evaluation.
5. Laboratory assessments listed were to be repeated either at the Day 0-4 evaluation or at the Day 5-14 evaluation. Laboratory tests were to be repeated as appropriate when results were abnormal.

Treatment-Group Assignment

This study was designed as an open, randomized, comparative clinical study. At each study location, patients were randomly assigned to receive one of the two treatments in a 1:1 (cefepime:ceftazidime) ratio.

Drug Information and Dose Selection

Cefepime was supplied by Bristol-Myers Squibb Company in vials containing 1 g or 500 mg of a dry-powder blend of cefepime dihydrochloride and L-arginine. Ceftazidime was supplied by Bristol-Myers Squibb in vials containing 1 g or 500 mg of ceftazidime in a dry powder.

Investigators were to administer cefepime or ceftazidime by intravenous infusion over a period of 30 minutes, with repeat dosing every 12 hours (2 g Q12h) for cefepime and every 8 hours (2 g Q8h) for ceftazidime for up to 28 days (Amendment 5 specified 28 days; original Protocol specified 14 days). Cefepime patients with renal impairment had doses adjusted (Amendment 4) as follows:

<u>Creatinine Clearance</u>	<u>Cefepime Regimen</u>
> 50 ml/min	2 g Q12h
31-50 ml/min	2 g Q12h
11-30 ml/min	2 g Q24h

Ceftazidime patients with renal impairment received doses of 2 g Q12h, 2 g Q24h, or 1 g Q24h, depending on their rate of creatinine clearance (added by Amendment 4).

For administration in the blinded studies, the first dose was to be active drug. For Study Center I-042, each patient assigned to cefepime was to receive two daily doses of 2 g administered every 12 hours and four daily doses of placebo (sterile saline solution) administered at 4, 8, 16, and 20 hours after the initial daily dose of cefepime. Each patient assigned to receive ceftazidime was to receive three daily doses of 2 g administered every eight hours and three daily doses of placebo administered at 4, 12, and 20 hours after the initial daily dose of ceftazidime. For Study Centers I-056, each patient assigned to cefepime was to receive two daily doses of 2 g administered every 12 hours and two daily doses of placebo (sterile saline solution) administered at 8 and 16 hours after the initial daily dose of cefepime. Each patient assigned to receive ceftazidime was to receive three daily doses of 2 g administered every eight hours and one daily dose of placebo (sterile saline solution) administered 12 hours after the initial daily dose of ceftazidime.

Blinding

This was an open study, except for Centers 042 and 056, which were blinded.

Microbiology Assessments

Bacterial isolates were tested for susceptibility to cefepime and ceftazidime by disc sensitivity or MIC method. Based on the disc sensitivity method, isolates were defined as susceptible if the zone diameter was 18 mm or greater, resistant if the zone diameter was 14 mm or less, and intermediate if the zone diameter was 15 mm to 17 mm. Based on results of MIC testing, isolates were defined as susceptible if the MIC was 8 mcg/ml or less, resistant if the MIC was 32 mcg/ml or greater, and intermediate if the MIC was 16 mcg/ml.

New Infection

According to the applicant, a new infection occurred if a different pathogen was cultured from the original infection site after the pre-treatment culture. Patients were also considered to have a new infection if either the original pathogen or a new pathogen caused an infection at a body site unrelated to the original site of infection. New infections were diagnosed based on the culture results; associated clinical signs and symptoms were not necessarily present. However, patients also could have a new infection diagnosed solely on the basis of clinical signs and symptoms.

Concomitant Therapy

The Protocol allowed medications, except for antimicrobial agents, to be administered as indicated to enrolled patients, and their use was to be recorded on the CRF. Antimicrobial therapy other than study drug was not allowed during the study and in the post-treatment follow-up period.

MEDICAL OFFICER'S COMMENTS:

The provision of allowing anti-infective drugs was modified retrospectively by the applicant in practice. They allowed a concomitant antimicrobial drug provided the "agent had no known activity against the genus of organism involved in the original infection." The reviewer believes that there was often insufficient information to identify the "true" pathogen; therefore antibacterial agents of any type were not permitted in the evaluable reviewer population. In rare instances, anti-infectives such as amphotericin or acyclovir were permitted.

Applicant Criteria for Evaluability

A patient was considered evaluable for efficacy only if the following criteria were met:

1. was diagnosed on clinical grounds and confirmed by a positive pretreatment culture.
2. The pretreatment clinical evaluation and bacteriologic culture were performed within 72 hours before treatment began and after termination of any prior antimicrobial therapy. For patients in the noncomparative arm of the study, the pretreatment clinical and bacteriologic evaluations were repeated after the last dose of ceftazidime and before the first dose of cefepime.

MEDICAL OFFICER'S COMMENTS:

The patients in the non-comparative arm were not identified in the applicant's patient profiles or the CANDA. They were also not discussed as a separate population in the study reports.

3. Any pathogen isolated in the pretreatment culture was identified and tested for susceptibility to cefepime and ceftazidime.
4. Pathogens had to be susceptible to both drugs.
5. During-treatment clinical and bacteriologic evaluations were not required for evaluability.

MEDICAL OFFICER'S COMMENTS:

This is a significant modification of the Protocol requirement.

6. Post-treatment clinical follow-up was conducted post-treatment Day 5-14.
7. Post-treatment culture was obtained post-treatment Day 3-14, if a suitable specimen source remained (the Protocol specified post-treatment Day 5-14).
8. Patients with a diagnosis of pneumonia or bronchitis had a pretreatment chest X-ray within 72 hours before (the original Protocol specified 48 hours before) or 24 hours after therapy began. Patients with pneumonia had a post-treatment chest X-ray on post-treatment Day 1-14 (the original Protocol specified a chest X-ray within 48 hours after completion of treatment or at the post-treatment evaluation). A during-treatment X-ray was also accepted if the patient had no post-treatment X-ray. NOTE: A few patients had clinical signs and symptoms of pneumonia, and pneumonia was diagnosed by the investigator even though the pretreatment chest X-ray did not confirm this diagnosis; if all other evaluability criteria were met, these patients were considered evaluable.

MEDICAL OFFICER'S COMMENTS:

This is a significant change in the Protocol requirement. The chest X-ray was supposed to be done 48 hours prior to or 24 hours after the patient was enrolled. The follow-up chest X-ray was to be completed post therapy, either at the end-of-treatment (10-14 days) or at the follow-up (15-14 days) visit. The modification was made retrospectively, at the time of the analysis.

9. After the pretreatment clinical assessment and culture, no concomitant systemic antimicrobial agent (that, according to official labeling in the 1990 PDR, had activity against the genus of pathogen being treated) was allowed before the post-treatment clinical and bacteriologic

assessments.

10. Cefepime and ceftazidime were administered intravenously at the dose, frequency, and duration specified in the appropriate Protocol or amendment; a minimum of 7 doses was received within a 96-hour period for Q12h administration, 4 consecutive doses for Q24h administration, or 11 doses within 96 hours for Q8h administration.

MEDICAL OFFICER'S COMMENTS:

The reviewer disagrees with the Protocol's request for a minimum number of doses (7 - cefepime; 11 - ceftazidime) required for efficacy. In general, a parenteral product is targeted primarily at the more severely ill patient. Therefore, a minimum of five days of therapy should be required; this concurs with the IDSA guideline of treatment for an evaluable patient with pneumonia/bronchitis.

11. Patients whose treatment was declared a clinical failure (unsatisfactory response to study drug) or a bacteriologic failure (pathogen persisted) and who had at least one reason for exclusion from the efficacy analyses were to be considered evaluable for efficacy, if the failure preceded the reason for exclusion.

Applicant Efficacy Criteria Definitions

Clinical Response

Satisfactory: All signs and symptoms of the infection that were present before therapy were improved or resolved, and no new signs or symptoms of the infection were present at the post-treatment follow-up.

Unsatisfactory: One or more signs or symptoms of the infection persisted or increased, or one or more new signs or symptoms of the infection were evident at the post-treatment follow-up.

Undetermined: All cases where a response could not be determined (e.g., no follow-up evaluation).

Bacteriologic Response

Eradicated: The pathogen was not present in the post-treatment culture; or, there was no suitable specimen source.

Persisted: The continued presence of the pathogen in the post-treatment culture.

Undetermined: The response could not be determined (e.g., no follow-up evaluation).

MEDICAL OFFICER'S COMMENTS:

To be strictly evaluable by the reviewer, a patient had to have.

1. met the inclusion and exclusion criteria defined by the applicant.
2. at least two signs and/or symptoms consistent with a infection. Pneumonia was differentiated from by the presence of an infiltrate on chest X-ray.

NOTE:

a. To support the observed diagnosis, the investigator could document the presence of signs and symptoms from a list of pre-selected terms. They were as follows:

Fever	Chills
Chest Pain	Malaise
Cough	Letnergy
Sputum Production	Signs of Lung Consolidation by Auscultation
Rales	Pleural Effusion
Dyspnea	Tachypnea

b. Respiratory rates were not recorded for any patient. Sputum production was not characterized with regard to quantity, quality or relationship to baseline. In patients with chronic respiratory disease, a change in sputum production and/or cough was also not noted.

c. The IDSA states that leukocytosis and pyrexia should be present to support the diagnosis of a infection. In this indication, many patients were afebrile and without a significant elevation of the white count. The study was not designed to capture information with respect to chronic administration of steroids and/or the use of acetaminophen or aspirin products. Therefore, this information could not be used as diagnostic criteria.

d. For a reviewer to validate the diagnosis of a specific respiratory illness, certain minimal clinical and laboratory information is necessary. In some instances, this includes baseline respiratory conditions and/or recent medications. Other helpful supporting data are respiratory rates or arterial oxygen content. This study as others in this indication had limited information to precisely characterize the respiratory condition; however, there was sufficient data to determine that a pulmonary process was present. To the reviewer, the minimum clinical observations required to support the diagnosis of pneumonia were cough, sputum production, and/or abnormal auscultatory sounds.

3. a culture documented pathogen susceptible to cefepime and ceftazidime.

NOTE:

a. A gram stain was requested by the applicant. However, a written description was provided at the discretion of the investigator.

b. For the most part, the type of specimen was not identified, e.g. transtracheal aspirate, deep expectorated sputum, etc., nor was the quality described e.g. mucoid, voluminous, blood tinged, etc.

c. Those patients with a documented, valid gram stain and/or positive blood culture constituted the "strictly evaluable" reviewer population.

4. received 24 hours or less of pre-study antimicrobial drug with activity against the identified pathogen or a demonstration of a pathogen resistant to the pre-study antimicrobial drug.

NOTE:

The reviewer believes that this criterion is critical in this study; because treatment by applicant definition could be short (i.e. 3.5 days) and the influence of the pre-study antibiotic is unknown. Second, because validated gram stains were not a study requirement, sputum samples could not always differentiate between a colonizing organism and a true pathogen. The applicant did not address the issue of pre-study antimicrobials in their protocol or study report. The reviewer refers the reader to the published IDSA general guideline which states that: "Patients may be enrolled if they have received < 24 hours of treatment with a presumably effective anti-infective drug for an infectious process thought (on the basis of published reference material) to require a standard duration of therapy of ≥ 7 days." The only extenuating circumstances where a patient may exceed the suggested 24 hour limit of pre-study therapy are illnesses which require lengthy therapy e.g. osteomyelitis and endocarditis or patients infected with a pathogen resistant to the initial anti-infective drug and sensitive to the study drug. (pp. S17-18)

Exceptions to this requirement were those patients who had an acceptable interval (five half-lives) between the administration of alternative systemic antimicrobials and study drug.

5. received a minimum of 4.5 days of therapy (i.e. 9 doses of cefepime or 13 doses of ceftazidime) for success. This requirement is consistent with the general IDSA guidelines which recommends a minimum 5 days of therapy for pneumonia. (However, a patient could be classified as a failure after only five cefepime doses.)
6. received a maximum of 18 days therapy. (The protocol specified a 14 day course of therapy. The protocol was later amended to extend the length of therapy to 28 days.)
7. had neither concomitant nor post-study antimicrobial therapy with activity against the identified pathogen in excess of a single dose.
8. had the minimum of three clinical evaluations: pre-therapy visit, during therapy visit and the follow-up visit (5-21 days).

NOTE:

In instances when an in-person test-of cure visit was not possible: The reviewer accepted telephone follow-up information provided by the patient (not a third party, e.g. relative), because this mechanism was mutually accepted during the development program. However, the reviewer would like to state her opinion that this information is of dubious value. There was no standard questionnaire to provide consistent data collection and documentation of these telephone conversations. Therefore, each investigator could ask a different battery of questions.

9. had evidence of bacterial clearance ("sputum production resolved") or a statement with regard to "No source to culture" at the follow-up visit (5-21 days).
10. had a pre-treatment chest X-ray and a post-treatment (either end of treatment or follow-up) chest x-ray. The IDSA guideline recommends that: "A chest radiograph will be obtained 3 days after the initiation of therapy, within 72 hours of completion of therapy, and at any other time the investigator deems necessary." (p. S85) It should be noted that the post-treatment X-ray was a requirement in the original protocol.

Clinical Response:

Satisfactory: Improvement and/or resolution of all pre-treatment signs and symptoms diagnostic of pneumonia/ at the test of cure visit (5-21 days). The end of treatment/follow-up chest X-ray had to show either improvement or lack of progression of the pneumonic process.

Unsatisfactory: Persistence or worsening of any clinical signs or symptoms associated with pneumonia/bronchitis during treatment or at the time of the follow-up evaluation (5-21 days). The end of treatment/follow-up chest X-ray showed no improvement or worsening.

Unevaluable: Assessment of the clinical outcome could not be determined e.g. the patient did not return for follow-up evaluation.

Bacteriologic Response:

Eradication - Either the causative pathogen(s) was not isolated from the follow-up culture or there was a presumptive eradication because there was no material available for culture.

Persistence - The original pathogen(s) was isolated from the follow-up culture or the patient was a clinical failure with a presumed pathogen persistence.

Unevaluable - It was not possible to determine a bacteriological response, e.g. because the patient did not return for follow-up.

The reviewer conducted an assessment of the "strictly evaluable" population based on the criteria described above. However, the reviewer feels that the design of this study was severely deficient. Problematic areas were as follows:

- a. Inadequate gram stain assessments/documentation*
- b. The lack of description with respect to quality and quantity of sputum samples*
- c. The lack of description of the method in which a sputum sample was collected*
- d. The absence of characterization of "change" of described signs and symptoms from baseline (especially in the patient with chronic lung disease)*
- e. The lack of a gradation system with respect to the improvement of signs and symptoms*
- f. The lack of assessments with respect to pre-treatment antibiotics on selected patients*
- g. The absence of correlation with white blood cell counts (elevations and/or bacteremia) and temperature*
- h. The absence of definition and attempts to clarify the setting of the pneumonic processes for either pneumonia (i.e. not all pneumonias are alike.)*
- i. The absence of pre-determined format or questionnaire to gather telephone follow-up data*

Not unexpectedly, there were few "strictly evaluable" patients. However, a secondary analysis of a "clinically evaluable" patient population was conducted. The "clinically evaluable" population met all the criteria described above with the exception of the valid pathogen requirement. These patients fell into four categories: a) those patients with an inadequate gram stain, b) those patients whose organism did not have sensitivities done, c) those patients with an inadequate gram stain and a resistant organism and d) those patients in which no organism was isolated. Obviously, this population subset contained patients whose respiratory illness was viral/other and not necessarily bacterial in origin. The reviewer believes that the outcome results of this population are more reflective of the "real world" clinical situation and are more consistent with how the drug will perform when used empirically.

Safety Assessments

All patients who received one dose of cefepime or ceftazidime were evaluable for safety. All adverse clinical events were reported on the CRF along with the investigator's judgement of the relationship of the reaction to cefepime or ceftazidime. Also recorded were the date of onset, duration, and severity of each ACE, and any change in a patient's treatment. If serious or alarming adverse experience(s) occurred, investigators were to stop administering the drug and notify Bristol-Myers Squibb Company.

Investigators recorded on the CRF whether cefepime or ceftazidime was well or poorly tolerated at the infusion site. The occurrence of phlebitis, hematoma, infiltration or other conditions was noted.

Laboratory assessments were required before, during, and after treatment. In addition, a patient with abnormal laboratory results was to be retested until the values returned to approximately the baseline levels for that patient. Data from all study sites were reviewed and analyzed at Bristol-Myers Squibb.

For safety analyses, the laboratory tests listed below were selected as the most appropriate indicators of toxicity. To identify clinical abnormalities, "direction of toxicity" was defined for each of the selected tests as follows (clinically relevant levels are also provided for each unit):

Decrease below the lower limit of normal:

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Hematocrit :	< 24 vol%
Neutrophil :	≤ 500/cmm
WBC :	≤ 2000/cmm
Platelet :	≤ 50,000/cmm
Prothrombin Ratio :	< 50%

Increase above the upper limit of normal:

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Alkaline phosphatase :	≥ 3 x UNL
AST, ALT :	≥ 3 x UNL
Total Bilirubin :	≥ 3.0 mg/dL
BUN :	≥ 50.0 mg/dL
BUR :	≥ 100.0 mg/d
Creatinine :	≥ 3.0 mg/dL
Prothrombin Time :	> 25 sec.
PTT :	> 90 sec.
Eosinophil :	≥ 1000/cmm

Outside normal limits :

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Sodium :	≤ 119 or ≥ 160 mEq/dL
Potassium :	≤ 2.4 or ≥ 6.5 mEq/dL
Calcium :	≤ 7.0 or ≥ 12.0 mg/dL
Phosphorus :	≤ 1.7 or ≥ 6.1 mg/dL

Additional criteria were implemented in testing for neutropenia and eosinophilia.

The following definitions apply to laboratory values :

Abnormal : Outside the normal range limit in the direction of toxicity.

Normal : All other laboratory values were defined to be normal.

Standard conversion factors were applied as needed to both test results and normal range values in order to express data in units as in the table above so that the data could be grouped and analyzed by a minimal number of algorithms.

Discontinuations

The protocol stated that any of the following conditions could justify the early discontinuation of a patient from cefepime treatment. However, investigators sometimes continued therapy for patients who improved clinically.

1. No pathogen isolated from the pre-treatment culture.
2. *In vitro* testing revealed that the causative pathogen was resistant to cefepime or ceftazidime (MIC ≥ 32 mcg/mL; zone size ≤ 14 mm for 30 mcg disc).
3. A poor clinical response was evident after 72 hours of therapy.

4. A serious or alarming adverse event.
5. Intercurrent illness.
6. Patient's decision not to participate further.
7. Investigator's decision that it was in the best interest of the patient to discontinue cefepime treatment.
8. Administrative reasons.

Deaths and discontinuations are summarized at the end of this report.

RESULTS:

There were a total of 393 lower respiratory tract patients enrolled in this study which was conducted at multiple sites. The open comparative study was conducted from October 12, 1988 to October 23, 1991. There were two centers who enrolled patients in a blinded fashion from June 12, 1989 to June 20, 1991. Of these 393 patients, 361 (80 in the blinded study) were diagnosed with pneumonia and 32 (2 in the blinded study) were diagnosed with pneumonia. In addition, there was a single center 411-097-027 which enrolled three patients (1 cefepime and 2 ceftazidime) diagnosed with pneumonia. This center was disqualified by the applicant due to data inconsistencies. These patients are listed for completeness in the table below.

STUDY 097 PNEUMONIA PATIENTS^{1,2}
N = 281
NON-BLINDED

CTR	INVESTIG STATE	CEFEPIME				CEFTAZIDIME			
		ENROLLED	BMS EVALUABLE	MO CLIN EVALUABLE	MO STRICT EVALUABLE	ENROLLED	BMS EVALUABLE	MO CLIN EVALUABLE	MO STRICT EVALUABLE
		001	MUSHER/TX	8	5	6	0	5	2
004	YOUNG/KY	6	3	2	1	10	3	4	0
006	WLODAVER/OK	0	0	0	0	1	0	0	0
007	NEU/NY	1	1	1	0	1	1	0	0
008	SCHLOSSBERG/PA	7	1	0	0	3	1	2	0
010	RYTEL/WI	1	0	0	0	1	0	0	0
012	CHRISTOU/CN	6	3	1	0	8	3	4	1
013	MARKOWITZ/MI	1	0	0	0	2	0	1	0
014	JAUREGUI/OH	9	4	3	1	8	4	3	0
015	PALMER/NM	24	12	13	0	22	9	10	1
016	SARUBBI/TN	10	7	7	0	8	5	4	1
017	BOHNNEN/CN	3	0	0	0	4	0	0	0
020	CONE/CA	5	2	2	0	6	2	2	1
021	RIFF/IL	2	0	0	0	1	0	0	0
025	PALADINO/NY	9	1	1	0	7	3	4	1
026	LIU/PA	0	0	0	0	1	0	0	0
027	(GENTRY)*/TX	(1)	(1)	0	0	(2)	(1)	0	0
028	HOLLOWAY/DE	1	1	1	1	2	2	2	0

CTR	INVESTIG STATE	CEFEPIME				CEFTAZIDIME			
		ENROLLED	BMS EVALUABLE	MO CLIN EVALUABLE	MO STRICT EVALUABLE	ENROLLED	BMS EVALUABLE	MO CLIN EVALUABLE	MO STRICT EVALUABLE
029	SCHWARTZ/FL	8	5	4	1	7	4	3	1
030	SCHLECH/CH	2	0	2	0	3	1	1	0
032	JEMSEK/NC	3	1	0	0	3	0	0	0
033	LEFROCK/FL	1	0	0	0	2	2	1	0
036	SLAMA/IN	0	0	0	0	1	0	0	0
037	FARKAS/OH	2	1	0	0	4	2	0	0
038	PETERSON/IA	1	0	0	0	1	0	0	0
041	EVERETT/MO	6	0	4	1	4	1	2	0
043	ROTSTEIN/NY	3	1	1	1	4	0	1	0
049	PACHUKI/IL	3	0	0	0	1	0	0	0
052	GALLIS/NC	1	0	0	0	2	0	0	0
053	SMITH/MO	3	0	0	0	2	0	1	0
054	RAMIREZ-RONDA/PR	3	1	2	0	2	1	0	0
058	SHARIFI/IL	1	0	1	0	0	0	0	0
059	GAJNER/WV	1	0	0	0	0	0	0	0
061	NOVAK/IL	1	0	0	0	0	0	0	0
065	JACOBSON/OR	0	0	0	0	2	2	2	0
072	BAUGHMAN/OH	3	3	2	0	3	1	0	0
074	MYERS/NY	1	0	0	0	0	0	0	0
075	DAVIS/ND	0	0	0	0	1	0	1	0
077	JONES/OR	3	0	0	0	0	0	0	0
078	ALGOZZINE/FL	1	0	0	0	2	0	0	0
079	MO/TX	2	1	0	0	3	0	1	0
084	BEUTNER/CA	1	0	0	0	0	0	0	0
088	GREENMAN/FL	0	0	0	0	1	0	0	0
TOT AL		143+(1)	53+(1)	53	6	138+(2)	49+(1)	51	6

*CENTER 027 (and numbers in parentheses) was disqualified by the applicant as a result of data inconsistencies.

¹Clinically evaluable patients were those patients who were enrolled with a _____ infection, who did not have a valid pathogen, but who met all other reviewer evaluability criteria.

²The strictly evaluable population included those patients who were followed clinically and whose identified pathogen was microbiologically evaluable. These patients had either a good gram stain recorded (i.e. ≥ 25 PMNs and ≤ 10 epithelial cells under low power magnification) or had a positive blood culture.

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STUDY 097 PNEUMONIA PATIENTS^{1,2}

N = 80

BLINDED

CENTER	INVESTIG STATE	CEFEPIME				CEFTAZIDIME			
		ENROLLED	BMS EVALUABLE	MO CLIN EVALUABLE	MO STRICT EVALUABLE	ENROLLED	BMS EVALUABLE	MO CLIN EVALUABLE	MO STRICT EVALUABLE
042	LEVINE/MI	45	7	9	1	33	8	8	1
056	PALMER/NM	1	0	0	0	1	0	0	0
TOTAL		46	7	9	1	34	8	8	1

¹Clinically evaluable patients were those patients who were enrolled with a _____ infection, who did not have a valid pathogen, but who met all other reviewer evaluability criteria.

²The strictly evaluable population included those patients who were followed clinically and whose identified pathogen was microbiologically evaluable. These patients had either a good gram stain recorded (i.e. ≥ 25 PMNs and ≤ 10 epithelial cells under low power magnification) or had a positive blood culture.

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REASONS PATIENTS COULD BE CONSIDERED NON-EVALUABLE BY THE REVIEWER:

1. The patient did not have the minimally required three clinical evaluations: a) pre-therapy, b) during/end of therapy and c) post-therapy.
2. The isolated pathogen was resistant to study drug.
3. No pathogen was isolated. There was always an additional reason why a patient in this category was unevaluable or he/she is listed in parentheses as a patient considered for the clinically evaluable category.
4. There were antimicrobials administered for greater than twenty-four hours prior to study start. Usually there was insufficient information to determine whether the antimicrobial administered did not impact on the clinical and/or microbiological outcome of the infection.
5. Additional antimicrobial therapy was prescribed between the end of treatment and follow-up assessments.
6. The patient received concomitant antimicrobial therapy.
7. There was no follow-up assessment made at the test of cure visit (5-21 days post-therapy).
8. The patient did not receive the minimum number of doses required for an assessment of cure (9 doses) or failure (5 doses) for cefepime or cure (13 doses) or failure (8 doses).
9. Therapy exceeded 18 days.
10. The patient did not have either pneumonia Or, an initial chest X-ray was indicated and it was not performed.
11. A pathogen was isolated and identified. However, no sensitivity testing (no zone sizes or MICs) was completed.
12. The dosage of the study drug administered was other than 2g BID or renal equivalent dosing.
13. The patient was also receiving another investigational drug.
14. No end-of treatment or follow-up chest X-ray was performed. Radiological assessments were acceptable after end of treatment ($\pm$ 1 day).
15. There was either no gram stain available, an inadequate gram stain was recorded and/or a blood culture was negative.

The above lists the possible reasons a patient could be classified as non-evaluable. The tabulation below serves only an indicator of the reasons patients were excluded from the efficacy analysis. Many patients had more than one reason; however, only one reason per patient was listed.

HOW TO READ THE FOLLOWING TABLE:

The tables below are composites of two tables (reasons patients were not clinically evaluable and reasons patients were not strictly evaluable). The gray shaded area labelled "subtotal" is the number of patients who were not clinically evaluable. The gray shaded area labelled "total" is the number patients who were excluded from the strictly evaluable population. The patients in the parentheses are those patients whose only reason for being excluded from the strictly evaluable population was an inappropriate pathogen (i.e. no gram stain documentation, a resistant organism identified, no sensitivities done or no pathogen at all was isolated). For example, listed under no pathogen/pneumonia patients, what does "41 + (6)" mean? This means that 45 patients had no pathogen identified and were excluded from the strictly evaluable population. Of these 45, there were 4 patients who met all other evaluability save for an appropriate pathogen. The other 41 patients were not eligible for the clinically evaluable population, because they had a second reason (not identified here) that made them non-evaluable. For example: Often, when an investigator determined that a patient's culture was negative; the patient was removed from the study. Because the patient was not followed to study completion, the patient could not be considered clinically evaluable.

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**CLINICAL EFFICACY
NON-BLIND**

PNEUMONIA (N = 281)

CLINICAL RESPONSE	BHS		NO CLINICALLY EVAL		NO STRICTLY EVAL	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
SATISFACTORY	31 (58%)	31 (63%)	36 (64%)	31 (61%)	3 (50%)	5 (83%)
UNSATISFACTORY	22 (42%)	18 (37%)	19 (36%)	20 (39%)	3 (50%)	1 (17%)
UNEVALUABLE	90	89	90	87	137	132
TOTALS (N)	143	138	143	138	143	138

The BACTERIOLOGICAL responses for pneumonia based on patients that were strictly evaluable are as follows:

	CEFEPIME:	CEFTAZIDIME:
<u>E. coli</u>	0/1 (0%)	
<u>K. pneumoniae</u>	1/2 (50%)	
<u>S. haemolyticus</u>	0/1 (0%)	
<u>S. pneumoniae</u>	1/2 (50%)	5/6 (83%)
<u>Strep. (Group A)</u>	1/1 (100%)	

**CLINICAL EFFICACY
BLIND**

PNEUMONIA (N = 80)

CLINICAL RESPONSE	BMS		NO CLINICALLY EVAL		NO STRICTLY EVAL	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
SATISFACTORY	5 (71%)	7 (88%)	3 (33%)	4 (50%)	1 (100%)	0 (0%)
UNSATISFACTORY	2 (29%)	1 (13%)	6 (67%)	4 (50%)	0 (0%)	1 (100%)
UNEVALUABLE	39	26	37	26	45	33
TOTALS (N)	46	34	46	34	46	34

The BACTERIOLOGICAL responses for pneumonia based on patients that were strictly evaluable are as follows:

S. pneumoniae
P. aeruginosa

CEFEPIME
1/1 (100%)

CEFTAZIDIME
0/1 (0%)

**CLINICAL EFFICACY
COMBINED EFFICACY**

PNEUMONIA (N = 361)

CLINICAL RESPONSE	BMS		NO CLINICALLY EVAL		NO STRICTLY EVAL	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
DRUG						
SATISFACTORY	36 (60%)	38 (67%)	37 (60%)	35 (59%)	4 (57%)	5 (71%)
UNSATISFACTORY	24 (40%)	19 (33%)	25 (40%)	24 (41%)	3 (43%)	2 (29%)
UNEVALUABLE	129	115	127	113	182	165
TOTALS (N)	189	172	139	172	189	172

The following tables examine efficacy related to various demographic variable to determine if there are intrapopulation variables which would require labelling modifications.

CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
PNEUMONIA N = 281
NON-BLIND

VARIABLE	BMS		MO CLINICALLY EVAL.		MO STRICTLY EVAL	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
ALL	31/53 (58%)	31/49 (63%)	34/53 (64%)	31/51 (61%)	3/6 (50%)	5/6 (83%)
WOMEN	9/11 (82%)	9/16 (56%)	6/7 (86%)	11/15 (73%)	-	1/1 (100%)
MEN	22/42 (52%)	22/33 (67%)	28/46 (61%)	20/36 (56%)	3/6 (50%)	4/5 (80%)
WHITE	21/41 (51%)	27/43 (63%)	27/44 (61%)	25/42 (74%)	3/5 (60%)	3/4 (75%)
BLACK	6/8 (75%)	2/3 (67%)	5/7 (71%)	2/3 (67%)	0/1 (0%)	-
OTHER	4/4 (100%)	2/3 (67%)	2/2 (100%)	4/6 (67%)	-	2/2 (100%)
< 65 YEARS	13/24 (54%)	14/18 (78%)	13/24 (54%)	13/23 (57%)	3/4 (75%)	4/5 (80%)
> 65 YEARS	18/29 (62%)	17/31 (55%)	21/29 (72%)	18/28 (64%)	0/2 (0%)	1/1 (100%)

The following tables examine efficacy related to various demographic variable to determine if there are intrapopulation variables which would require labelling modifications.

CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
PNEUMONIA N = 80

VARIABLE	BMS		MO CLINICALLY EVAL.		MO STRICTLY EVAL.	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
ALL	5/7 (71%)	7/8 (88%)	3/9 (33%)	4/8 (50%)	1/1 (100%)	0/1 (0%)
WOMEN	3/3 (100%)	1/2 (50%)	2/2 (100%)	1/3 (33%)	-	0/1 (0%)
MEN	2/4 (50%)	6/6 (100%)	1/7 (14%)	3/5 (60%)	1/1 (100%)	-
WHITE	-	2/2 (100%)	0/1 (0%)	2/2 (100%)	-	-
BLACK	5/7 (71%)	5/6 (83%)	2/7 (29%)	2/6 (33%)	1/1 (100%)	0/1 (0%)
OTHER	-	-	1/1 (100%)	-	-	-
< 65 YEARS	3/4 (75%)	6/7 (86%)	2/7 (29%)	3/7 (43%)	1/1 (100%)	0/1 (0%)
> 65 YEARS	2/3 (67%)	1/1 (100%)	1/2 (50%)	1/1 (100%)	-	-

The following table evaluates the effect of underlying lung disease and/or smoking. In the data collection, the information provided included the presence or absence of disease. The specific disease process or length of its existence was not usually recorded. Further information was sometimes available in the investigator's note.

EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS
PNEUMONIA N = 281
NON-BLIND

RESPIRATORY STATUS	BMS		NO CLINICAL EVAL.		NO STRICTLY EVAL.	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
ALL	31/53 (58%)	31/49 (63%)	34/53 (64%)	31/51 (61%)	3/6 (50%)	5/6 (83%)
SMOKER	4/4 (100%)	4/7 (57%)	5/5 (100%)	4/9 (44%)	1/1 (100%)	1/1 (100%)
LUNG DISEASE	5/15 (60%)	3/10 (30%)	6/11 (55%)	7/13 (54%)	-	2/3 (67%)
SMOKER & LUNG DISEASE	10/23 (43%)	17/21 (81%)	14/27 (52%)	14/19 (74%)	1/3 (33%)	2/2 (100%)
NONSMOKER	8/11 (73%)	7/11 (64%)	9/10 (90%)	6/10 (60%)	1/2 (50%)	-

The following table evaluates the effect of underlying lung disease and/or smoking. In the data collection, the information provided included the presence or absence of bronchopulmonary disease. The specific disease process or length of its existence was not usually recorded. Further information was sometimes available in the investigator's note.

EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS
PNEUMONIA N = 80
BLIND

RESPIRATORY STATUS	BMS		NO CLINICAL EVAL.		NO STRICTLY EVAL.	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
ALL	5/7 (71%)	7/8 (88%)	3/9 (33%)	4/8 (50%)	1/1 (100%)	0/1 (0%)
SMOKER	1/1 (100%)	3/3 (100%)	1/3 (33%)	3/4 (75%)	1/1 (100%)	-
LUNG DISEASE	1/1 (100%)	-	2/2 (100%)	0/1 (0%)	-	0/1 (0%)
SMOKER & LUNG DISEASE	2/4 (50%)	3/4 (75%)	0/3 (0%)	1/3 (33%)	-	-
NONSMOKER	1/1 (100%)	1/1 (100%)	0/1 (0%)	-	-	-

SAFETY EVALUATION

Of the 393 (plus 3 patients disqualified from center 027) patients with infections who were enrolled in Study 411-097, there were 34 (34/396 = 9%) deaths. There were 15/208 (7%) cefepime deaths and 19/188 (10%) ceftazidime deaths. This was further subdivided as follows:

Non-Blinded:

PNEUMONIA (N = 281)

treated with cefepime	13/144 = 9%
treated with ceftazidime	16/140 = 11%

Blinded:

PNEUMONIA (N = 80)

treated with cefepime	1/46 = 2%
treated with ceftazidime	1/34 = 3%

PNEUMONIA - CEFEPIME - NONBLIND

The patient was a 73 year old white woman who was admitted for surgical evacuation of a subarachnoid hemorrhage and repair of the cerebral aneurysm. Six days after admission, the patient developed bilateral infiltrates on chest X-ray and a urinary tract infection. Cefepime was instituted. The patient also received nafcillin concomitantly. The patient's respiratory symptoms improved during her fourteen day course of treatment. However, the patient developed a fungal infection in the bladder which required irrigation with amphotericin. Seventeen days after study drug was discontinued, the patient experienced a respiratory arrest (thought to be related to brain injury) and expired.

The patient was a 76 year old white man with multiple cardiac problems who was admitted for cardiac surgery. He developed intra- and post-operative complications. The patient received treatment with imipenem for thirteen days for unclear reasons. He required a cholecystectomy and heparinization for a deep venous thrombosis. The patient subsequently developed intra-abdominal bleeding which required surgical repair. A Greenfield filter was also placed in his vena cava. At the time of the last surgery, it was also noted that the patient had bilateral lower lobe infiltrates on chest X-ray. The patient's antimicrobial therapy was then switched to cefepime. Therapy continued for eight days without clinical improvement. The patient also developed renal failure requiring peritoneal dialysis. Cefepime was discontinued at that time. Eight days later, the patient required an additional surgery to repair a source of bleeding and subhepatic bile leakage. The patient died shortly after surgery. At the post-mortem, it was noted that one of the patient's venous grafts had occluded and there was an associated subendocardial infarction. A left upper lobe and lower lobe pneumonia was also present. The causes of death were listed as myocardial infarction, intraperitoneal hemorrhage, bile spillage and renal failure.

The patient was a 71 year old white man with a history of chronic obstructive pulmonary disease who was originally admitted for surgical treatment of an esophageal stricture. The hospital course was complicated by multiple episodes of mechanical respirator dependent respiratory distress. He was treated with cefepime for one of these episodes. He received four doses without response and was switched to alternative therapy. He died 66 days after discontinuation of the study drug as a result of his underlying pulmonary disease.

The patient was a 78 year old man with multiple medical problems who was admitted for treatment of upper gastrointestinal bleeding. He underwent a successful surgical repair. Three weeks later, the patient underwent a second surgery for an aortofemoral bypass graft and reimplantation of his inferior mesenteric artery. Post-operatively, the patient remained ventilator dependent. His secretions changed and he was enrolled in the study. He received four doses without clinical change and was switched to alternative therapy. His clinical status continued to decline and extraordinary measures were withdrawn. He expired 24 days after the study drug was discontinued from multi-system failure.

The patient was a 90 year old black man who was admitted for treatment of a severe left-sided pneumonia, bacteremia and shock. The patient was treated with cefepime for eight days without clinical improvement. Extraordinary measures were withdrawn and the patient expired.

The patient was a 72 year old white man with many medical problems who was admitted for treatment of malnutrition secondary to his Crohn's disease. Three weeks after his admission, the patient developed lung consolidation. The patient was enrolled in the study and received treatment with cefepime for 10 days. He improved clinically and therapy was discontinued. The patient expired 65 days after study drug was discontinued as a result of his multiple underlying medical problems.

The patient was a 62 year old man with a history of many medical problems admitted to the hospital for treatment of pneumonia. He was randomized to receive treatment with cefepime. He received nine doses of study drug without clinical improvement. His renal status also deteriorated. He died of multisystem failure one day after therapy was discontinued.

The patient was a 75 year old white man who was admitted for an exacerbation of his chronic pulmonary disease. A chest X-ray and examination revealed right sided lung consolidation. He was placed on cefepime for 12 days. He clinically responded. Therapy was discontinued because of a rash. He could not however, be weaned from the respirator. Eighteen days after therapy was discontinued, the patient requested removal from the ventilator and expired.

The patient was a 67 year old woman who was admitted to the hospital for treatment of a right middle lobe pneumonia. She was treated with five doses of cefepime and concomitant therapy with erythromycin and tobramycin. The patient clinically did not improve and alternative therapy was instituted. At the time of the initial hospitalization, the patient underwent an embolectomy and aortoiliac bypass graft. Her course was also complicated by thrombosis at the graft site and a spontaneous pneumothorax. The patient developed coma; and at the family's request, the patient's ventilatory support was withdrawn. She died 15 days after study drug was discontinued.

The patient was an 84 year old white woman who was admitted to the hospital for an unknown reason. Six days into the hospitalization, the patient was diagnosed with pneumonia. She was treated for 14 days with cefepime with an apparent clinical improvement. The applicant designated the clinical response unsatisfactory for unknown reasons. The patient expired 26 days after therapy was discontinued. The case report form states that the patient did not die; however, the applicant lists the cause of death as ischemic heart disease. More information is not available.

The patient was a 65 year old black man who was admitted for treatment of an exacerbation of his chronic obstructive pulmonary disease. He received therapy with multiple antimicrobial drugs without success. He was started on cefepime therapy and received a total of nine doses without improvement. Alternative therapy was started. His respiratory status continued to decline and the patient died 123 days after study drug was discontinued.

The patient was a 68 year old man who was admitted for chemotherapy for non-Hodgkin's lymphoma. The patient experienced several infections during his hospital course. Eight weeks after he was admitted, he was diagnosed with a bilateral pneumonia, urinary tract infection and bacteremia. He was placed on cefepime therapy for a total of 10 days. He showed some initial improvement; but his condition continued to deteriorate. He was placed on alternative antimicrobial therapy. He died six days after therapy with cefepime was discontinued. The cause of death was listed as renal failure and lymphoma.

The patient was a 59 year old man with a history of lung cancer and chronic obstructive pulmonary disease who was admitted for treatment of a right sided pneumonia, anemia and right ventricular cardiac failure. The patient was enrolled in the study to receive therapy with cefepime. He did not respond and therapy was discontinued after treatment for 11 days. Alternative antibiotics were administered with improvement. However, the patient expired 11 days after study drug therapy was discontinued. The investigator lists the cause of death as an incompletely resolved bronchopneumonia and pulmonary malignancy.

PNEUMONIA - CEFTAZIDIME - NONBLIND

The patient was a 91 year old woman who was enrolled in the study for treatment of a right sided pneumonia. The patient received 11 days treatment with ceftazidime. She responded well and was discharged to a nursing home. One month later, she was re-admitted to the hospital with a urinary tract infection;. She became septic and expired. She died 28 days after study drug was discontinued.

The patient was 40 year old white man with a history of chronic alcoholism, cirrhosis and tuberculosis who was admitted for treatment of a lower respiratory infection. He was treated successfully. However, one month later, the patient again had symptoms consistent with lower respiratory tract infection. He was enrolled in the study and received 8 days of treatment with ceftazidime. During treatment, a chest tube was inserted for a pneumothorax and possible empyema; he responded well to therapy. The patient expired 23 days after ceftazidime was discontinued of liver failure.

The patient was a 65 year old white woman who was admitted for treatment of a massive myocardial infarction with papillary muscle necrosis and valvular dysfunction. The patient's course was complicated by emboli to both lower extremities which required removal. She then underwent a below the knee amputation. During this hospitalization, she developed bilateral pneumonia. She was placed on ceftazidime therapy for eight days without improvement. Alternative therapy was started, but the patient's condition continued to decline. She developed signs of cardiogenic shock and acute respiratory distress syndrome. Extraordinary measures were withdrawn and the patient expired. She died 14 days after study drug was discontinued. The causes of death were listed as acute myocardial infarction, renal failure and possible bowel ischemia.

The patient was a 72 year old man with a history of multiple medical problems who was admitted to the hospital for evaluation of a fall. He developed bronchitis while in hospital and was initially treated with cephalexin. He condition deteriorated to pneumonia and he was enrolled in the study. He received treatment with ceftazidime for six days without improvement. Alternative therapy was given also without improvement. He died four days after study drug was discontinued. The cause of death was a cardiopulmonary arrest related to his pulmonary infection.

The patient was a 69 year old white man with a history of bladder carcinoma who was admitted for treatment of bowel obstruction. On physical examination, the patient also had symptoms consistent with pneumonia. He was treated with ceftazidime for five days. Therapy was changed when a question of antibiotic resistance was raised. The patient's clinical condition continued to deteriorate. He expired 15 days after the study drug was discontinued. The causes of death were persistent pneumonia, acute renal failure and underlying carcinoma.

The patient was a 40 year black, diabetic woman who was admitted for treatment of a large ischiorectal abscess. She was initially treated with cefoxitin and penicillin. During her course of her hospitalization, a chest X-ray demonstrated signs of lung consolidation. She was enrolled in the study and received treatment with ceftazidime for nine days. She deteriorated rapidly requiring intubation and mechanical ventilation. Clindamycin and piperacillin were added to the treatment regimen. The patient died in septic shock on the last day of therapy.

The patient was a 67 year old woman with a history of multiple medical problems including oat cell carcinoma who was admitted to the hospital for treatment of symptoms of a lower respiratory tract infection. The patient received 6 days of therapy with ceftazidime without clinical improvement. The patient was then given alternative antibiotics including cefepime. During an attempt to wean the patient (21 days post ceftazidime discontinuation), a cardiopulmonary arrest occurred. She was not resuscitated.

The patient was a 71 year old white man with a history of alcohol abuse and cirrhosis who was admitted for an emergency resection of a ruptured abdominal aneurysm. He had a very complicated post-operative course including an embolectomy and subsequent below the knee amputation. One week after admission, he developed symptoms of a lower respiratory tract infection. He was started on ceftazidime. He developed renal failure while on therapy; however, the investigator felt that it was not related to the study drug. Metronidazole and ampicillin were added to his treatment regimen. After nine days, the symptoms of pneumonia were not improved. He died of infection and multi-organ failure.

The patient was a 97 year old white woman who was admitted for treatment of a lower respiratory tract and urinary tract infection. She was placed on ceftazidime therapy with an initial positive response. Subsequently, however, the patient's respiratory status worsened. She died of a cardiopulmonary arrest after 10 days of ceftazidime treatment.

The patient was a 69 year old white man who was admitted for a syncopal episode and found to have coronary artery disease. He underwent bypass surgery and the placement of an automatic defibrillator. Five days post-operatively, the patient developed pneumonia and catheter related infections. The patient was randomized to receive therapy with ceftazidime. He had improvement of his pulmonary symptoms, although fever and tachypnea persisted. After a total of 10 days of therapy, ceftazidime was discontinued. After 48 hours, an infection around the defibrillator was detected. Therapy with vancomycin, tobramycin and metronidazole was instituted. He had a respiratory arrest and lapsed into a coma. He died of an arrhythmia 42 days after study was discontinued.

The patient was an 83 year old woman who was admitted for a surgical repair of an upper

gastrointestinal bleeding artery. Three days post-operatively, she developed symptoms of pneumonia. She was placed on ceftazidime therapy. The patient remained febrile and clinically deteriorating. At the family's request, no aggressive measures were taken. She expired on day six of therapy of heart failure and her underlying conditions.

The patient was an 82 year old white man who was admitted with a fracture of his right hip. Shortly after admission, it was noticed that the patient had an infiltrate on his chest X-ray. He rapidly deteriorated and required ventilatory assistance. He was initially treated with multiple antibiotics. After five days of several switches in therapy, he was enrolled in the study. He was randomized to receive treatment with ceftazidime. The fever resolved and he improved clinically. There was a question of resistance occurring and the study drug was discontinued. He was observed off antibiotics, but the sputum became more purulent. Alternative antibiotics were again instituted. He was slowly improving, but maintained a low grade fever. Twenty-five days after the ceftazidime was discontinued, the patient's heart arrested. The investigator listed the causes of death as cardiorespiratory arrest, ARDS, and disseminated intravascular clotting.

The patient was a 65 year old white man with chronic lymphocytic leukemia who was hospitalized for chemotherapy. The patient was also diagnosed with probable pneumonia on admission. Although a sputum sample showed only normal respiratory flora, he was randomized to receive empiric therapy with ceftazidime. He did not improve clinically and the radiograph of his chest worsened. He was removed from the study after 11 days of therapy and placed on other antimicrobial drugs including isoniazid and rifampin. He died three days after ceftazidime was discontinued. At autopsy, an interstitial pneumonitis of unknown origin was discovered.

The patient was an 84 year old woman with a history of multiple medical problems including breast cancer who was admitted for treatment of a recent hip fracture. During hospitalization, the patient developed pneumonia. Purulent material as well as acid fast bacilli were discovered by bronchoscopy. The patient received treatment with ceftazidime as well as anti-tuberculous agents. The patient's respiratory status improved on therapy and it was discontinued after 9 days. She expired suddenly one day after therapy was discontinued. The cause of death was equivocal. The investigator listed the causes of death as mucous plugging, pulmonary edema and reactivation tuberculosis (no AFB growth at six weeks).

The patient was a 77 year old white man who was admitted with a non-hemorrhagic cerebrovascular accident. A CAT scan also showed evidence of sinusitis. The patient received a short course of penicillin and clindamycin. He quickly developed symptoms of a lower respiratory tract infection that required mechanical intubation and assistance. He was then randomized to receive treatment with ceftazidime. Blood cultures were also positive for a coagulase negative staphylococcus. Initially, he responded well. However, amikacin was added by the housestaff because of a persistent leukocytosis. Vancomycin was also added. He received seven days of therapy with ceftazidime and expired two days after it was discontinued. The causes of death were related to stroke and the bronchopneumonia.

The patient was a 97 year old woman with multiple medical problems who was admitted with fever, lethargy, a urinary tract infection and a questionable left sided pneumonia. She was randomized to receive treatment with ceftazidime. A repeat chest X-ray showed increasing pulmonary edema and pleural effusions. By the end of treatment at fourteen days, the patient had some symptomatic improvement but worsening of the chest X-ray. She died three days after study therapy was discontinued. The investigator listed cardiorespiratory arrest, pneumonia and heart disease as the causes of death.

PNEUMONIA - CEFEPIME - BLIND

The patient was a 76 year old black man with a history of coronary artery disease and small cell carcinoma of the lung who underwent coronary artery bypass surgery. Seven days post-operatively, he developed signs and symptoms consistent with pneumonia. The patient was enrolled in the blinded protocol and received twenty-two days of treatment with cefepime. During that period, the patient

remained on the ventilator, had a low grade fever and leukocytosis. The day after therapy was discontinued, the patient had a positive blood culture with *Enterococcus* species. This organism was also isolated from a catheter tip. Therapy was initiated with vancomycin. He had several other complications including bowel obstruction and cardiac arrhythmias. He expired 17 days after study drug was discontinued. The investigator believed the cause of death was related to the underlying malignancy and coronary artery disease.

PNEUMONIA - CEFTAZIDIME - BLIND

The patient was a 38 year old black man with a history of self abusive behavior who was admitted to the hospital for treatment of bilateral pneumonia. He received a single dose of study drug and was removed from the study at the private physician's request because of the gravity of the patient's illness. He was then treated with penicillin for a presumed *S. pneumoniae* pneumonia. The patient clinically deteriorated and died 12 days after receiving study drug.

Discontinuations due to an Adverse Event:

MEDICAL OFFICER'S COMMENTS:

Much of the data that follows is derived directly from the applicant's study reports.

NONBLIND

Of the total (all indications) study population, there were 14/439 (3%) patients in the cefepime group and 15/443 (3%) in the ceftazidime group who discontinued therapy due to an adverse clinical event.

Of the infections including pneumonia the discontinuations were as follows:

PNEUMONIA (N = 284)	
treated with cefepime	3/144 = 2%
treated with ceftazidime	2/140 = 1%

BLIND

Of the total (all indications) study population, 2/104 (2%) patients in the cefepime group and 4/103 (4%) in the ceftazidime group discontinued because of an adverse clinical event.

Of the infections including pneumonia, the discontinuations were as follows:

PNEUMONIA (N = 80)	
treated with cefepime	1/46 = 2%
treated with ceftazidime	2/34 = 6%

Patients Who Discontinued Due to Adverse Clinical Events
Study 411-097-ALL

Patient	Adverse Event ^a	Severity	Total Dose ^b (g)	Rel ^c	Outcome ^d
CEFEPIME					
	Renal failure ^e	Severe	26	Not	T/H
	Headache ^f	Moderate	12	Prob	T/S-T
	Sore throat	Moderate	16	Unk	T/R
	Rash ^e	Mild	28	Prob	T/S-T
	Itching ^e	Mild	28	Prob	T/S-T
	Nausea	Moderate	28	Unk	NT/R
	Pulmonary effusion	Moderate	28	Unk	NT/R
	Rash ^e	Mild	44	Prob	NT/R
CEFTAZIDIME					
	Pain, neck	Mild	22	Prob	T/R
	Rash, trunk ^e	Moderate	24	Prob	T/S-T
	Rash ^e	Mild	50	Prob	T/R

a Investigator's term.

b Total dose at onset

c Rel = Relationship to cefepime, where Prob is probably related, Unk is of unknown relationship, and Not is not related.

d Indicates outcome of adverse event, whether it was treated (T), not treated (NT), whether patient recovered (R), was hospitalized (H), was disabled (D), whether sequelae occurred and were treated (S-T), or whether there was no follow-up (NF).

e Event led to discontinuation of therapy.

f Event led to interruption of dosing.

Patients Who Discontinued Due to Adverse Clinical Events
Study 411-097-Blinded

Patient	Adverse Event ^a	Severity	Dose ^b	Rel. ^c	Outcome ^d
CEFEPIME					
	Diarrhea ^e	Moderate	5	Unk	NT/R
	Nervousness	Moderate	11	Unk	T/R
CEFTAZIDIME					
	Erythematous, skin ^e	Moderate	1	Prob	T/R
	Itching ^e	Moderate	1	Prob	T/R
	Nausea	Severe	1	Not	T/R
	Vomiting	Severe	1	Not	T/R
	Dysuria, acute	Severe	1	Not	T/R
	Dyspnea ^e	Severe	13	Unk	T/R
	Tachypnea ^e	Severe	13	Unk	T/R
	Headache	Mild	3	Unk	T/R
	Tremor, lip	Mild	7	Not	NT/R
	Tightness, chest	Moderate	11	Unk	NT/R

a Investigator's term.

b Total number of doses (both active drug and placebo) at onset.

c Rel = Relationship to study drug, where Prob = probably related,
Unk = of unknown relationship, Not = Not related.

d Indicates outcome of adverse event, whether it was treated (T),
not treated (NT), whether patient recovered (R) or sequelae occurred (S).

e Event led to discontinuation of therapy.

Discontinuation due to a Laboratory event:NONBLIND:

PNEUMONIA (N = 284)

treated with cefepime	2/143 = 1%
treated with ceftazidime	1/138 = 1%

Treatment with cefepime was discontinued for Patient _____ when the investigator noted that the patient's pretreatment renal (BUN/Cr) and hepatic (transaminases) laboratory values were elevated.

Treatment with cefepime was discontinued for Patient _____ when the investigator noted that the patient's leukocyte count increased from 13,700 to 54,000 cells/cc.

Treatment with ceftazidime was discontinued for Patient _____ when the investigator noted that the patient's liver enzymes increased on therapy.

BLIND:

There were no discontinuations due to an abnormal laboratory event in those patients with pneumonia and bronchitis enrolled in the blinded centers.

Local Tolerance:

In the non-blind portion of the study (including all patients, all indications), 404/439 (92%) of the cefepime group tolerated the infusions well. Thirty-five (8%) patients reported intolerance at the infusion or injection site. Of the 443 patients who received ceftazidime, 419 (95%) tolerated administration well. The remaining 24 (5%) patients reported intolerance at the infusion site.

In the blinded portion of the study (including all patients, all indications), 99/104 (95%) of the patients treated with cefepime tolerated the infusions well. Five patients experienced local intolerance (3 had infiltration, one had phlebitis and 1 had erythema). Of the 103 patients who were treated with ceftazidime, 93 (90%) tolerated the administration well. The remaining 10 experienced some discomfort (six had infiltration, one had burning, one had clots in the tubing, one had pain and one had both pain and swelling at the infusion site). One patient in the ceftazidime group _____ required discontinuation from the study because of the appearance of blood clots in the intravenous tubing.

ADVERSE EVENTS:**NONBLIND:**

In the entire study, 117 (27%) of the 439 patients in the cefepime group, reported at least one adverse clinical event during the study; 277 events were reported. Thirteen adverse clinical events affected at least 1% of patients: headache and nausea (17 events each); diarrhea (16 events); rash (15 events); pruritus (13 events); vomiting (11 events); abdominal pain and constipation (9 events each); confusion, dizziness, and insomnia (7 events each); dyspepsia and paresthesia (6 events each).

In the ceftazidime group, 128 (29%) of the 443 patients reported at least one ACE during the study; 267 adverse clinical events were reported. Eleven events affected at least 1% of the patients: diarrhea (29 events), rash (20 events), headache (18 events), nausea (15 events), constipation (12 events), pruritus (8 events), insomnia (6 events), abdominal pain, cardiovascular chest pain, edema, and vomiting (5 events each).

BLIND: In the entire study, fifty-three (51%) of the 104 patients in the cefepime group experienced at least 1 adverse clinical event during the study; 119 events were reported. Adverse clinical events affecting more than 2 patients included headache (11 cases), constipation (9 cases), pruritus (7 cases), vomiting (5 cases), nausea (4 cases), and abdominal pain, depression, diarrhea, edema, hemorrhage, insomnia, pain, and sweating (3 cases each).

Fifty-five (53%) of the 103 patients in the ceftazidime group experienced at least 1 adverse clinical event during the study; 122 events were reported. Adverse clinical events affecting more than 2 ceftazidime patients included headache (12 cases), edema (6 cases), chest pain, diarrhea, insomnia, nausea, and vomiting (5 cases each), and convulsion, dyspnea, erythema, pruritus, and rash (3 cases each).

MEDICAL OFFICER'S COMMENTS:

The above safety information was provided by the applicant for the entire A1411-097 study. Adverse clinical events or laboratory abnormalities were not presented separately by indication by the applicant. In order to have a further appreciation of these events per indication, the applicant prepared tables with respect to the entire indication. This information is presented in the summary section of this report.

SUSCEPTIBILITY

Determinations of susceptibility were made by disc susceptibility and/or MIC methods. The criteria used to define sensitivity to cefepime or ceftazidime are as follows:

Disc sensitivity : Susceptible $\geq$ 18 mm
 Intermediate $>$ 14 and $<$ 18 mm
 Resistant $\leq$ 14 mm

MIC sensitivity : Susceptible $\leq$ 8 mcg/ml
 Intermediate $>$ 8 and $<$ 32 mcg/ml
 Resistant $\geq$ 32 mcg/ml

Susceptibility data were requested for all patients with a causative pathogen.

MEDICAL OFFICER'S COMMENTS:

The following susceptibility data was prepared by the applicant.

**Sensitivity of Pathogens to Study Drugs
 All Patients
 Study 411-097-BLINDEX**

Infection Type/ Pathogen	----- Number (%) of Pathogens* -----				-----			
	<u>Cefepime Sensitivity</u>				<u>Ceftazidime Sensitivity</u>			
	Susc.	Inter.	Res.	Total	Susc.	Inter.	Res.	Total
Strep. (Group G)	1			1	1			1
S. aureus	1			1	1			1
S. pneumoniae	13			13	13			13
P. aeruginosa	5	1		6	6			6
E. coli	2			2	2			2
S. marcescens	1	1		2	2			2
H. influenzae	3			3	3			3
H. influenzae (p-)	1			1	1			1
M. catarrhalis	<u>1</u>			<u>1</u>	<u>1</u>			<u>1</u>
Total	28	2		30	30			30
Percent	(93)	(7)			(100)			

Sensitivity of Pathogens to Study Drugs
All Patients
Study 411-097-NON-BLINDED

Infection Type/ Pathogen	----- Number of Pathogens* -----							
	<u>Cefepime Sensitivity</u>				<u>Ceftazidime Sensitivity</u>			
	Susc.	Inter.	Res.	Total	Susc.	Inter.	Res.	Total
Strep. (Group A)	1			1	1			1
Strep. (alpha hemo.)	1			1	1			1
Strep. (beta hemo.)	1			1	1			1
Enterococcus		1		1		1		1
Strep. (Group F)	2			2	2			2
Strep. (Group B)	1			1	1			1
S. mitis	3			3	3			3
S. sanguis	1			1	1			1
S. aureus	19	1	2	22	16	3	2	21
S. aureus (MR)			1	1			1	1
S. aureus (MS)		1		1		1		1
S. epidermidis	4	1		5	3	2		5
S. pneumoniae	42	1		43	42	1		43
P. aeruginosa	22	3	3	28	25	2	1	28
E. coli	11			11	11			11
Citrobacter sp.	1			1	1			1
C. freundii	2			2	2			2
C. diversus	1			1	1			1
Klebsiella sp.	2			2	2			2
K. pneumoniae	15			15	15			15
K. oxytoca	2			2	2			2
Enterobacter sp.	1			1	1			1
E. cloacae	6		1	7	4		3	7
E. aerogenes	8			8	5		3	8
E. intermedium		1		1		1		1
S. marcescens	8			8	8			8
P. mirabilis	9			9	9			9
P. vulgaris	1			1	1			1
P. stuartii	1			1	1			1
E. agglomerans	1			1	1			1
Haemophilus sp.	1			1	1			1
H. influenzae	28	1		29	27	1		28
H. influenzae (p+)	5			5	5			5
H. influenzae (p-)	15			15	15			15
H. parainfluenzae	10			10	10			10
H. parahaemolyticus	2			2	2			2
H. aphrophilus	1			1	1			1
N. meningitidis	2			2	2			2
A. calcoaceticus	2			2	2			2
A. anitratus	2			2	2			2
M. catarrhalis	6			6	5			5
M. catarrhalis (p+)	5			5	5			5
Total LRTI	245	10	7	262	237	11	11	259
Percent	(94)	(4)	(3)		(92)	(4)	(4)	

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PNEUMONIA**PROTOCOL A1411-106 All European Investigators** (NDA volumes 1.149-153)

TITLE: A Comparative Study of Cefepime Dihydrochloride and Cefotaxime in the Treatment of Patients Infections.
(Low Dose 1g q12h & High Dose 2g q12h)

MEDICAL OFFICER'S COMMENTS:

The following protocol description was excerpted from the applicant's study reports (volume 1.149 & 1.151); the reviewer has made minor editorial changes. Infections included patients with pneumonia and occasionally other infections. For this review, pneumonia were analyzed separately for safety and efficacy; patients with other respiratory diagnoses were evaluated for safety only. It should also be noted that the protocol did not make any separate provisions to distinguish patients versus patients with pneumonia.

STUDY DESIGN:

This trial was an open, Phase III, Multi-Investigator, Comparative Evaluation of the Safety and Therapeutic Efficacy of Cefepime and Cefotaxime in the Treatment of Infections. There was a single investigator that enrolled patients in the low dose study and two investigators that enrolled patients in the high dose study. A single amendment replaced the low dosage with the higher dosage.

Inclusion Criteria:

1. Provide informed consent;
2. 18 years of age or older and of any race;

Note: Women of childbearing potential had to have a negative pregnancy test result immediately prior to enrollment with the exception of patients who were taking oral contraceptives in the prescribed manner, patients who were post-menopausal or patients who had been surgically sterilized.

3. Had a proven or suspected infection caused by a pathogen(s) susceptible to the study drugs;
4. Had signs and symptoms consistent with a infection;

Exclusion Criteria

1. had a history of a hypersensitivity reaction to a cephalosporin or penicillin antibiotic (Patients with Type I hypersensitivity reaction to penicillin could be given the study drug with caution. Study drug had to be discontinued immediately if a reaction occurred);
2. had cystic fibrosis;
3. had a diagnosis for which long term (more than 14 days) therapy was expected, e.g. empyema, lung abscess, pneumonia distal to obstructive carcinoma, etc.;
4. had a diagnosis that was likely to require other antimicrobial drugs concomitant with the study medication;
5. lactation;
6. had renal function impairment (baseline serum creatinine levels of 1.7 mg/dL or greater) or been dependent on renal dialysis;
7. had hepatic function impairment;
8. had a granulocyte count of less than 500 mm³
9. had a diagnosis for which drug therapy constituted prophylactic or early treatment of a contaminated wound or extensive physical trauma;
10. had been previously enrolled in the study;
11. had a medically significant disease or disorder which could have had a bearing on the outcome of the study;
12. had any other condition which in the opinion of the principal investigator might have increased the risk to the subject or compromised the study.

Procedures and Observations

The table below lists the procedures and observations that were specified in the Protocol.

Study Schedule
Study 411-106

Procedure	<u>Pre-treatment</u> Within 48 hrs Preceding Therapy to Day 1	<u>During-Treatment</u> Day 2 to the End of Therapy	<u>Post-treatment</u> Day +1 to +14
Informed Consent	X	-	-
Medical History	X	-	-
Physical Examination	X	X	X
Laboratory Testing:			
Hematology	X	X	X
Serum Chemistry	X	X	X
Urinalysis	X	X	X
Chest X-ray	X (1)	-	X (1)
Bacteriologic Testing			
Culture	X	X (2)	X (2)
Susceptibility	X	X	X
Subculture	X	X (3)	X (3)
Evaluation of Clinical Signs & Symptoms of Infection	X	X	X (4)

- (1) Pre-treatment chest X-rays for patients with pneumonia were to be obtained within 72 hours prior to, or 24 hours after start of therapy. Post-treatment X-ray was required on all patients with a diagnosis of pneumonia (confirmed by pre-treatment X-ray).
- (2) During and post-treatment cultures were to be obtained if there was a source to culture. If there was no source to culture due to diminished or absent sputum production the date of the follow-up was to be documented in the CRF with the notation "No Source to Culture".
- (3) Subcultures were to be obtained only if a pathogen was present.
- (4) Follow-up was to be obtained approaching two weeks post-therapy (5-14 days) either in hospital, at a clinic or office visit or by telephone call documented in the investigators records.

MEDICAL OFFICER'S COMMENTS:

The time table above is consistent with the time table as written in the Protocol. The study report contains modifications of the defined windows that were "extended at the time of the analysis." At the time of the analysis, the applicant changed a number of the requirements specified by the protocol including the end of treatment radiological assessment and the appropriate follow-up (+5-14 days) evaluation interval.

Pre-Treatment Procedures

1. Within 48 hours before treatment began, a medical history was to be recorded and a physical examination was to be completed.
2. The presence of clinical signs and symptoms of infection were to be evaluated within 48 hours of beginning therapy and after any previous antimicrobial therapy.

MEDICAL OFFICER'S COMMENTS:

The applicant did not address the influence of other antimicrobial therapy on the clinical outcome. This should have been considered, because not all therapy switches were as a result of treatment failure.

3. Bacteriologic confirmation of the infection was to be obtained by culturing the infected site(s) within 48 hours prior to treatment and after any previous antimicrobial.
 - A suctioned sputum specimen (transtracheal, endotracheal, or bronchoscopy) by sterile technique or a deep-cough, purulent expectorated sputum sample was obtained. A pre-treatment specimen was to be gram stained to determine if a predominant pathogen was present. The specimen was to be purulent as demonstrated by the presence of leukocytes. A second pre-treatment sample was to be obtained if large numbers of squamous epithelial cells were present suggesting oral contamination.

MEDICAL OFFICER'S COMMENTS:

For the most part, this descriptive and/or qualitative or quantitative information was not recorded on the case report form.

4. Each pathogen(s) was identified and tested for susceptibility to cefepime and to cefotaxime by disc or Minimum Inhibitory Concentration methods.
5. A chest X-ray was to be done on each patient within 72 hours before or 24 hours after the beginning of study drug treatment to confirm diagnosis of pneumonia.
6. Laboratory studies were requested within 48 hours prior to treatment. Additional laboratory tests were done at the discretion of the investigator. The requested assessments were:

Hematology

Hemoglobin
Hematocrit
WBC count, total and differential
Platelet count or estimate from smear
Erythrocyte sedimentation rate (ESR)
Prothrombin time (PT)
Partial thromboplastin time (PTT)

Serum Chemistry

AST (SGOT)
ALT (SGPT)
Total bilirubin
Alkaline phosphatase
Blood urea nitrogen (BUN) or blood urea
Creatinine
Glucose (random)
Sodium
Potassium
Calcium
Phosphorus

Urinalysis

Albumin	By dipstick
Blood	"
Glucose	"

During-Treatment Procedures

The following procedures were to be performed by investigators at least once during (Day 2-6) therapy:

1. An abbreviated physical examination was to be conducted.
2. Clinical signs and symptoms of infection were to be assessed.
3. A during-therapy culture was to be prepared from an appropriate specimen.
 - All causative pathogens from a positive culture were to be isolated, identified and tested for susceptibility. At the same time, the investigator determined whether a patient with a positive culture should be discontinued and placed on alternative therapy.
 - The occurrence of a negative culture was recorded.
 - If a specimen could not be obtained for culturing because sputum could not be produced, the attempt and date were noted on the CRF with the statement "No Source to Culture".
4. Pathogens from concurrent infections that developed were appropriately cultured and tested

for susceptibility.

5. Laboratory evaluations were performed as above.
6. Chest X-rays were to be repeated as deemed appropriate.

Post-Treatment Procedures

The procedures listed below were to be completed between Day +1 to +14 after therapy and before another antimicrobial product was given.

MEDICAL OFFICER'S COMMENTS:

The protocol emphasized the following: "in addition, for patients with a satisfactory clinical response the investigator must confirm the response remains satisfactory without additional anti-microbial therapy for all clinical signs and symptoms for a period approaching two weeks (5-14 days) following treatment." However, at the time of the analysis, the applicant apparently accepted the +1 to +14 day post-therapy interval.

1. A physical examination was performed.
2. Assessment of clinical signs and symptoms of infection.
3. A post-treatment culture was to be obtained. Any causative pathogen cultured was to be identified and tested for susceptibility. The lack of a suitable specimen source was to be recorded on CRF with the statement "No Source to Culture".
4. At least one post-treatment chest X-ray was required for patients with a confirmed diagnosis of pneumonia.

MEDICAL OFFICER'S COMMENTS:

The applicant modified this requirement "retroactively" such that the post treatment X-ray could be waived "if an X-ray taken during therapy was negative."

5. Required laboratory evaluations were to be performed and repeated as appropriate.

Treatment Group Assignment

This study was designed as an open, comparative study. Each patient was randomly assigned to one of two treatment groups at a ratio of 2:1 i.e., two patients would receive cefepime for each one receiving cefotaxime.

Drug Information and Dose Selection

Cefepime was supplied by Bristol-Myers Squibb Company in vials containing 1 g of dry-powder blend of cefepime with L-arginine. Cefotaxime was supplied by Bristol-Myers Squibb Company in vials containing 1 g of cefotaxime.

Investigators prepared cefepime or cefotaxime for infusion and administered the resulting solution by intramuscular or intravenous injection over 30 minutes. The protocol stipulated dosing of 1g Q12h for cefepime and 1g Q8h for cefotaxime. The amendment for the high dose group stipulated dosing of 2g Q12h for cefepime and 2g Q8h for cefotaxime.

Length of Therapy

The treatment period was to be for a maximum fourteen days.

New Infections

Although the protocol defined new infections only for cases where the original pathogen was eradicated, in practice new infections were labelled as such regardless of the status of the original pathogen. Thus, a new infection occurred up to 14 days following the treatment if (1) a different causative pathogen was cultured from the original infection site, or (2) either the original pathogen or a new organism caused an infection at a body site unrelated to the original site.

Concomitant Therapy

The investigator was asked to record on the CRF all concomitant medications and therapy. Drugs other than antimicrobial agents were permitted as required. Systemic antimicrobial therapy other than study drug was not allowed during the study or in the post-treatment follow-up period.

Applicant Criteria for Evaluability

A patient was considered evaluable for efficacy only if the following criteria were met:

1. An infection of the lower respiratory tract was diagnosed on clinical grounds and confirmed by a positive pre-treatment culture.
2. Any causative pathogen isolated in the pre-treatment culture was identified and shown to be susceptible to cefepime and to cefotaxime.
3. Post-treatment procedures specific to diagnosis were conducted on the days specified.
4. Patients diagnosed as having pneumonia had pre-, during- and post-treatment X-ray examinations that confirmed the diagnosis and response, respectively. The initial chest X-ray which confirmed the diagnosis of pneumonia had to be done within 72 hours before or 24 hours after treatment began.
5. No other systemic antimicrobial agent that had activity against the pathogen being treated was taken during the time between the pre-treatment and the post-treatment culture and clinical evaluations.
6. The study medication, cefepime or cefotaxime, was administered as specified. Within 96 hours each patient received a minimum of 7 doses of cefepime or 11 doses of cefotaxime.
7. Patients who were declared clinical or bacteriologic failures and who had at least one reason for exclusion from the efficacy analyses were considered evaluable for efficacy if the failure preceded the reason for exclusion. If the reason for exclusion from the efficacy analyses preceded the failure, the patient was not evaluable for efficacy.

Applicant Efficacy Criteria Definitions**Clinical Response**

Satisfactory: All signs and symptoms of the infection that were present prior to therapy were improved or resolved, and no new signs or symptoms were present at the post-treatment follow-up, and the post-therapy chest X-ray did not demonstrate new or increased infiltrate.

Unsatisfactory: One or more signs or symptoms of the infection persisted or increased, or one or more new signs or symptoms were evident at the post-treatment follow-up, or post-therapy chest X-ray demonstrated presence of infiltrate.

Unable to Determine : The response could not be evaluated: a) Other antimicrobial given between pre- and post-treatment evaluation of the study drug; b) Patient lost to follow-up, no post-treatment evaluation of the study drug.

Bacteriologic Response

Eradicated: The original pathogen was not present in the post-treatment culture, or there was no source to culture.

Persisted: Continued presence of the original pathogen in the post-treatment culture.

Unable to Determine: The response could not be evaluated: a) Resistant pathogen or inappropriate pathogen; b) Other antimicrobial given between pre- and post-treatment evaluation of the study drug; c) Patient lost to follow-up, no post-treatment evaluation of the study drug.

MEDICAL OFFICER'S COMMENTS:

To be strictly evaluable by the reviewer, a patient had to have:

1. met the inclusion and exclusion criteria established by the applicant.
2. at least two signs and/or symptoms consistent with a *[redacted]* infection. Pneumonia was differentiated *[redacted]* by the presence of an infiltrate on chest X-ray.

NOTE:

a. To support the observed diagnosis, the investigator could document the presence of signs and symptoms from a list of pre-selected terms. They were as follows:

Fever	Chills
Chest Pain	Cough
Wheeze	Restlessness
Sputum Production	Signs of Lung Consolidation by Auscultation
Rales	Percussion Dullness
Dyspnea	Tachypnea
Tactile Fremitus	Chest Retractions
Increased Breath Sounds	Diminished Breath Sounds
Circumoral Cyanosis	Facial Flush

b. Respiratory rates were not recorded for any patient. Sputum production was not characterized with regard to quantity, quality or relationship to baseline. In patients with chronic respiratory disease, a change in sputum production and/or cough was also not noted.

c. The IDSA states that leukocytosis and pyrexia should be present to support the diagnosis of a *[redacted]* infection. In this indication, many patients were afebrile and without a significant elevation of the white count. The study was not designed to capture information with respect to chronic administration of steroids and/or the use of acetaminophen or aspirin products. Therefore, this information could not be used as diagnostic criteria.

d. For a reviewer to validate the diagnosis of a specific respiratory illness, certain minimal clinical and laboratory information is necessary. In some instances, this includes baseline respiratory conditions and/or recent medications. Other helpful supporting data are respiratory rates or arterial oxygen content. This study as others in this indication had limited information to precisely characterize the respiratory condition; however, there was sufficient data to determine that a pulmonary process was present. To the reviewer, the minimum clinical observations required to support the diagnosis of pneumonia *[redacted]* were cough, sputum production, and/or abnormal auscultatory sounds.

3. a culture documented pathogen susceptible to cefepime and cefotaxime.

NOTE:

a. A gram stain was requested by the applicant. However, a written description was provided at the discretion of the investigator.

b. For the most part, the type of specimen was not identified, e.g. transtracheal aspirate, deep expectorated sputum, etc., nor was the quality described e.g. mucoid, voluminous, blood tinged, etc.

c. Those patients with a documented, valid gram stain and/or positive blood culture constituted the "strictly evaluable" reviewer population.

4. received 24 hours or less of pre-study antimicrobial drug with activity against the identified pathogen or a demonstration of a pathogen resistant to the pre-study antimicrobial drug.

NOTE:

The reviewer believes that this criterion is critical in this study; because treatment by applicant definition could be short (i.e. 3-5 days) and the influence of the pre-study antibiotic is unknown. Second, because validated gram stains were not a study requirement, sputum samples could not always differentiate between a colonizing organism and a true pathogen. The applicant did not address the issue of pre-study antimicrobials in their protocol or study report. The reviewer refers the reader to the published IDSA general guideline which states that: "Patients may be enrolled if they have received < 24 hours of treatment with a presumably effective anti-infective drug for an infectious process thought (on the basis of published reference material) to require

a standard duration of therapy of ≥ 7 days." The only extenuating circumstances where a patient may exceed the suggested 24 hour limit of pre-study therapy are illnesses which require lengthy therapy e.g. osteomyelitis and endocarditis or patients infected with a pathogen resistant to the initial anti-infective drug and sensitive to the study drug. (pp. S17-18)

Exceptions to this requirement were those patients who had an acceptable interval (five half-lives) between the administration of alternative systemic antimicrobials and study drug.

5. received a minimum of 4.5 days of therapy (i.e. 9 doses of cefepime or thirteen doses of cefotaxime) for success. This requirement is consistent with the general IDSA guidelines which recommends a minimum 5 days of therapy for pneumonia (However, a patient could be classified as a failure after only five cefepime doses.)
6. received a maximum of 18 days therapy. (The protocol specified a fourteen day course of therapy.)
7. had neither concomitant nor post-study antimicrobial therapy with activity against the identified pathogen in excess of a single dose.
8. had the minimum of three clinical evaluations: pre-therapy visit, during therapy visit and the follow-up visit (5-21 days).

NOTE:

In instances when an in-person test-of cure visit was not possible: The reviewer accepted telephone follow-up information provided by the patient (not a third party, e.g. relative), because this mechanism was mutually accepted during the development program. However, the reviewer would like to state her opinion that this information is of dubious value. There was no standard questionnaire to provide consistent data collection and documentation of these telephone conversations. Therefore, each investigator could ask a different battery of questions.

9. had evidence of bacterial clearance ("sputum production resolved") or a statement with regard to "No source to culture" at the follow-up visit (5-21 days).
10. had a pre-treatment chest X-ray and a post-treatment (either end of treatment or follow-up) chest x-ray. The IDSA guideline recommends that: "A chest radiograph will be obtained 3 days after the initiation of therapy, within 72 hours of completion of therapy, and at any other time the investigator deems necessary." (p. S85) It should be noted that the post-treatment X-ray was a requirement in the original protocol.

Clinical Response:

Satisfactory: Improvement and/or resolution of all pre-treatment signs and symptoms diagnostic of pneumonia/ at the test of cure visit (5-21 days). The end of treatment/follow-up chest X-ray had to show either improvement or lack of progression of the pneumonic process.

Unsatisfactory: Persistence or worsening of any clinical signs or symptoms associated with pneumonia during treatment or at the time of the follow-up evaluation (5-21 days). The end of treatment/follow-up chest X-ray showed no improvement or worsening.

Unevaluable: Assessment of the clinical outcome could not be determined e.g. the patient did not return for follow-up evaluation.

Bacteriologic Response:

Eradication - Either the causative pathogen(s) was not isolated from the follow-up culture or there was a presumptive eradication because there was no material available for culture.

Persistence - The original pathogen(s) was isolated from the follow-up culture or the patient was a clinical failure with a presumed pathogen persistence.

Unevaluable - It was not possible to determine a bacteriological response, e.g. because the patient did not return for follow-up.

The reviewer conducted an assessment of the "strictly evaluable" population based on the criteria described above. However, the reviewer feels that the design of this study was severely deficient. Problematic areas were as follows:

- a. *Inadequate gram stain assessments/documentation*
- b. *The lack of description with respect to quality and quantity of sputum samples*
- c. *The lack of description of the method in which a sputum sample was collected*
- d. *The absence of characterization of "change" of described signs and symptoms from baseline (especially in the patient with chronic lung disease)*
- e. *The lack of a gradation system with respect to the improvement of signs and symptoms*
- f. *The lack of assessments with respect to pre-treatment antibiotics on selected patients*
- g. *The absence of correlation with white blood cell counts (elevations and/or bandemia) and temperature*
- h. *The absence of definition and attempts to clarify the setting of the pneumonic processes for either pneumonia i.e. not all pneumonias (infections are alike.)*
- i. *The absence of pre-determined format or questionnaire to gather telephone follow-up data*

Not unexpectedly, there were few "strictly evaluable" patients. However, a secondary analysis of a "clinically evaluable" patient population was conducted. This "clinically evaluable" population met all the criteria described above with the exception of the valid pathogen requirement. These patients fell into four categories: a) those patients with an inadequate gram stain, b) those patients whose organism did not have sensitivities done, c) those patients with an inadequate gram stain and a resistant organism and d) those patients in which no organism was isolated. Obviously, this population subset contained patients whose respiratory illness was viral/other and not necessarily bacterial in origin. The reviewer believes that the outcome results of this population are more reflective of the "real world" clinical situation and are more consistent with how the drug will perform when used empirically.

Safety Assessments

All patients who received one dose of cefepime or cefotaxime were evaluable for safety. All adverse clinical events were reported on the CRF along with the investigator's judgement of the relationship of the reaction to cefepime or cefotaxime. Also recorded were the date of onset, duration, and severity of each ACE, and any change in a patient's treatment. If serious or alarming adverse experience(s) occurred, investigators were to stop administering the drug and notify Bristol-Myers Squibb Company.

Investigators recorded on the CRF whether cefepime or cefotaxime was well or poorly tolerated at the infusion site. The occurrence of phlebitis, hematoma, infiltration or other conditions was noted.

Laboratory assessments were required before, during, and after treatment. In addition, a patient with abnormal laboratory results was to be retested until the values returned to approximately the baseline levels for that patient. These assessments were not always done. However, all available laboratory test results were evaluated with respect to normal ranges by the investigators, who recorded on the CRF the relationship of any abnormal or unusual result to cefepime or cefotaxime. Data from all study sites were reviewed and analyzed at Bristol-Myers Squibb.

For safety analyses, the laboratory tests listed below were selected as the most appropriate indicators of toxicity. To identify clinical abnormalities, "direction of toxicity" was defined for each of the selected tests as follows (clinically relevant levels are also provided for each unit):

Decrease below the lower limit of normal:

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Hematocrit :	< 24 vol%
Neutrophil :	≤ 500/cmm
WBC :	≤ 2000/cmm
Platelet :	≤ 50,000/cmm
Prothrombin Ratio :	< 50%

Increase above the upper limit of normal:

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Alkaline phosphatase :	≥ 3 x UNL
AST, ALT :	≥ 3 x UNL
Total Bilirubin :	≥ 3.0 mg/dL
BUN :	≥ 50.0 mg/dL
BUR :	≥ 100.0 mg/d
Creatinine :	≥ 3.0 mg/dL
Prothrombin Time :	> 25 sec.
PTT :	> 90 sec.
Eosinophil :	≥ 1000/cmm

Outside normal limits :

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Sodium :	≤ 119 or ≥ 160 mEq/dL
Potassium :	≤ 2.4 or ≥ 6.5 mEq/dL
Calcium :	≤ 7.0 or ≥ 12.0 mg/dL
Phosphorus :	≤ 1.7 or ≥ 6.1 mg/dL

Additional criteria were implemented in testing for neutropenia and eosinophilia.

The following definitions apply to laboratory values :

Abnormal : Outside the normal range limit in the direction of toxicity.

Normal : All other laboratory values were defined to be normal.

Standard conversion factors were applied as needed to both test results and normal range values in order to express data in units as in the table above so that the data could be grouped and analyzed by a minimal number of algorithms.

Discontinuations

The protocol stated that any of the following conditions could justify the early discontinuation of a patient from cefepime treatment. However, investigators sometimes continued therapy for patients who improved clinically.

1. No pathogen isolated from the pre-treatment culture.
2. *In vitro* testing revealed that the causative pathogen was resistant to cefepime (MIC $\geq$ 32 mcg/mL; zone size $\leq$ 14 mm for 30 mcg disc) or cefotaxime (MIC $\geq$ 64 mcg/mL; zone size $\leq$ 14 mm for 30 mcg disc).
3. A poor clinical response was evident after 72 hours of therapy.
4. A serious or alarming adverse event.
5. Intercurrent illness.
6. Patient's decision not to participate further.
7. Investigator's decision that it was in the best interest of the patient to discontinue cefepime treatment.
8. Administrative reasons.

Deaths and discontinuations are summarized at the end of this report.

RESULTS:

Low Dose: There were a total of 18 patients with lower respiratory tract infections in this single investigator study; twelve patients received treatment with cefepime and six received treatment with cefotaxime. The study was conducted between August 25, 1989 and February 2, 1990.

High Dose: There were a total of 62 patients with lower respiratory tract infections enrolled by two investigators in this study; forty-one patients received treatment with cefepime and twenty-one received treatment with cefotaxime. The study was conducted between May 25, 1989 and March 23, 1990.

STUDY 106 PNEUMONIA PATIENTS^{1,2}

CENTER	INVESTIG COUNTRY	CEFEPIME ENROLLED	BMS EVALUABLE	NO CLIN EVALUABLE	NO STRICT EVALUABLE	CEFOTAXIME ENROLLED	BMS EVALUABLE	NO CLIN EVALUABLE	NO STRICT EVALUABLE
LOW DOSE N = 4									
003	VANDENBRG /BELGIUM	2	0	0	0	2	0	2	1
HIGH DOSE N = 48									
001	BARCKOW /GERMANY	25	8	20	0	12	0	9	0
002	SCHWIGON /GERMANY	9	6	8	0	2	2	2	0
TOTAL		34	14	28	0	14	2	11	0

¹Clinically evaluable patients were those patients who were enrolled with a _____ infection, who did not have a valid pathogen, but who met all other reviewer evaluability criteria.

²The strictly evaluable population included those patients who were followed clinically and whose identified pathogen was microbiologically evaluable. These patients had either a good gram stain recorded (i.e. ≥ 25 PMNs and ≤ 10 epithelial cells under low power magnification) or had a positive blood culture.

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REASONS PATIENTS COULD BE CONSIDERED NON-EVALUABLE BY THE REVIEWER:

1. The patient did not have the minimally required three clinical evaluations: a) pre-therapy, b) during/end of therapy and c) post-therapy.
2. The isolated pathogen was resistant to study drug.
3. No pathogen was isolated. There was always an additional reason why a patient in this category was unevaluable or he/she is listed in parentheses as a patient considered for the clinically evaluable category.
4. There were antimicrobials administered for greater than twenty-four hours prior to study start. Usually there was insufficient information to determine whether the antimicrobial administered did not impact on the clinical and/or microbiological outcome of the infection.
5. Additional antimicrobial therapy was prescribed between the end of treatment and follow-up assessments.
6. The patient received concomitant antimicrobial therapy.
7. There was no follow-up assessment made at the test of cure visit (5-21 days post-therapy).
8. The patient did not receive the minimum number of doses required for an assessment of cure (9 doses) or failure (5 doses) for cefepime or cure (13 doses) or failure (8 doses).
9. Therapy exceeded 18 days.
10. The patient did not have either pneumonia Or, an initial chest X-ray was indicated and it was not performed.
11. A pathogen was isolated and identified. However, no sensitivity testing (no zone sizes or MICs) was completed.
12. The dosage of the study drug administered was other than 2g BID or renal equivalent dosing.
13. The patient was also receiving another investigational drug.
14. No end-of treatment or follow-up chest X-ray was performed. Radiological assessments were acceptable after end of treatment ($\pm$ 1 day).
15. There was either no gram stain available, an inadequate gram stain was recorded and/or a blood culture was negative.

The above lists the possible reasons a patient could be classified as non-evaluable. The tabulation below serves only an indicator of the reasons patients were excluded from the efficacy analysis. Many patients had more than one reason; however, only one reason per patient was listed.

HOW TO READ THE FOLLOWING TABLE:

The table below is a composite of two tables (reasons patients were not clinically evaluable and reasons patients were not strictly evaluable). The gray shaded area labelled "subtotal" is the number of patients who were not clinically evaluable. The gray shaded area labelled "total" is the number patients who were excluded from the strictly evaluable population. The patients in the parentheses are those patients whose only reason for being excluded from the strictly evaluable population was an inappropriate pathogen (i.e. no gram stain documentation, a resistant organism identified, no sensitivities done or no pathogen at all was isolated). For example, listed under high dose no pathogen /pneumonia patients, what does "3 + (6)" mean? This means that 9 patients had no pathogen identified and were excluded from the strictly evaluable population. Of these 9, there were 6 patients who met all other evaluability save for an appropriate pathogen. The other 3 patients were not eligible for the clinically evaluable population, because they had a second reason (not identified here) that made them non-evaluable. For example: Often, when an investigator determined that a patient's culture was negative; the patient was removed from the study. Because the patient was not followed to study completion, the patient could not be considered clinically evaluable.

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CLINICAL EFFICACY

PNEUMONIA

CLINICAL RESPONSE	BMS		NO CLINICALLY EVAL		NO STRICTLY EVAL	
	CEFEPIME	CEFOTAX	CEFEPIME	CEFOTAX	CEFEPIME	CEFOTAX
LOW DOSE						
DRUG	CEFEPIME	CEFOTAX	CEFEPIME	CEFOTAX	CEFEPIME	CEFOTAX
SATISFACTORY	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	1 (100%)
UNSATISFACTORY	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)
UNEVALUABLE	?	2	2	0	0	1
TOTALS	2	2	2	2	2	2
HIGH DOSE						
DRUG	CEFEPIME	CEFOTAX	CEFEPIME	CEFOTAX	CEFEPIME	CEFOTAX
SATISFACTORY	13 (93%)	2 (100%)	17 (61%)	6 (55%)	0 (0%)	0 (0%)
UNSATISFACTORY	1 (7%)	0 (0%)	11 (39%)	5 (45%)	0 (0%)	0 (0%)
UNEVALUABLE	20	12	6	3	34	14
TOTALS	34	14	34	14	34	14

The BACTERIOLOGICAL response for pneumonia based on the low dose cefotaxime patient that was strictly evaluable is:

S. pneumoniae

1/1 (100%)

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The following tables examine efficacy related to various demographic variable to determine if there are intrapopulation variables which would require labelling modifications.

CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
PNEUMONIA

VARIABLE	BMS		NO CLINICALLY EVAL.		NO STRICTLY EVAL	
	CEFEPIME	CEFOTAX	CEFEPIME	CEFOTAX	CEFEPIME	CEFOTAX
LOW DOSE						
ALL	0 (0%)	0 (0%)	0 (0%)	1/2 (50%)	0 (0%)	1/1 (100%)
WOMEN	-	-	-	0/1 (0%)	-	-
MEN	-	-	-	1/1 (100%)	-	1/1 (100%)
WHITE	-	-	-	1/2 (50%)	-	1/1 (100%)
BLACK	-	-	-	-	-	-
OTHER	-	-	-	-	-	-
< 65 YEARS	-	-	-	-	-	-
> 65 YEARS	-	-	-	1/2 (50%)	-	1/1 (100%)
HIGH DOSE						
ALL	13/14 (93%)	2/2 (100%)	17/28 (61%)	6/11 (55%)	0 (0%)	0 (0%)
WOMEN	7/8 (88%)	1/1 (100%)	6/11 (55%)	1/4 (25%)	-	-
MEN	6/6 (100%)	1/1 (100%)	11/17 (64%)	5/7 (71%)	-	-
WHITE	12/13 (92%)	2/2 (100%)	16/27 (59%)	6/11 (55%)	-	-
BLACK	-	-	-	-	-	-
OTHER	1/1 (100%)	-	1/1 (100%)	-	-	-
< 65 YEARS	6/6 (100%)	1/1 (100%)	9/11 (82%)	2/5 (40%)	-	-
> 65 YEARS	7/8 (88%)	1/1 (100%)	8/17 (47%)	4/6 (67%)	-	-

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The following table evaluates the effect of underlying lung disease and/or smoking. In the data collection, the information provided included the presence or absence of disease. The specific disease process or length of its existence was not usually recorded. Further information was sometimes available in the investigator's note.

EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS
PNEUMONIA

RESPIRATORY STATUS	BMS		MO CLINICAL EVAL.		MO STRICTLY EVAL.	
LOW DOSE						
DRUG	CEFEPIME	CEFTAX	CEFEPIME	CEFTAX	CEFEPIME	CEFTAX
ALL	0 (0%)	0 (0%)	0/2 (0%)	1/2 (50%)	0 (0%)	1/1 (100%)
SMOKER	-	-	-	-	-	-
LUNG DISEASE	-	-	-	1/2 (50%)	-	1/1 (100%)
SMOKER & LUNG DISEASE	-	-	-	-	-	-
NONSMOKER	-	-	-	-	-	-
HIGH DOSE						
DRUG	CEFEPIME	CEFTAX	CEFEPIME	CEFTAX	CEFEPIME	CEFTAX
ALL	13/14 (93%)	2/2 (100%)	17/28 (61%)	6/11 (55%)	0 (0%)	0 (0%)
SMOKER	1/1 (100%)	-	2/3 (67%)	2/5 (40%)	-	-
LUNG DISEASE	5/5 (100%)	2/2 (100%)	8/9 (88%)	3/4 (75%)	-	-
SMOKER & LUNG DISEASE	1/2 (50%)	-	1/5 (20%)	-	-	-
NONSMOKER	6/6 (100%)	-	6/11 (55%)	1/2 (50%)	-	-

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SAFETY EVALUATIONLow Dose:

Of the total 18 patients enrolled with _____ infections, there was a single patient (1/18 = 5%) who died. There were no deaths (0/12 = 0%) in the cefepime treated group. In the cefotaxime treated group, there was one (1/6 = 17%) death.

	cefepime	cefotaxime
Pneumonia	0/2 (0%)	1/2 (50%)

High Dose:

Of the total 62 patients enrolled with _____ infections, there were a total of nineteen (19/62 = 31%) deaths outlined below. In the cefepime treated group, there were fifteen (15/41 = 37%) deaths. In the cefotaxime treated group, there were four (4/21 = 19%) deaths.

	cefepime	cefotaxime
Pneumonia	11/34 (32%)	3/14 (21%)

LOW DOSE - PNEUMONIA - CEFOTAXIME

The patient was a 66 year old woman with a history of chronic bronchitis, Arnold-Chiari syndrome and paraplegia was admitted for treatment of severe bronchopneumonia. The patient was randomized to receive treatment with cefotaxime. She was treated for five days without clinical improvement. The patient died one day after the study drug was discontinued. Death was due to respiratory compromise and compression of the brainstem, a complication of the patient's underlying condition.

HIGH DOSE - PNEUMONIA - CEFEPIME

The patient was an 84 year old white man with a history of chronic obstructive pulmonary disease who was admitted for acute respiratory insufficiency. He was diagnosed with pneumonia and randomized to receive treatment with cefepime. The patient was treated for seven days and was clinically improved five days after therapy was discontinued. The patient died as a result of lung carcinoma forty-two days after cefepime therapy was discontinued.

The patient was a 51 year old man with a history of multiple medical problems who was admitted for the treatment of a myocardial infarction and aspiration. During the hospitalization, the patient developed symptoms of acute alcohol withdrawal. Pneumonia secondary to aspiration was diagnosed; therapy with cefepime was instituted. Tobramycin and vancomycin were added on days 3 and 4 respectively. The patient received six days of treatment with cefepime without clinical improvement. The patient developed a cardiac arrhythmia and died. An autopsy revealed evidence of a myocardial infarction and coronary artery disease.

The patient was a 74 year old white woman who was admitted for treatment of a myocardial infarction and left ventricular failure. On admission, the patient had symptoms suggestive of pneumonia and an

X-ray showed evidence of an infiltrate. The investigator diagnosed pneumonia and started treatment with cefepime. Three days after therapy was instituted, the patient developed acute renal failure and the dosage of cefepime was adjusted. At this time, gentamicin was also added. The patient showed some improvement; treatment continued for a total of eight days. Death occurred ten days after cefepime was discontinued from complications of a second myocardial infarction.

The patient was an 86 year old white man who was admitted to the hospital for treatment of a myocardial infarction with congestive heart failure. The patient was also diagnosed with pneumonia and was treated with cefepime. The patient received four days of treatment and died of complications of the myocardial infarction.

The patient was a 69 year old white, comatose man who was admitted for treatment of a myocardial infarction. During the hospitalization, the patient developed an uncomplicated bilateral bronchopneumonia. The patient received therapy with cefepime for four days without improvement; alternative antibiotic therapy was instituted. The patient died 20 days after cefepime had been discontinued. The investigator listed the cause of death as cardiac insufficiency.

The patient was a 75 year old white man who was admitted for treatment of bilateral pneumonia. The patient received treatment with cefepime for four days without clinical or radiological improvement. Cefepime was discontinued and alternative therapy was started. The patient died (one day after cefepime was discontinued) as a result of surgery for a repair of an acute obstruction of the aortic bifurcation.

The patient was a 78 year old white woman who was admitted for treatment of a myocardial infarction complicated by an acute, severe right-sided bronchopneumonia. The patient was started on cefepime therapy and after four days was assessed as a clinical failure. Alternative antimicrobial therapy was started; the patient expired six days after cefepime therapy was discontinued. Death was thought to be a result of acute cardiac failure; an autopsy was not permitted.

The patient was a 68 year old woman who was admitted with a posterior myocardial infarction with right ventricular failure. During the hospitalization, the patient developed a right-sided pneumonia that was treated with cefepime for eight days. The patient responded well to therapy. However, ten days post-treatment, the patient again developed signs and symptoms of a respiratory infection. Imipenem was selected to treat the respiratory infection for eight days. No further information was given by the investigator. The patient died of heart failure 51 days after cefepime was discontinued.

The patient was a 68 year old white woman with multiple medical problems who was treated with cefepime for eight days for a right-sided, moderately severe bronchopneumonia. The patient had a

satisfactory clinical response. She died suddenly of a probable pulmonary embolus eight days after treatment was discontinued.

The patient was a 56 year old man who was admitted for treatment of a pulmonary embolus. During the hospitalization, the patient was diagnosed with pneumonia and treated with cefepime without a favorable response. Alternative antimicrobial therapy also did not produce improvement. The patient died sixteen days after cefepime was discontinued of right ventricular failure and pulmonary infarction. In retrospect, the investigator attributed all symptoms as a result of pulmonary infarction. At autopsy, a new myocardial infarct was discovered.

The patient was a 65 year old white woman with multiple medical problems who was diagnosed with a left sided pneumonia and *Salmonella species* bacteremia. Cefepime was instituted; however, alternative therapy was instituted after five days because of a lack of a satisfactory clinical response. The patient was treated with erythromycin and ciprofloxacin. The patient did not improve and she died 10 days after cefepime was discontinued. The cause of death was listed by the investigator as circulatory collapse.

HIGH DOSE - PNEUMONIA - CEFOTAXIME

The patient was an 83 year old white man with several medical problems who was admitted for treatment of left ventricular failure. During the hospitalization, the patient was diagnosed with a right sided bronchopneumonia. The patient received seven days of treatment with cefotaxime with clinical improvement. Seven days later, the patient was given azlocillin for a positive (?) culture. No new infection was noted. The patient expired 26 days after therapy with cefotaxime was discontinued. The cause of death was as result of coronary artery disease.

The patient was a 79 year old white man admitted for treatment of a right-sided pneumonia. He received four doses of cefotaxime before he died of an acute cardiac arrest.

The patient was a 72 year old white woman with multiple medical problems admitted for treatment of bronchopneumonia. She was treated with erythromycin for two days and then switched to treatment with cefotaxime. She did not improve and alternative therapy with imipenem was selected. She showed improvement with this therapy. She died 16 days after study drug was discontinued of cardiac failure.

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LABORATORY ABNORMALITIES:

Low Dose: There was a single patient in the cefepime group with normal pre-treatment liver function tests who developed a clinically relevant elevation of the liver transaminases (SGOT/AST and SGPT/ALT). There were no clinically relevant abnormalities in the laboratory values of the cefotaxime treated patients.

High Dose: In the cefepime group, 13 (32%) of 41 patients who had normal pre-treatment laboratory test values developed abnormal (clinically relevant) laboratory values during treatment or in the post-treatment period. In the cefotaxime group, 7 (33%) of a total of 21 patients, who had normal pre-treatment laboratory test values, developed abnormal clinically relevant values during treatment or during the post-treatment period. The list below catalogues the patients (by number) who developed laboratory abnormalities.

Cefepime GroupSGOT N = 2I-001-102
I-002-212SGPT N = 1

I-001-102

Blood Urea N = 3I-001-107
I-002-207
I-002-219Prothrombin Ratio N = 2I-001-111
I-001-124PTT N = 3I-001-111
I-001-132
I-001-133Eosinophil Count N = 1

I-001-109

Potassium N = 2I-001-120
I-001-124Calcium N = 1

I-001-113

Phosphorus N = 1

I-001-111

Cefotaxime GroupSGOT N = 1

I-002-201

Bilirubin N = 1

I-001-117

Blood Urea N = 2I-001-126
I-002-201Prothrombin Ratio N = 2I-001-125
I-001-136PTT N = 2I-001-110
I-001-134Platelet Count N = 1

I-001-117

LOW DOSE
Overall Changes in Laboratory Test Values
for Patients with Normal Pre-Treatment
Values by Treatment Group
Study 411-106-003

Laboratory Test	Number (%) of Patients					
	Cefepime			Cefotaxime		
	N ^a	Abnormal	Clinically Relevant Test Results	N ^a	Abnormal	Clinically Relevant Test Results
Hematology						
Hematocrit	8	3 (37.5)	0 (0.0)	4	3 (75.0)	0 (0.0)
Leukocyte count	12	1 (8.3)	0 (0.0)	4	0 (0.0)	0 (0.0)
Neutrophil count ^b	12	0 (0.0)	0 (0.0)	4	0 (0.0)	0 (0.0)
Eosinophil count ^b	11	2 (18.2)	0 (0.0)	3	1 (33.3)	0 (0.0)
Platelet count	12	1 (8.3)	0 (0.0)	4	0 (0.0)	0 (0.0)
Coagulation						
Prothrombin Ratio	12	0 (0.0)	0 (0.0)	4	1 (25.0)	0 (0.0)
PTT	12	0 (0.0)	0 (0.0)	4	0 (0.0)	0 (0.0)
Prothrombin time	0	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)
Renal Function						
Creatinine	12	1 (8.3)	0 (0.0)	4	0 (0.0)	0 (0.0)
BUN	0	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)
Blood urea	12	2 (16.7)	0 (0.0)	4	1 (25.0)	0 (0.0)
Liver Function						
ALT (SGPT)	11	1 (9.1)	1 (9.1)	3	0 (0.0)	0 (0.0)
AST (SGOT)	11	1 (9.1)	1 (9.1)	4	0 (0.0)	0 (0.0)
Alkaline phosphatase	11	1 (9.1)	0 (0.0)	3	0 (0.0)	0 (0.0)
Total bilirubin	11	0 (0.0)	0 (0.0)	4	0 (0.0)	0 (0.0)
Electrolytes						
Sodium	10	1 (10.0)	0 (0.0)	4	1 (25.0)	0 (0.0)
Potassium	10	5 (50.0)	0 (0.0)	4	1 (25.0)	0 (0.0)
Calcium	10	4 (40.0)	0 (0.0)	3	2 (66.7)	0 (0.0)
Phosphorus	8	2 (25.0)	0 (0.0)	2	0 (0.0)	0 (0.0)

^a Includes all patients with pre-treatment values within investigator's normal range limits and with at least one post-therapy value obtained

^b Calculated: WBC x (% neutrophils/100) or WBC x (% eosinophils/100)

LOW DOSE
Overall Changes in Laboratory
Test Values for Patients
with Abnormal Pre-Treatment Values by Treatment Group
Study 411-106-003

	Number (%) of Patients					
	Cefepime			Cefotaxime		
	Abnormal Pre-Rx Test Results	Improved* or Unchanged*	Worsened*	Abnormal Pre-Rx Test Results	Improved* or Unchanged*	Worsened*
Hematology						
Hematocrit	4	4(100)	0	0	0	0
Leukocyte count	0	0	0	0	0	0
Neutrophil count	0	0	0	0	0	0
Eosinophil count	1	1(100)	0	1	1(100)	0
Platelet count	0	0	0	0	0	0
Coagulation						
Prothrombin time	0	0	0	0	0	0
Prothrombin ratio	0	0	0	0	0	0
T	0	0	0	0	0	0
Renal Function						
Creatinine	0	0	0	0	0	0
BUN	0	0	0	0	0	0
Blood urea	0	0	0	0	0	0
Liver Function						
AST (SGOT)	1	0	1(100) ^b	0	0	0
ALT (SGPT)	1	0	1(100) ^b	1	1(100)	0
Alkaline phosphatase	1	1(100)	0	1	1(100)	0
Total bilirubin	0	0	0	0	0	0
Electrolytes						
Sodium	1	1(100)	0	0	0	0
Potassium	1	1(100)	0	0	0	0
Calcium	1	1(100)	0	0	0	0
Phosphorus	3	3(100)	0	1	1(100)	0

* During- or post-Rx as compared to pre-treatment. Changes are between relative classes of abnormalities not only in the absolute values.

^b Patients with clinically relevant test results.

HIGH DOSE

Overall Changes in Laboratory Test Values
for Patients with Normal Pre-treatment Values by Treatment Group
Study 411-106

Laboratory Test	Number (%) of Patients		
	Normal Pre-Rx Test Results*	Abnormal During-/or Post-Rx Test Results	Clinically Relevant Test Results
CEFEPIME			
<u>Hematology</u>			
Hematocrit	13	10 (76.9)	0 (0.0)
Leukocyte count	39	0 (0.0)	0 (0.0)
Neutrophil count	34	1 (2.9)	0 (0.0)
Eosinophil count	26	3 (11.5)	1 (3.8)
Platelet count	39	2 (5.1)	0 (0.0)
<u>Coagulation</u>			
Prothrombin Time	0	0 (0.0)	0 (0.0)
Prothrombin Ratio	28	9 (32.1)	2 (7.1)
P/TT	22	12 (54.5)	3 (13.6)
<u>Renal Function</u>			
Creatinine	14	4 (28.6)	0 (0.0)
BUN	0	0 (0.0)	0 (0.0)
Blood Urea	18	11 (61.1)	3 (16.7)
<u>Liver Function</u>			
ALT (SGPT)	19	14 (73.7)	1 (5.3)
AST (SGOT)	14	10 (71.4)	2 (14.3)
Alkaline phosphatase	22	1 (4.5)	0 (0.0)
Total bilirubin	18	5 (27.8)	0 (0.0)
<u>Electrolytes</u>			
Sodium	26	10 (38.5)	0 (0.0)
Potassium	30	10 (33.3)	2 (6.7)
Calcium	6	4 (66.7)	1 (16.7)
Phosphorus	3	3 (100.0)	2 (66.7)

* Includes all patients with pre-treatment values within investigator's normal range limits and with at least one post-therapy value obtained.

Overall Changes in Laboratory Test Values
for Patients with Normal Pre-treatment Values by Treatment Group
Study 411-106
(HIGH DOSE Continued)

Laboratory Test	Number (%) of Patients		
	Normal Pre-Rx Test Results*	Abnormal During-/or Post-Rx Test Results	Clinically Relevant Test- Results
CEFOTAXIME			
<u>Hematology</u>			
Hematocrit	7	6 (85.7)	0 (0.0)
Leukocyte count	20	0 (0.0)	0 (0.0)
Neutrophil count	18	0 (0.0)	0 (0.0)
Eosinophil count	13	2 (15.4)	0 (0.0)
Platelet count	20	1 (5.0)	1 (5.0)
<u>Coagulation</u>			
Prothrombin Time	0	0 (0.0)	0 (0.0)
Prothrombin Ratio	18	5 (27.8)	2 (11.1)
PTT	12	9 (75.0)	3 (25.0)
<u>Renal Function</u>			
Creatinine	6	2 (33.3)	0 (0.0)
BUN	0	0 (0.0)	0 (0.0)
Blood Urea	9	5 (55.6)	2 (22.2)
<u>Liver Function</u>			
ALT (SGPT)	8	5 (62.5)	0 (0.0)
AST (SGOT)	6	1 (16.7)	1 (16.7)
Alkaline phosphatase	13	6 (46.2)	0 (0.0)
Total bilirubin	11	6 (54.5)	1 (9.1)
<u>Electrolytes</u>			
Sodium	14	7 (50.0)	0 (0.0)
Potassium	15	6 (40.0)	0 (0.0)
Calcium	5	2 (40.0)	0 (0.0)
Phosphorus	2	1 (50.0)	0 (0.0)

* Includes all patients with pre-treatment values within investigator's normal range limits and with at least one post-therapy value obtained.

HIGH DOSE
**Overall Changes in Laboratory
 Test Values for Patients
 with Abnormal Pre-Treatment Values by Treatment Group
 Study 411-106**

CEFEPIME

Number (%) of Patients

Laboratory Test

Clinically

	Abnormal pre- Rx Test Results	Improved* or Unchanged*	Worsened*	Relevant Test Results
<u>Hematology:</u>				
Hematocrit	27	20 (74.1)	7 (25.9)	0 (0.0)
Leukocyte count	1	0 (0.0)	1 (100.0)	0 (0.0)
Neutrophil count	0	0 (0.0)	0 (0.0)	0 (0.0)
Eosinophil count	0	0 (0.0)	0 (0.0)	0 (0.0)
Platelet count	0	0 (0.0)	0 (0.0)	0 (0.0)
<u>Coagulation:</u>				
Prothrombin time	0	0 (0.0)	0 (0.0)	0 (0.0)
Prothrombin ratio	12	11 (91.7)	1 (8.3)	1 (100.0)
PTT	16	16 (100.0)	0 (0.0)	0 (0.0)
<u>Renal Function:</u>				
Creatinine	26	15 (57.7)	11 (42.3)	6 (54.5)
BUN	0	0 (0.0)	0 (0.0)	0 (0.0)
Blood urea	20	11 (55.0)	9 (45.0)	5 (55.6)
<u>Liver Function:</u>				
AST (SGOT)	22	21 (95.5)	1 (4.5)	1 (100.0)
ALT (SGPT)	17	15 (88.2)	2 (11.8)	2 (100.0)
Alkaline phosphatase	8	7 (87.5)	1 (12.5)	0 (0.0)
Total bilirubin	5	5 (100.0)	0 (0.0)	0 (0.0)
<u>Electrolytes:</u>				
Sodium	13	13 (100.0)	0 (0.0)	0 (0.0)
Potassium	9	6 (66.7)	3 (33.3)	1 (33.3)
Calcium	5	4 (80.0)	1 (20.0)	0 (0.0)
Phosphorus	6	6 (100.0)	0 (0.0)	0 (0.0)

* During- or post-Rx as compared to pre-treatment. Changes are between relative classes of abnormalities not only in the absolute values.

Overall Changes in Laboratory
Test Values for Patients
with Abnormal Pre-Treatment Values by Treatment Group
Study 411-106
(HIGH DOSE Continued)

CEFOTAXIME

Number (%) of Patients

Laboratory Test	Abnormal Pre- Rx Test Results	Improved* or Unchanged*	Worsened*	Clinically Relevant Tests Result
Hematology:				
Hematocrit	13	9 (69.2)	4 (30.8)	1 (25.0)
Leukocyte count	0	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophil count	0	0 (0.0)	0 (0.0)	0 (0.0)
Eosinophil count	0	0 (0.0)	0 (0.0)	0 (0.0)
Platelet count	0	0 (0.0)	0 (0.0)	0 (0.0)
Coagulation:				
Prothrombin time	0	0 (0.0)	0 (0.0)	0 (0.0)
Prothrombin ratio	2	2 (100.0)	0 (0.0)	0 (0.0)
PTT	8	8 (100.0)	0 (0.0)	0 (0.0)
Renal Function:				
Creatinine	14	11 (78.6)	3 (21.4)	1 (33.3)
BUN	0	0 (0.0)	0 (0.0)	0 (0.0)
Blood urea	11	5 (45.5)	6 (54.5)	4 (66.7)
Liver Function:				
AST (SGOT)	13	11 (84.6)	2 (15.4)	1 (50.0)
ALT (SGPT)	11	8 (72.7)	3 (27.3)	1 (33.3)
Alkaline phosphatase	2	1 (50.0)	1 (50.0)	0 (0.0)
Total bilirubin	2	2 (100.0)	0 (0.0)	0 (0.0)
Electrolytes:				
Sodium	6	6 (100.0)	0 (0.0)	0 (0.0)
Potassium	5	4 (80.0)	1 (20.0)	0 (0.0)
Calcium	4	4 (100.0)	0 (0.0)	0 (0.0)
Phosphorus	3	2 (66.7)	1 (33.3)	1 (100.0)

* During- or post-Rx as compared to pre-treatment. Changes are between relative classes of abnormalities not only in the absolute values.

SUSCEPTIBILITY

Determinations of susceptibility were made by disc diffusion and/or MIC methods. The criteria to classify the causative pathogen according to their susceptibility to both study drugs that have been used are:

	Cefepime	Cefotaxime
Disc sensitivity	Susceptible ≥ 18 mm	≥ 23 mm
	Intermediate > 14 and < 18 mm	> 14 and < 23 mm
	Resistant ≤ 14 mm	≤ 14 mm
Mic Sensitivity	Susceptible ≤ 8 mcg/ml	≤ 8 mcg/ml
	Intermediate > 8 and < 32 mcg/ml	> 8 and < 64 mcg/ml
	Resistant ≥ 32 mcg/ml	≥ 64 mcg/ml

Susceptibility data were obtained for the patients with a causative pathogen, whether isolated from LRTI source, blood, infected wound, urine or faeces.

Susceptibility of Initial Causative Pathogen to Cefepime
All Patients
Study 411-106-003/US
LOW DOSE

Organism	Number (%) of Tested Isolates*				Total
	Suscep- tible	Inter- mediate	Resistant	Not Done	
<i>S. pneumoniae</i>	4 (100)	0	0	3	7
<i>H. influenzae</i>	2 (67)	0	1 (33)	0	3
<i>Klebsiella</i> sp.	2 (100)	0	0	0	2
<i>Pseudomonas</i> sp.	1 (100)	0	0	0	1
<i>E. coli</i>	3 (100)	0	0	0	3
<i>P. aeruginosa</i>	1 (100)	0	0	0	1
<i>Serratia</i> sp.	1 (100)	0	0	0	1
<i>M. catarrhalis</i>	1 (100)	0	0	0	1
<i>Acetivobacter</i> sp.	1 (100)	0	0	0	1
<i>P. mirabilis</i>	1 (100)	0	0	0	1
Total	17 (94%)	0	1 (6%)	3	21

* Pathogens not tested are not included in the percentages.

Susceptibility of Initial Pathogen to Cefepime
Study 411-106
HIGH DOSE

Isolates*	Number (%) of Tested				
	Susceptible	Intermediate	Resistant	Not done	Total
C. diversus	0	1 (100)	0	0	1
E. agglomerans	0	1 (100)	0	0	1
E. cloacae	1 (33)	2 (66)	0	0	3
E. coli	2 (100)	0	0	0	2
H. influenzae	4 (100)	0	0	2	6
K. oxytoca	2 (100)	0	0	0	2
K. pneumoniae	1 (50)	1 (50)	0	1	3
M. morgani	0	0	0	1	1
P. aeruginosa	1 (100)	0	0	2	3
P. mirabilis	0	3 (100)	0	0	3
P. vulgaris	0	0	0	1	1
S. aureus	13 (57)	10 (43)	0	3	26
S. liquifaciens	1 (100)	0	0	0	1
S. pneumoniae	0	0	0	4	4
Staph. coagulase (-)	0	1 (100)	0	0	1
Salmonella sp.	1 (100)	0	0	0	1
Strep. sp.	0	0	0	3	3
Total	26 (58)	19 (42)	0	17	62

* Pathogens not tested are not included in the percentages

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PNEUMONIAPROTOCOL AI411-111 All European Investigators (NDA volume 1.216-224)

TITLE: A Multi-Investigator Comparative Study of Cefepime and Ceftazidime in the Treatment of Serious Bacterial Infections.

MEDICAL OFFICER'S COMMENTS:

The following protocol description was excerpted from the applicant's study report (volume 1.216); the reviewer has made minor editorial changes. The protocol was designed to study patients with many infections; however, the discussion that follows will be limited to the infections included patients with pneumonia and occasionally other infections. For this review, pneumonia were analyzed separately for safety and efficacy; patients with other respiratory diagnoses were analyzed for safety only. It should also be noted that the protocol did not make any separate provisions to distinguish patients versus patients with pneumonia.

STUDY DESIGN:

This trial was an open, Phase III, Multi-Investigator, randomized Comparative Study of Cefepime and Ceftazidime in the Treatment of Serious Bacterial infections. There were six investigators that enrolled patients in this study, but only five enrolled patients with infections. There were no amendments.

Inclusion Criteria:

1. Provide informed consent;
2. 18 years of age or older;

Note: Women of childbearing potential had to have a negative pregnancy test result immediately prior to enrollment with the exception of patients who were taking oral contraceptives in the prescribed manner, patients who were post-menopausal or patients who had been surgically sterilized.

3. Had a proven or suspected infection caused by a pathogen(s) susceptible to the study drugs;
4. Had signs and symptoms consistent with a serious infection including but not limited to multilobar pneumonias, hospital acquired pneumonia occurring in the intensive care setting, or parenchymal Pseudomonas infections.

Exclusion Criteria

1. Previous enrollment in the study;
2. History of a serious hypersensitivity reaction to a cephalosporin or penicillin antibiotic;
3. Pregnant and/or lactating women;
4. Anuric patients or those on hemo or peritoneal dialysis;
5. Granulocyte count of less than 500 mm³ or expected to become less than 500 mm³ as a result of underlying disease or cytotoxic therapy;
6. Treatment regimen likely to include other antimicrobial drugs during therapy with the study medication or during the post-treatment period;
7. Requirement for long term (greater than 14 days) antimicrobial therapy for treatment of clinical symptoms or eradication of the causative pathogen(s) (e.g. osteomyelitis, empyema, lung abscess);
8. Drug therapy constituting empiric management of a contaminated body site;
9. Signs and symptoms of CNS infection;
10. Presence of medically significant disease or disorder which may have a bearing on the outcome on the study;
11. A very severe, life-threatening infection (patients with symptoms and signs of septic shock; patients with granulocytopenia secondary to infection rather than underlying disease or chemotherapy; or patients with organ failure of more than one organ system); or
12. Placed a "do not resuscitate (DNR)" or "No code" status.
13. Cystic fibrosis, empyema, lung abscess or pneumonia distal to obstructive carcinoma

Procedures and Observations

The table below lists the procedures and observations that were specified in the Protocol for infections.

Procedure	Study Schedule Study 411-111			
	Pre-Rx Within 48 hrs	During-Rx Day 3-5	End-of-Rx Day 0-4	Post-Rx Day 5-14
Informed Consent	X	-	-	-
Medical History	X	-	-	-
Physical Examination	X	X	X	-
Clinical Evaluation	X	X	X	X
Chest X-ray (LRTI only)	X	X ^a	X ^a	-
Bacteriologic Tests	X	X ^b	X ^b	X ^b
Laboratory Tests	X	X	X	-

- a Applies only to patients with a diagnosis of pneumonia. During-treatment X-ray as clinically indicated. End-of-treatment X-ray within 48 hours of completion of treatment or at the time of the post-treatment evaluation.
- b During- and post-treatment cultures will be obtained if there is a source to culture. If there is no source to culture due to diminished sputum, lack of purulent material or healing of the infection, the date of this observation should be documented in the CRF with the notation "No Source to Culture." Subcultures were obtained only if a causative pathogen was present.

MEDICAL OFFICER'S COMMENTS:

The time table above is consistent with the protocol as written. The applicant's study report contains modifications of the defined windows that were extended "at the time of the analysis."

Pre-treatment Procedures

1. Within 48 hours before treatment began, a medical history was recorded and a physical examination was to be completed.
2. Clinical signs and symptoms of infection were to be evaluated.

NOTE: In the event prior antimicrobials had been administered, the clinical examination and the appropriate specimens were to be performed following termination of other antimicrobial therapy.

MEDICAL OFFICER'S COMMENTS:

The applicant did not address the influence of other antimicrobial therapy on the clinical outcome. This should have been considered, because not all therapy switches were as a result of treatment failure.

3. Bacteriologic confirmation of the infectious process was to be made by a positive culture from the infected site or blood within 72 hours prior to start of therapy (Day 1) and after the

completion of any previous antimicrobial.

- Specimens were obtained by sterile suction (trans-tracheal or endotracheal aspirate or bronchoscopy) or deep-coughed purulent expectorated sputum as demonstrated by the presence of leukocytes. A gram stain was to be recorded. A second specimen was to be obtained if large numbers of squamous epithelial cells were present suggesting contamination with oral secretions.

4. Each pathogen(s) was to be tested *in-vitro* and found susceptible to cefepime or ceftazidime by disc and/or Minimum Inhibitory Concentration methods.
5. A chest X-ray and radiologic interpretation was required for patients. A chest X-ray was to be obtained within two days prior to or one day following initiation of study therapy.

MEDICAL OFFICER'S COMMENTS:

In the applicant analysis, the interval for the chest X-ray was extended to three days prior and to two days following initiation of therapy.

6. Laboratory studies were requested within 48 hours before treatment. The assessments performed were:

HEMATOLOGY

Hemoglobin
Hematocrit
WBC count, total and differential
Platelet count or estimate from smear
Prothrombin time
Partial thromboplastin time (PTT)
Erythrocyte Sedimentation Rate (ESR)

SERUM CHEMISTRY

Aspartate aminotransferase (AST/SGOT)
Alanine aminotransferase (ALT/SGPT)
Total bilirubin
Alkaline phosphatase
Blood urea nitrogen (BUN)
Creatinine
Glucose
Electrolytes (sodium, potassium, calcium, and phosphorus)

URINALYSIS

Albumin
Glucose
Blood (by dipstick)

During-Treatment Procedures

The following procedures were to be performed by investigator at least once during therapy:

1. An abbreviated physical examination.
2. Assessment of clinical signs and symptoms of infection.
3. A culture was to be obtained from the infected site and/or blood (if the pretreatment blood culture was positive) between Day 3-5 of therapy.
 - a. All pathogens from a positive culture were to be isolated, identified and tested for susceptibility.
 - b. At the same time, the investigator was to determine whether a patient with a positive culture should be discontinued and placed on other therapy.
 - c. For patients with _____ if there is no source to culture due to diminished sputum production or healing of the infected site, the date of the attempted culture was recorded in the patient's record and on the CRF with the statement "No Source to Culture".
4. Laboratory tests were to be repeated as above and at the discretion of the investigator.
5. Chest X-rays were to be repeated as needed.
6. Pathogens from concurrent infections that developed were appropriately cultured and tested for susceptibility.

MEDICAL OFFICER'S COMMENTS:

The applicant's retrospective analysis waived all the above (1-6) during therapy assessments.

7. Ceftazidime treated study patients whose pre-therapy pathogens were resistant to ceftazidime, but susceptible to cefepime could be entered in the non-comparative arm of the study and treated with cefepime. For these patients, ceftazidime would be discontinued, a new culture obtained and treatment with cefepime was initiated.

End-of-Treatment Procedures

The following procedures were to be performed between the last day of therapy and four days after completion of therapy:

1. A physical examination.
2. Assessment of clinical signs and symptoms of infection.
3. If an end-of-treatment culture was positive, the organism was to be identified and tested for susceptibility to both study drugs.
4. For patients with _____ a culture was to be obtained if there was a source to culture. If there was no source to culture due to lack of sputum, then the date of attempted culture was documented in the patient's records and on the bacteriologic data section of the CRF. If

material was present, then arrangements to have a repeat sputum culture at the 5-14 follow-up visit was made.

5. For bacteremia, an end-of-treatment blood culture was to be obtained.
6. A chest X-ray and radiologic interpretation was performed on all patients with confirmed pneumonia. This was done within 48 hours of completion of therapy or at the time of the post-treatment evaluation.

MEDICAL OFFICER'S COMMENTS:

The applicant modified this requirement "retroactively" such that "the post-treatment X-ray could be waived if an X-ray was taken during therapy was negative."

In fact, the applicant also waived the end of treatment assessment altogether. In the study report, it states "In practice, it was accepted if these (end of treatment) procedures were not performed."

7. Laboratory studies were to be repeated.

Post-Treatment Procedures

The investigator was requested to complete the procedures listed below between 5-14 days after completion of therapy. Most clinical evaluations were to occur more than 10 days following termination of therapy.

1. Assessment of clinical signs and symptoms of infection.
2. If material was available to culture from the original site of infection or a new site, then a specimen for the culture was to be obtained.

Treatment Group Assignment

Patients were assigned to one of two treatment groups (cefepime or ceftazidime) according to a randomization schedule. The randomization scheme called for the allocation of patients to the two treatment groups at a 1:1 ratio.

Drug Information and Dose Selection

Cefepime was supplied by Bristol-Myers Squibb Company in vials containing 1 gram of a dry-powder blend of cefepime dihydrochloride and L-arginine. Conditions for storage were specified on the label of each vial.

Ceftazidime was supplied by Bristol-Myers Squibb Company in 1 gram vials.

Investigators prepared cefepime or ceftazidime for infusion and administered the resulting solution intravenously over 30 minutes. Patients allocated to cefepime treatment received 2 grams every 12 hours. Ceftazidime was administered at a dose of 2 grams every 8 hours.

**Recommended Dosage Adjustments for
Renally Impaired Patients**

Creatinine Clearance (ml/min)	Recommended Dose and Frequency of Dosing
Cefepime :	
> 50	2 g Q12h
31-50	2 g Q24h
11-30	1 g Q24h
Ceftazidime :	
> 50	2 g Q8h
31-50	2 g Q12h
16-30	2 g Q24h
11-15	1 g Q24h

Length of Therapy

Treatment was to be "up to 14 days." Because of the serious nature of the infections, it was estimated that many patients would require ten days of therapy.

New Infection

A new infection was defined by the presence of new, persistent or worsening symptoms and/or signs of infection associated with the isolation of a new pathogen from the original site(s) of infection or any pathogen from a new site of infection.

Concomitant Therapy

Investigators were asked to record on the CRF all concomitant medications and therapy. No other systemic antimicrobials having activity against the genus of the pathogen isolated were permitted concomitantly with cefepime or ceftazidime.

Applicant Criteria for Evaluability

A patient was considered evaluable for efficacy only if the following criteria were met:

1. Any infection was diagnosed on clinical grounds and confirmed by a positive pre-treatment culture taken after discontinuation of any previous antimicrobial treatment.
2. Susceptibility testing was performed with both cefepime and ceftazidime against all pathogens.
3. At least one causative pathogen was isolated in the pre-treatment culture. Any such pathogen isolated was shown to be susceptible to the study drug administered.

4. During-treatment procedures, clinical and bacteriologic, specific to diagnosis were conducted on the days specified.
5. Post-treatment procedures, clinical and bacteriologic, specific to diagnosis were conducted on the days specified.
6. Patients diagnosed as having pneumonia had pre-treatment and during- or post-treatment X-ray examinations that confirmed the diagnosis and response, respectively.
7. No other systemic antimicrobial agent having activity against the genus of the pathogen isolated was taken during the time between the pre-treatment culture and the post-treatment culture and clinical evaluation.
8. Cefepime and ceftazidime were administered intravenously at the dose, frequency, and duration specified in the Protocol; a minimum of seven doses of cefepime and 11 doses of ceftazidime was required within a 96-hour period in patients for whom no dosage adjustments due to renal impairment were required.

MEDICAL OFFICER'S COMMENTS:

The reviewer disagrees with the Protocol's request for a minimum number of 7 doses of cefepime or 11 doses of ceftazidime required for efficacy. In general, a parenteral product is targeted primarily at the more severely ill patient. Therefore, a minimum of five days of therapy should be required; this concurs with the IDSA guideline of treatment for an evaluable patient with pneumonia.

9. Patients who were declared Clinical or Bacteriologic Failures but who had one or more reasons for exclusion from the efficacy analyses were considered evaluable for efficacy if the failure preceded the reason for exclusion.

Applicant Efficacy Criteria Definitions

Clinical Response

Satisfactory: All signs and symptoms relevant to the infection were improved or resolved, and no new clinical signs or symptoms were present at the post-treatment follow-up. For pneumonia patients whose clinical signs and symptoms had improved but whose X-rays showed an increase or worsening of the infiltrate, the investigator determined the response based on the clinical setting.

Unsatisfactory: One or more signs or symptoms relevant to the original infection persisted or worsened for 72 hours or more after the start of therapy, and a clinical decision was made to change the antimicrobial agent, or any clinical signs and symptoms relevant to the original infection persisted or worsened following initial improvement or by the time of the post-therapy follow-up.

Unable to Determine: A response could not be determined: a) Other antimicrobial administered between the pre- and post-therapy assessments, b) Pre-treatment or follow-up chest X-ray not done for patients; or c) Patient lost to follow-up.

Bacteriologic Response

Eradicated: The Bacteriologic Response was considered eradicated if the pre-therapy causative pathogen was not present in the post-therapy culture (3-14 days post-therapy) or there was no source to culture due to diminished sputum production.

Persisted: The Bacteriologic Response was considered persisted if the pre-therapy causative pathogen was present in the post-therapy culture. If the patient had been removed from the study and the last culture obtained was positive, then the Bacteriologic Response was considered persisted.

Undetermined: A response could not be determined: a) Other antimicrobial given between pre- and post-therapy cultures; b) Patient lost to follow-up; c) Resistant pathogen.

MEDICAL OFFICER'S COMMENTS:

To be strictly evaluable by the reviewer, a patient had to have:

1. *met the inclusion and exclusion criteria established by the applicant.*
2. *at least two signs and/or symptoms consistent with a infection. Pneumonia was differentiated by the presence of an infiltrate on chest X-ray.*

NOTE:

a. To support the observed diagnosis, the investigator could document the presence of signs and symptoms from a list of pre-selected terms. They were as follows:

<i>Fever</i>	<i>Chills</i>
<i>Chest Pain</i>	<i>Cough</i>
<i>Malaise</i>	<i>Lethargy</i>
<i>Sputum Production</i>	<i>Signs of Lung Consolidation by Auscultation</i>
<i>Rales</i>	<i>Pleural Effusion</i>
<i>Dyspnea</i>	<i>Tachypnea</i>

b. Respiratory rates were not recorded for any patient. Sputum production was not characterized with regard to quantity, quality or relationship to baseline. In patients with chronic respiratory disease, a change in sputum production and/or cough was also not noted.

c. The IDSA states that leukocytosis and pyrexia should be present to support the diagnosis of a infection. In this indication, many patients were afebrile and without a significant elevation of the white count. The study was not designed to capture information with respect to chronic administration of steroids and/or the use of acetaminophen or aspirin products. Therefore, this information could not be used as diagnostic criteria.

d. For a reviewer to validate the diagnosis of a specific respiratory illness, certain minimal clinical and laboratory information is necessary. In some instances, this includes baseline respiratory conditions and/or recent medications. Other helpful supporting data are respiratory rates or arterial oxygen content. This study as others in this indication had limited information to precisely characterize the respiratory condition; however, there was sufficient data to determine that a pulmonary process was present. To the reviewer, the minimum clinical observations required to support the diagnosis of pneumonia were cough, sputum production, and/or abnormal auscultatory sounds.

3. *a culture documented pathogen susceptible to cefepime and ceftazidime.*

NOTE:

a. A gram stain was requested by the applicant. However, a written description was provided at the discretion of the investigator.

b. For the most part, the type of specimen was not identified, e.g. transtracheal aspirate, deep expectorated sputum, etc., nor was the quality described e.g. mucoid, voluminous, blood tinged, etc.

c. Those patients with a documented, valid gram stain and/or positive blood culture constituted the "strictly evaluable" reviewer population.

4. received 24 hours or less of pre-study antimicrobial drug with activity against the identified pathogen or a demonstration of a pathogen resistant to the pre-study antimicrobial drug.

NOTE:

The reviewer believes that this criterion is critical in this study; because treatment by applicant definition could be short (i.e. 3.5 days) and the influence of the pre-study antibiotic is unknown. Second, because validated gram stains were not a study requirement, sputum samples could not always differentiate between a colonizing organism and a true pathogen. The applicant did not address the issue of pre-study antimicrobials in their protocol or study report. The reviewer refers the reader to the published IDSA general guideline which states that: "Patients may be enrolled if they have received <24 hours of treatment with a presumably effective anti-infective drug for an infectious process thought (on the basis of published reference material) to require a standard duration of therapy of ≥ 7 days." The only extenuating circumstances where a patient may exceed the suggested 24 hour limit of pre-study therapy are illnesses which require lengthy therapy e.g. osteomyelitis and endocarditis or patients infected with a pathogen resistant to the initial anti-infective drug and sensitive to the study drug. (pp. S17-18)

Exceptions to this requirement were those patients who had an acceptable interval (five half-lives) between the administration of alternative systemic antimicrobials and study drug.

5. received a minimum of 4.5 days of therapy (i.e. 9 doses of cefepime or 13 doses of ceftazidime) for success. This requirement is consistent with the general IDSA guidelines which recommends a minimum 5 days of therapy for pneumonia. (However, a patient could be classified as a failure after only five cefepime doses.)
6. received a maximum of 18 days therapy. (The protocol specified a maximum of 14 days of therapy.)
7. had neither concomitant nor post-study antimicrobial therapy with activity against the identified pathogen in excess of a single dose.
8. had the minimum of three clinical evaluations: pre-therapy visit, during therapy visit and the follow-up visit (5-21 days).

NOTE:

In instances when an in-person test-of-cure visit was not possible: The reviewer accepted telephone follow-up information provided by the patient (not a third party, e.g. relative), because this mechanism was mutually accepted during the development program. However, the reviewer would like to state her opinion that this information is of dubious value. There was no standard questionnaire to provide consistent data collection and documentation of these telephone conversations. Therefore, each investigator could ask a different battery of questions.

9. had evidence of bacterial clearance ("sputum production resolved") or a statement with regard to "No source to culture" at the follow-up visit (5-21 days).
10. had a pre-treatment chest X-ray and a post-treatment (either end of treatment or follow-up) chest x-ray. The IDSA guideline recommends that: "A chest radiograph will be obtained 3 days after the initiation of therapy, within 72 hours of completion of therapy, and at any other time the investigator deems necessary." (p. S85) It should be noted that the post-treatment X-ray was a requirement in the original protocol.

Clinical Response:

Satisfactory: Improvement and/or resolution of all pre-treatment signs and symptoms diagnostic of pneumonia/ at the test of cure visit (5-21 days). The end of treatment/follow-up chest X-ray had to show either improvement or lack of progression of the pneumonic process.

Unsatisfactory: Persistence or worsening of any clinical signs or symptoms associated with pneumonia during treatment or at the time of the follow-up evaluation (5-21 days). The end of treatment/follow-up chest X-ray showed no improvement or worsening.

Unevaluable: Assessment of the clinical outcome could not be determined e.g. the patient did not return for follow-up evaluation.

Bacteriologic Responses:

Eradication - Either the causative pathogen(s) was not isolated from the follow-up culture or there was a presumptive eradication because there was no material available for culture.

Persistence - The original pathogen(s) was isolated from the follow-up culture or the patient was a clinical failure with a presumed pathogen persistence.

Unevaluable - It was not possible to determine a bacteriological response, e.g. because the patient did not return for follow-up.

The reviewer conducted an assessment of the "strictly evaluable" population based on the criteria described above. However, the reviewer feels that the design of this study was severely deficient. Problematic areas were as follows:

- a. Inadequate gram stain assessments/documentation
- b. The lack of description with respect to quality and quantity of sputum samples
- c. The lack of description of the method in which a sputum sample was collected
- d. The absence of characterization of "change" of described signs and symptoms from baseline (especially in the patient with chronic lung disease)
- e. The lack of a gradation system with respect to the improvement of signs and symptoms
- f. The lack of assessments with respect to pre-treatment antibiotics on selected patients
- g. The absence of correlation with white blood cell counts (elevations and/or bacteremia) and temperature
- h. The absence of definition and attempts to clarify the setting of the pneumonic processes for either pneumonia (i.e. not all pneumonias infections are alike.)
- i. The absence of pre-determined format or questionnaire to gather telephone follow-up data

Not unexpectedly, there were few "strictly evaluable" patients. However, a secondary analysis of a "clinically evaluable" patient population was conducted. The "clinically evaluable" population met all the criteria described above with the exception of the valid pathogen requirement. These patients fell into four categories: a) those patients with an inadequate gram stain, b) those patients whose organism did not have sensitivities done, c) those patients with an inadequate gram stain and a resistant organism and d) those patients in which no organism was isolated. Obviously, this population subset contained patients whose respiratory illness was viral/other and not necessarily bacterial in origin. The reviewer believes that the outcome results of this population are more reflective of the "real world" clinical situation and are more consistent with how the drug will perform when used empirically.

Safety Assessments

All patients who received one dose of cefepime or ceftazidime were evaluable for safety. All adverse clinical events were reported on the CRF along with the investigator's judgement of the relationship of the reaction to cefepime or ceftazidime. Also recorded were the date of onset, duration, and severity of each ACE, and any change in a patient's treatment. If serious or alarming adverse

experience(s) occurred, investigators were to stop administering the drug and notify Bristol-Myers Squibb Company.

Investigators recorded on the CRF whether cefepime or ceftazidime was well or poorly tolerated at the infusion site. The occurrence of phlebitis, hematoma, infiltration or other conditions was noted.

Laboratory assessments were required before, during, and after treatment. In addition, a patient with abnormal laboratory results was to be retested until the values returned to approximately the baseline levels for that patient. These assessments were not always done. However, all available laboratory test results were evaluated with respect to normal ranges by the investigators, who recorded on the CRF the relationship of any abnormal or unusual result to cefepime. Data from all study sites were reviewed and analyzed at Bristol-Myers Squibb.

For safety analyses, the laboratory tests listed below were selected as the most appropriate indicators of toxicity. To identify clinical abnormalities, "direction of toxicity" was defined for each of the selected tests as follows (clinically relevant levels are also provided for each unit):

Decrease below the lower limit of normal:

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Hematocrit :	< 24 vol%
Neutrophil :	≤ 500/cmm
WBC :	≤ 2000/cmm
Platelet :	≤ 50,000/cmm
Prothrombin Ratio :	< 50%

Increase above the upper limit of normal:

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Alkaline phosphatase :	≥ 3 x UNL
AST, ALT :	≥ 3 x UNL
Total Bilirubin :	≥ 3.0 mg/dL
BUN :	≥ 50.0 mg/dL
BUR :	≥ 100.0 mg/d
Creatinine :	≥ 3.0 mg/dL
Prothrombin Time :	> 25 sec.
PTT :	> 90 sec.
Eosinophil :	≥ 1000/cmm

Outside normal limits :

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Sodium :	≤ 119 or ≥ 160 mEq/dL
Potassium :	≤ 2.4 or ≥ 6.5 mEq/dL
Calcium :	≤ 7.0 or ≥ 12.0 mg/dL
Phosphorus :	≤ 1.7 or ≥ 6.1 mg/dL

Additional criteria were implemented in testing for neutropenia and eosinophilia.

The following definitions apply to laboratory values :

Abnormal : Outside the normal range limit in the direction of toxicity.

Normal : All other laboratory values were defined to be normal.

Standard conversion factors were applied as needed to both test results and normal range values in order to express data in units as in the table above so that the data could be grouped and analyzed by a minimal number of algorithms.

Discontinuations

The protocol stated that any of the following conditions could justify the early discontinuation of a patient from cefepime treatment. However, investigators sometimes continued therapy for patients who improved clinically.

1. No pathogen isolated from the pre-treatment culture.
2. *In vitro* testing revealed that the causative pathogen was resistant to cefepime or ceftazidime (MIC $\geq$ 32 mcg/mL; zone size $\leq$ 14 mm for 30 mcg disc).
3. A poor clinical response was evident after 72 hours of therapy.
4. A serious or alarming adverse event.
5. Intercurrent illness.
6. Patient's decision not to participate further.
7. Investigator's decision that it was in the best interest of the patient to discontinue cefepime treatment.
8. Administrative reasons.

Deaths and discontinuations are summarized at the end of this report.

RESULTS:

There were a total of 348 patients enrolled in this study which was conducted at multiple sites from March 14, 1989 to April 22, 1991. Of these 348 patients, 124 patients were enrolled with pneumonia and 17 patients were enrolled

STUDY 111 PNEUMONIA PATIENTS^{1,2}
N = 124

CENTER	INVESTIG COUNTRY	CEFEPIME ENROLLED	BMS EVALUABLE	NO CLIN EVALUABLE	NO STRICT EVALUABLE	CEFTAZIDIME ENROLLED	BMS EVALUABLE	NO CLIN EVALUABLE	NO STRICT EVALUABLE
003	HOEPELMAN /HOLLAND	37	4	15	0	29	5	13	3
004	MEUNIER /BELGIUM	17	5	7	2	21	8	7	2
005	KOSMIDIS /GREECE	2	2		0	0	0	0	0
006	STRAND /SWEDEN	4	1	1	0	3	1	2	0
008	GILLESPIE /ENGLAND	2	0	0	0	3	0	0	0
010	RIDDELL /IRELAND	3	0	2	0	3	1	1	0
TOTAL		65	12	27	2	7	15	23	5

¹Clinically evaluable patients were those patients who were enrolled with a _____ infection, who did not have a valid pathogen, but who met all other reviewer evaluability criteria.

²The strictly evaluable population included those patients who were followed clinically and whose identified pathogen was microbiologically evaluable. These patients had either a good gram stain recorded (i.e. ≥ 25 PMNs and ≤ 10 epithelial cells under low power magnification) or had a positive blood culture.

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RESULTS:

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STUDY 111 PNEUMONIA PATIENTS^{1,2}
N = 124

CENTER	INVESTIG COUNTRY	CEFEPIME ENROLLED	BMS EVALUABLE	NO CLIN EVALUABLE	NO STRICT EVALUABLE	CEFTAZIDIME ENROLLED	BMS EVALUABLE	NO CLIN EVALUABLE	NO STRICT EVALUABLE
003	HOEPELMAN /HOLLAND	37	4	15	0	29	5	13	3
004	MEUNIER /BELGIUM	17	5	7	2	21	8	7	2
005	KOSMIDIS /GREECE	2	2	2	0	0	0	0	0
006	STRAND /SWEDEN	4	1	1	0	3	1	2	0
008	GILLESPIE /ENGLAND	2	0	0	0	3	0	0	0
010	PIDDELL /IRELAND	3	0	2	0	3	1	1	0
TOTAL		55	12	27	2	59	15	23	5

¹Clinically evaluable patients were those patients who were enrolled with a _____ infection, who did not have a valid pathogen, but who met all other reviewer evaluability criteria.

²The strictly evaluable population included those patients who were followed clinically and whose identified pathogen was microbiologically evaluable. These patients had either a good gram stain recorded (i.e. ≥ 25 PMNs and ≤ 10 epithelial cells under low power magnification) or had a positive blood culture.

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REASONS PATIENTS COULD BE CONSIDERED NON-EVALUABLE BY THE REVIEWER:

1. The patient did not have the minimally required three clinical evaluations: a) pre-therapy, b) during/end of therapy and c) post-therapy.
2. The isolated pathogen was resistant to study drug.
3. No pathogen was isolated. There was always an additional reason why a patient in this category was unevaluable or he/she is listed in parentheses as a patient considered for the clinically evaluable category.
4. There were antimicrobials administered for greater than twenty-four hours prior to study start. Usually there was insufficient information to determine whether the antimicrobial administered did not impact on the clinical and/or microbiological outcome of the infection.
5. Additional antimicrobial therapy was prescribed between the end of treatment and follow-up assessments.
6. The patient received concomitant antimicrobial therapy.
7. There was no follow-up assessment made at the test of cure visit (5-21 days post-therapy).
8. The patient did not receive the minimum number of doses required for an assessment of cure (9 doses) or failure (5 doses) for cefepime or cure (13 doses) or failure (8 doses).
9. Therapy exceeded 18 days.
10. The patient did not have either pneumonia Or, an initial chest X-ray was indicated and it was not performed.
11. A pathogen was isolated and identified. However, no sensitivity testing (no zone sizes or MICs) was completed.
12. The dosage of the study drug administered was other than 2g BID or renal equivalent dosing.
13. The patient was also receiving another investigational drug.
14. No end-of treatment or follow-up chest X-ray was performed. Radiological assessments were acceptable after end of treatment ($\pm$ 1 day).
15. There was either no gram stain available, an inadequate gram stain was recorded and/or a blood culture was negative.

The above lists the possible reasons a patient could be classified as non-evaluable. The tabulation below serves only an indicator of the reasons patients were excluded from the efficacy analysis. Many patients had more than one reason; however, only one reason per patient was listed.

HOW TO READ THE FOLLOWING TABLE:

The table below is a composite of two tables (reasons patients were not clinically evaluable and reasons patients were not strictly evaluable). The gray shaded area (labelled "subtotal" is the number of patients who were not clinically evaluable. The gray shaded area labelled "total" is the number patients who were excluded from the strictly evaluable population. The patients in the parentheses are those patients whose only reason for being excluded from the strictly evaluable population was an inappropriate pathogen (i.e. no gram stain documentation, a resistant organism identified, no sensitivities done or no pathogen at all was isolated). For example, listed under no pathogen/pneumonia patients, what does "21 + (13)" mean? This means that 34 patients had no pathogen identified and were excluded from the strictly evaluable population. Of these 34, there were 13 patients who met all other evaluability save for an appropriate pathogen. The other 21 patients were not eligible for the clinically evaluable population, because they had a second reason (not identified here) that made them non-evaluable. For example: Often, when an investigator determined that a patient's culture was negative; the patient was removed from the study. Because the patient was not followed to study completion, the patient could not be considered clinically evaluable.

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CLINICAL EFFICACY

PNEUMONIA (N = 124)

CLINICAL RESPONSE	BMS		NO CLINICALLY EVAL		NO STRICTLY EVAL	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
SATISFACTORY	9 (75%)	13 (87%)	19 (70%)	18 (78%)	1 (50%)	3 (60%)
UNSATISFACTORY	3 (25%)	2 (13%)	8 (30%)	5 (22%)	1 (50%)	2 (40%)
UNEVALUABLE	53	44	37	36	63	54
TOTALS (N)	65	59	65	59	65	59

The BACTERIOLOGICAL responses for pneumonia based on patients that were strictly evaluable are as follows:

<u>E. coli</u>	CEFEPIME	CEFTAZIDINE
<u>K. pneumoniae</u>	0/1 (0%)	1/2 (50%)
<u>S. pneumoniae</u>	1/1 (100%)	2/3 (67%)

The following tables examine efficacy related to various demographic variable to determine if there are intrapopulation variables which would require labelling modifications.

CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
PNEUMONIA N = 124

VARIABLE	BMS		NO CLINICALLY EVAL.		NO STRICTLY EVAL.	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
ALL	9/12 (75%)	13/15 (87%)	19/27 (70%)	18/23 (78%)	1/2 (50%)	3/5 (60%)
WOMEN	3/3 (100%)	4/4 (100%)	10/11 (91%)	6/6 (100%)	0/1 (0%)	2/2 (100%)
MEN	6/9 (67%)	9/11 (82%)	9/16 (56%)	12/17 (71%)	1/1 (100%)	1/3 (33%)
WHITE	9/12 (75%)	12/14 (86%)	19/27 (70%)	18/23 (78%)	1/2 (50%)	3/5 (60%)
BLACK	-	-	-	-	-	-
OTHER	-	1/1 (100%)	-	-	-	-
< 65 YEARS	2/4 (50%)	5/6 (83%)	1/6 (17%)	7/9 (78%)	1/2 (50%)	1/1 (100%)
> 65 YEARS	7/8 (88%)	8/9 (89%)	18/21 (86%)	11/14 (79%)	-	2/4 (50%)

The following table evaluates the effect of underlying lung disease and/or smoking. In the data collection, the information provided included the presence or absence of disease. The specific disease process or length of its existence was not usually recorded. Further information was sometimes available in the investigator's note.

EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS
PNEUMONIA N = 124

RESPIRATORY STATUS	BMS		NO CLINICAL EVAL.		NO STRICTLY EVAL.	
	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ	CEFEPIME	CEFTAZ
ALL	9/12 (75%)	13/15 (87%)	19/27 (70%)	18/23 (78%)	1/2 (50%)	3/5 (60%)
SMOKER	-	3/4 (75%)	1/2 (50%)	4/4 (100%)	-	-
LUNG DISEASE	6/7 (86%)	3/4 (75%)	11/14 (79%)	5/7 (71%)	-	2/2 (100%)
SMOKER & LUNG DISEASE	2/4 (50%)	2/2 (100%)	3/6 (50%)	4/4 (100%)	1/1 (100%)	-
NONSMOKER	1/1 (100%)	5/5 (100%)	4/5 (80%)	5/8 (63%)	0/1 (0%)	1/3 (33%)

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SAFETY EVALUATION

Of the 348 patients that were enrolled in this study, there were 30 patient deaths with infections. Four of these patients had pneumonia and 26 of these patients had pneumonia. There were 19/73 (26%) cefepime patients and 11/68 (16%) ceftazidime patients who died.

Pneumonia (26/124 = 21%)	
treated with cefepime	(18/65 = 28%)
treated with ceftazidime	(8/59 = 14%)

PNEUMONIA - CEFEPIME

The patient was a 79 year old white man with a history of chronic obstructive pulmonary disease with multiple medical problems who was admitted for treatment of pneumonia with bacteremia. The patient received two doses of cefepime. The patient subsequently refused treatment; he died the following day of respiratory insufficiency.

The patient was a 72 year old white woman with multiple medical problems including adenocarcinoma and lung metastases who was admitted with bacteremia. The pre-treatment X-ray was negative except for evidence of metastases; a second chest X-ray suggested an infiltrate. The patient received treatment with cefepime for four doses. The patient's course was complicated by ileus and recurrent pulmonary emboli. Alternative antimicrobials were instituted; the patient continued to deteriorate and died 18 days after cefepime was discontinued.

The patient was a 64 year old white man with a history of cardiovascular disease and a aortic aneurysm repair was admitted for treatment of a right lower lobe pneumonia. The patient received 5 doses of cefepime and was clinically responding. The patient died suddenly of a ruptured aortic aneurysm.

The patient was an 83 year old man who was admitted for treatment of bilateral pneumonia. He received a single dose of cefepime and died six hours later of respiratory failure.

The patient was a debilitated, 91 year old man who was admitted for treatment of bilateral pneumonia. The patient received a single dose of cefepime and died 18 hours later. The investigator believed that the cause of death was related to the patient's underlying prostate carcinoma.

The patient was a 68 year old white old woman who was transferred from another clinic after a respiratory arrest secondary to bronchospasm. During the hospitalization, the patient developed severe bronchopneumonia. She was received antibiotic therapy for five days and was then placed on cefepime therapy. After seven days, the patient did not respond clinically; another antimicrobial was instituted. The patient died the following day of an acute gastrointestinal hemorrhage.

The patient was a 74 year old man who was admitted for treatment of pneumonia. Treatment was started with cefepime. After four days of therapy, fever and leukocytosis persisted. The chest X-ray also worsened. Alternative antimicrobial therapy was instituted. The patient died 72 days after cefepime was discontinued. The cause of death was not listed by the investigator.

The patient was a 50 year old white man with multiple medical problems who received treatment with cefepime for right sided, multilobar pneumonia. Concomitant treatment with clindamycin was also begun. Six days after therapy was discontinued fever, cough and sputum production worsened. The patient expired 82 days after therapy was discontinued. The cause of death is unknown.

The patient was a 78 year old man with a history of lung cancer with metastases to the brain. A clinical diagnosis of bronchopneumonia was made; no chest X-ray was done. Cefepime therapy was given for five days without improvement. The patient died on the fifth day of therapy from the underlying carcinoma.

The patient was a 64 year old man with a history of laryngeal carcinoma who was admitted for treatment of bilateral pneumonia with bacteremia. A single dose of cefepime was administered; the patient died the same day of sepsis.

The patient was a 59 year old white man, with multiple medical problems including head and neck cancer, who was admitted for treatment of a left-sided bronchopneumonia. The patient was treated for twelve days, but the patient's clinical condition deteriorated. Alternative antibiotics were instituted. In addition, the patient developed an abscess at the site of a gastrostomy. The patient died of complications of the underlying neoplasm fifty days after the last dose of cefepime was administered.

The patient was a 53 year old man with a history of thyroid carcinoma who was admitted for treatment of his neoplasm. He developed pneumonia while in the hospital and was started on cefepime therapy. He received two doses and expired. The cause of death was listed as thyroid carcinoma with pulmonary metastases.

The patient was a 57 year old man with metastatic lung carcinoma who was admitted for treatment of pneumonia and an intra-abdominal infection. The patient was treated with cefepime in addition to other antibiotics for twelve days. The patient expired seven days after cefepime was discontinued. The investigator listed the cause of death as neoplastic disease.

The patient was a 50 year old man with a history of prostatic carcinoma who was diagnosed with right-sided pneumonia. The patient received treatment with cefepime for six days during which time the patient's condition deteriorated. Alternative antibiotics were started. The patient died nine days after cefepime therapy was discontinued. The cause of death was respiratory insufficiency superimposed on the underlying neoplastic disease.

The patient was a 58 year old woman with a history of metastatic breast cancer who was admitted to the hospital for chemotherapy. During the hospitalization, she developed bronchopneumonia and bacteremia. The patient clinically responded initially; however, five days post-therapy the patient again exhibited symptoms of a respiratory infection. The patient expired 22 days after cefepime therapy was discontinued. The factors contributing to the patient's death were metastatic breast cancer, cardiac failure and respiratory infection.

The patient was a 40 year old man with a history of esophageal carcinoma and other medical problems who was hospitalized due to a deterioration in his general condition. During his hospitalization, the patient developed bronchopneumonia and vascular access associated bacteremia. Teicoplanin and cefepime were administered simultaneously. Due to a lack of clinical improvement, cefepime was discontinued and other antimicrobial therapy was instituted. The patient expired 21 days after study drug was discontinued. The investigator attributed the cause of death to the underlying neoplasm, pulmonary embolus and fungal infection.

The patient was a 64 year old white man with a history of multiple medical problems who was admitted for a Whipple's procedure for treatment of an ampullary carcinoma. During hospitalization, the patient developed a right-sided pneumonia. The patient received three doses of cefepime therapy and then he expired. The cause of death was his underlying disease and acute renal failure.

The patient was a 78 year woman who was admitted with lobar pneumonia and bacteremia. She received three doses of cefepime without improvement. The physician prescribed alternative antibiotics. The patient expired seven days after cefepime was discontinued. The patient's medical record was lost; therefore, the exact cause of death is unknown.

PNEUMONIA-CEFTAZIDIME

The patient was an 83 year old white man admitted to the hospital for treatment of a recent myocardial infarction and left ventricular failure. On admission, it was determined that the patient also had pneumonia and bacteremia with *S. pneumoniae*. He was enrolled in the study and received ceftazidime for fifteen days. During the hospitalization, the patient developed bacteremia with *Enterococcus species* as a result of a central venous catheter. At this point, study drug was discontinued and alternative therapy instituted. The patient's course was also complicated renal failure and hemodynamic instability. The patient's health continued to decline and she expired 15 days after study drug was discontinued. At autopsy, significant findings were a hypertrophic heart with subendothelial fibrosis and evidence of a gram positive tricuspid valve endocarditis and a hemorrhagic bronchopneumonia.

The patient was a 70 year old woman admitted for radiation treatment of her epidermoid carcinoma. During the hospitalization, the patient developed a gram negative, nosocomial pneumonia. She was enrolled in the study and received treatment with ceftazidime. The patient's condition continued to decline and she expired on day five of therapy.

The patient was a 63 year old white man with multiple medical problems who was admitted for treatment of cancer. During the hospitalization, the patient developed bronchopneumonia. She was treated with ceftazidime for 12 days. There was an initial clinical improvement; but at the time of death, the patient had recurrent dyspnea with sputum production. There were few details of the death. The patient expired two days after therapy was discontinued. The investigator listed the causes of death as chronic pulmonary insufficiency and acute renal failure (creatinine 2 mg/dL).

The patient was a 63 year old woman with a history of multiple medical problems who was admitted for treatment of her neoplasm. During the hospitalization, the patient developed a right lower lobe pneumonia. She was treated for 15 days with ceftazidime. There was clinical improvement, but five days post therapy the patient developed malaise and lethargy. Six days after therapy was discontinued, the patient died. The investigator listed the causes of death as underlying carcinoma, cardiac arrhythmia and arterial thrombosis of the leg.

The patient was an 80 year old white man who was admitted for colectomy for carcinoma. Post-operatively, the recovery course was complicated by pyrexia, confusion, agitation and hypoxia. The patient was clinically diagnosed as having bronchopneumonia; no diagnostic X-ray was done. The patient was treated with ceftazidime for the presumed pneumonia. Two days after therapy was started, an entero-cutaneous fistula developed. Further complications occurred including bronchial obstruction. After 16 days, antimicrobial therapy was discontinued. Four days later, the patient expired; the cause of death was gastrointestinal hemorrhage (confirmed at autopsy) and hypovolemic shock.

The patient was a 43 year old woman with a history of metastatic renal carcinoma who was admitted for treatment of a right sided bronchopneumonia. The patient was treated with ceftazidime for eight days with clinical improvement. The patient expired 23 days after treatment with study drug of her underlying neoplasm.

The patient was a 98 year old man who was admitted for a radical resection of a parotid tumor. Post-operatively, the patient developed pneumonia that was initially treated with a beta-lactam antibiotic. After no improvement, the patient was enrolled in the study and treated with ceftazidime. The patient was treated for nine days without improvement. Study drug was discontinued and alternative antibiotics were started. However, the patient's condition continued to decline. The patient developed heart failure and died 19 days after ceftazidime was discontinued.

The patient was an 82 year old white man with a history of chronic obstructive pulmonary disease who was admitted for treatment of a right sided pneumonia. The patient was randomized to receive treatment with ceftazidime. The patient received two doses of study drug and expired.

Discontinuation

There was one patient diagnosed with pneumonia and treated with cefepime (1/65 = 2%) who had to discontinue treatment due to an adverse clinical event. There were no discontinuations due to an adverse clinical event for pneumonia patients treated with ceftazidime.

<u>Patient</u>	<u>Adverse Event</u>	<u>Severity</u>	<u>Total Dose</u>	<u>Rel.</u>	<u>Outcome</u>
	Rash	Mild	3g	Unknown	Recovered

There were NO discontinuations as a result of a laboratory abnormality nor infusion intolerance.

ADVERSE EVENTS:

Of the 348 patients enrolled in the study, 14 (14/173 = 8%) patients in the cefepime treatment group reported 15 adverse clinical events. Twelve (12/175 = 7%) patients in the ceftazidime group reported 12 adverse clinical events. Of the events thought to be related to study drug, the most common events observed were rash, diarrhea and candidiasis. The latter conditions were observed with both cefepime and ceftazidime.

LOCAL TOLERANCE:

Of the 173 patients who received cefepime, 151 (87%) tolerated treatment well. Twenty-two (13%) patients developed phlebitis and 1 (1%) patient developed hematoma and extravasation. One hundred sixty-four (94%) of the 175 patients in the ceftazidime group tolerated the treatment well. Eleven (6%) of the patients reported phlebitis.

MEDICAL OFFICER'S COMMENTS:

Although laboratory results were discussed in general for this study, they were not discussed per indication. At the reviewer's request, tables for laboratory values and their resultant changes with therapy were submitted in an amendment (number 71). However, each study was not itemized by the applicant. Tables for the entire indication are presented in the summary section of this review.

SUSCEPTIBILITY

Determinations of susceptibility were made by disc susceptibility and/or MIC methods. The criteria used to define sensitivity to cefepime or ceftazidime are as follows:

Disc sensitivity :	Susceptible	≥ 18 mm
	Intermediate	> 14 and < 18 mm
	Resistant	≤ 14 mm
MIC sensitivity :	Susceptible	≤ 8 mcg/ml
	Intermediate	> 8 and < 32 mcg/ml
	Resistant	≥ 32 mcg/ml

Susceptibility data were requested for all patients with a causative pathogen.

**Susceptibility of Causative Organisms
Isolated Pre-Treatment
to All Cefepime Patients
Study 411-111**

Organism	Number (%) of Isolates*				
	Susceptible	Inter- mediate	Resistant	Not Done	Total
<i>A. calcoaceticus</i>				1	1
<i>A. hydrophila</i>	1 (100)				1
<i>A. lwoffii</i>	2 (100)				2
<i>Acinetobacter sp.</i>	1 (100)				1
<i>B. fragilis</i>				3	3
<i>Bacteroides sp.</i>				1	1
<i>B. ovatus</i>				1	1
<i>C. albicans</i>				2	2
<i>C. diversus</i>	1 (100)				1
<i>C. fraundii</i>	2 (100)				2
<i>Corynebacterium sp.</i>				1	1
<i>C. perfringens</i>				1	1
Diphtheroids		1 (100)			1
<i>E. aerogenes</i>	1 (100)				1
<i>E. agglomerans</i>				1	1
<i>E. cloacae</i>	6 (75)	1 (13)	1 (13)	1	9
<i>E. coli</i>	84 (99)		1 (1)	13	98
<i>Enterobacter sp.</i>	2 (100)				2
<i>Enterococcus</i>	1 (20)		4 (80)	3	8
<i>H. alvei</i>	1 (100)				1
<i>H. influenzae</i>	7 (100)			5	12
<i>H. parainfluenzae</i>	1 (100)				1
<i>K. oxytoca</i>	4 (100)				4
<i>K. ozenae</i>				1	1
<i>K. pneumoniae</i>	23 (100)			1	24
<i>Klebsiella sp.</i>	2 (100)				2
<i>L. monocytogenes</i>				1	1
<i>M. catarrhalis</i>	2 (100)				2
<i>M. morgani</i>	4 (100)				4
<i>P. aeruginosa</i>	20 (77)	3 (12)	3 (12)	8	34
<i>P. maltophilia</i>		1 (50)	1 (50)		2
<i>P. mirabilis</i>	13 (93)	1 (17)		5	19
<i>P. vulgaris</i>	3 (100)			1	4
<i>Peptostreptococcus sp.</i>				1	1
<i>Proteus sp.</i>	1 (100)				1
<i>Pseudomonas sp.</i>	1 (100)				1
<i>S. aureus</i>	11 (79)		3 (21)	4	18
<i>S. bovis</i>			1 (100)		1
<i>S. epidermidis</i>	7 (54)		6 (46)	2	15

Susceptibility of Causative Organisms
Isolated Pre-Treatment
to All Cefepime Patients
Study 411-111

Organism	Number (%) of Isolates*				Total
	Susceptible	Inter- mediate	Resistant	Not Done	
<i>S. faecalis</i>			4 (100)		4
<i>S. liquefaciens</i>	3 (100)				3
<i>S. marcescens</i>	3 (60)		2 (40)	1	6
<i>S. milleri</i>				1	1
<i>S. mutans</i>	1 (100)				1
<i>S. pneumoniae</i>	23 (100)			4	27
<i>S. typhi</i>			1 (100)		1
<i>Salmonella sp.</i>	5 (100)				5
Strep.(beta-hemolytic)	1 (100)				1
Strep.(Group A)	1 (100)			1	2
Strep.(Group B)	1 (50)	1 (50)			2
Strep.(Group D)			1 (100)		1
Strep.(Group G)				1	1
Total	239 (87)	8 (3)	28 (10)	65	340

* Pathogens not tested are not included in the percentages.

**CONCLUSIONS FOR
STUDY AI411-111
INFECTIONS**

1. This study was an open, randomized, multi-investigator comparative study of cefepime and ceftazidime in the treatment of serious bacterial infections conducted in Europe. This study included infections urinary tract and skin and skin structures.
Patients received either 2 grams BID of cefepime or 2 grams TID of ceftazidime.

There were 124 patients who were diagnosed with pneumonia; 65 received treatment with cefepime and 59 received treatment with ceftazidime. There were 17 patients diagnosed with *eight were treated with cefepime and nine were treated with ceftazidime.* Many of the patients were severely ill with multiple medical problems complicating their conditions. Assessments were often difficult, because there was little information by the investigators to differentiate underlying diseases (e.g. neoplasia) from primary infections. In addition, there was little, if any descriptive information with regard to the sputum samples obtained. Differentiation with regard to pneumonia,

2. The most common reason patients were not evaluable for the applicant was the lack of an identifiable pathogen. The reviewer included a clinically evaluable population; these were patients for whom treatment was completed, but in whom a pathogen was not identified. In the clinically evaluable population, the success rates for cefepime were (19/27) 70% and (3/5) 60% for pneumonia the success rates for ceftazidime were (18/23) 78% for pneumonia
The numbers of strictly evaluable patients were too small to be meaningful.
3. With regard to safety, the drug was apparently well tolerated. There were nineteen (19/73 = 26%) deaths in the cefepime group and eleven (11/68 = 16%) deaths in the ceftazidime group. The deaths did not appear related to the administration of cefepime. There was one discontinuation due to an adverse event (rash); this was a cefepime patient. The infusion of cefepime was well tolerated. Laboratory abnormalities were not examined in this report, but will be addressed in the summary statement at the conclusion of this report.

PNEUMONIAPROTOCOL AI411-115 European Investigator (NDA volume 1.237)

TITLE: A Study of Cefepime in the Treatment of Serious Bacterial Infections.

MEDICAL OFFICER'S COMMENTS:

The following protocol description was excerpted from the applicant's study report (volume 1.237); the reviewer has made minor editorial changes. The protocol was designed to study patients with many infections; however, the discussion that follows will be limited to the pneumonia and occasionally other infections. For this review, pneumonia were analyzed separately for safety and efficacy; patients with other respiratory diagnoses were analyzed for safety only. It should also be noted that the protocol did not make any separate provisions to distinguish patients versus patients with pneumonia.

STUDY DESIGN:

This trial was a single investigator, non-comparative study of cefepime in the treatment of serious infections of the urinary tract, skin and skin structures (There were no amendments.)

Inclusion Criteria

1. 18 years of age or older

Note: Women of childbearing potential had to have a negative pregnancy test result immediately before enrollment in this study. (Exception: women who were taking an oral contraceptive in the prescribed manner, who were post-menopausal or who had been surgically sterilized).

2. Have had signs and symptoms consistent with a serious infection including but not limited to multilobar pneumonias, hospital acquired pneumonia occurring in the intensive care setting (particularly if the infection was the cause of the ICU admission), or parenchymal pseudomonas infections.
3. Had a proven or suspected infection caused by a pathogen(s) which is susceptible to the study drug.
4. Provided informed consent.

Exclusion Criteria

1. Had been previously enrolled in the study.
2. Had a history of a serious hypersensitivity reaction to cephalosporin or penicillin antibiotic.
3. Were anuric or on hemo- or peritoneal dialysis.
4. Had a granulocyte count less than 500 mm^3 or which was expected to become less than 500 mm^3 as a result of an underlying disease or cytotoxic therapy.
5. Were pregnant/or lactating.
6. Had a treatment regimen likely to include other antimicrobial drugs during therapy with the study medication or during a period approaching 2 weeks post-treatment with cefepime.
7. Had, in the opinion of the investigator, a requirement for long-term (greater than 14 days) antimicrobial therapy for treatment of clinical symptoms or eradication of the causative pathogen(s).
8. Had required drug therapy constituting empiric management of a contaminated body site (e.g. immediate treatment of post-traumatic injury).
9. Had signs and symptoms of CNS infection.
10. Had a medically significant disease or disorder which may have had a bearing on the outcome of the study (e.g. an HIV positive patient with suspected because of possibility of Pneumocystis; AIDS or HIV-positive patient with perirectal ulcer because of possibility of herpes, etc.).
11. Had a very severe, life-threatening infection (e.g. signs and symptoms of septic shock, granulocytopenia secondary to infection rather than underlying disease or chemotherapy, organ failure of more than one organ system).
12. Had been placed on "do not resuscitate (DNR)" or "No Code" status (including patients for whom ventilator support would not be administered).
13. Had cystic fibrosis, empyema, lung abscess or pneumonia distal to obstructive carcinoma.

Pages 271-273

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Post-Treatment Procedures

The investigator was requested to complete the procedures listed below between 10-14 days after completion of therapy.

1. Assessment of clinical signs and symptoms of infection.
2. If material was available to culture from the original site of infection or a new site, then a specimen for the culture was to be obtained.

Drug Information and Dose Selection

Cefepime was supplied by Bristol-Myers Squibb Company in vials containing 1 gram dry-powder blend of cefepime dihydrochloride and L-arginine. Conditions for storage were specified on the label of each vial. The investigator prepared cefepime for infusion and administered the resulting solution intravenously over 30 minutes. The protocol stipulated dosing of 2 g Q12h for up to 14 days, in practice dosing up to 30 days was accepted.

MEDICAL OFFICER'S COMMENTS:

The length of therapy was modified by the investigator as stated above.

The dosage of cefepime was adjusted for patients with renal impairment according to the following:

<u>Creatinine clearance (ml/min)</u>	<u>Dose and frequency of cefepime</u>
> 50	2 g Q12h
31-50	2 g Q24h
11-30	1 g Q24h

New Infection

Although the Protocol defined new infections only for cases where the original pathogen was eradicated, in practice new infections were labelled as such regardless of the status of the original pathogen. A new infection occurred up to 14 days following completion of cefepime treatment if (1) a different pathogen was cultured from the original infection site, or (2) either the original pathogen or a new organism caused an infection at a body site unrelated to the original site.

Concomitant Therapy

The investigator was asked to record on the CRF all concomitant medications and therapy. Drugs other than antimicrobial agents were permitted as required. Antimicrobial therapy other than study drug was allowed during the study or in the post-treatment follow-up period only if the concomitant agent was shown to have no activity against the genus of pathogen involved in the original infection. No other systemic antimicrobials were to be given during therapy with cefepime or during the required post-therapy follow-up period. (Exception: treatment failures).

Applicant Criteria for Evaluability

1. Patients must have had at least 1 pre-therapy sign and/or symptom of that was confirmed by a positive pre-treatment culture obtained for the site of infection.
2. A pre-therapy clinical evaluation of signs and symptoms and pre-therapy culture(s) must have been obtained after the termination of prior antimicrobial therapy;
3. Cefepime susceptibility testing must have been performed on all causative pathogens isolated pre-treatment; and these causative pathogens must have been found to be susceptible to cefepime.
4. A clinical follow-up + 1 to + 14 days post-therapy was required.

MEDICAL OFFICER'S COMMENTS:

The end-of-Phase II meeting established that minimum follow-up evaluation should occur on Days + 5 to + 14.

5. Patients diagnosed as having pneumonia had pre-treatment and during-or post-treatment X-ray examinations that confirmed the diagnosis and response, respectively.
6. A post-therapy culture of sputum or the documentation "No Source to Culture" was required within the window as specified.
7. The study drug must have been administered at the dose, frequency, and duration specified in the protocol although dosing up to 30 days was acceptable, a minimum of 7 doses were required within a 96-hour period.

MEDICAL OFFICER'S COMMENTS:

The protocol specified a length of treatment as 14 days and a minimum treatment of seven days. The reviewer disagrees with the Protocol's request for a minimum number of 7 doses of cefepime required for efficacy. In general, a parenteral product is targeted primarily at the more severely ill patient. Therefore, a minimum of five days of therapy should be required; this concurs with the IDSA guideline of treatment for an evaluable patient with pneumonia

8. The patient must not have received any other systemic antimicrobial agent between the time of pre-treatment culture and post-treatment: clinical and bacteriologic assessments (EXCEPTION: patients who failed to respond to the study drug, or who developed signs and symptoms of infection after completion of therapy and before the time of post-treatment culture. For such a patient, a culture should have been obtained before the initiation of additional antibiotic therapy and the reason for this treatment should have been recorded on the case report form).

Applicant Efficacy Criteria Definitions

Clinical Response

Satisfactory: All clinical signs and symptoms relevant to the infection were resolved or improved and no new clinical signs or symptoms relevant to the infection were present at the time of the post-therapy follow-up evaluation. For patients with pneumonia, if the chest X-ray showed worsening of the infiltrate, but signs and symptoms of the infection had improved, the investigator could determine the response based on the clinical setting.

Unsatisfactory: The persistence or worsening of clinical signs and symptoms relevant to the original infection for 72 hours or more after the initiation of therapy and an accompanying clinical decision to change antimicrobial therapy; or the increase, persistence or worsening of any clinical signs or symptoms that were related to the original site of infection following initial improvement or by the time of the post-therapy evaluation (NOTE: this classification was used unless specific criteria for a new infection were met).

Unable to Determine: The absence of appropriate follow-up evaluations or any other reason that the response could not be classified: a) Other antimicrobial given between pre- and post-treatment evaluation of the study drug; b) Pre-treatment or follow-up chest X-ray not done if pneumonia was diagnosed; c) Patient lost to follow-up, no post-treatment evaluation of the study drug.

Bacteriologic Response

Eradicated: The Bacteriologic Response was considered eradicated if the pre-therapy causative pathogen was not present or if there was no source to culture following therapy (diminished sputum production.)

Persisted: The Bacteriologic Response was classified as persistent if the pre-therapy causative pathogen was present in the post-therapy culture. If the patient was removed from the study and the last culture obtained was positive, then the Bacteriologic Response was also classified as persistent.

Unable to Determine: When it was not possible to evaluate the response: a) Other antimicrobial given between pre- and post-treatment evaluation of the study drug; b) Pre-treatment or follow-up chest X-ray not done if pneumonia was diagnosed; c) Patient lost to follow-up, no post-treatment evaluation of the study drug; or d) No post-treatment culture obtained.

MEDICAL OFFICER'S COMMENTS:

To be strictly evaluable by the reviewer, a patient had to have:

1. met the inclusion and exclusion criteria established by the applicant.
2. at least two signs and/or symptoms consistent with a *respiratory tract infection*. Pneumonia was differentiated by the presence of an infiltrate on chest X-ray.

NOTE:

a. To support the observed diagnosis, the investigator could document the presence of signs and symptoms from a list of pre-selected terms. They were as follows:

Fever	Chills
Chest Pain	Cough
Malaise	Lethargy
Sputum Production	Signs of Lung Consolidation by Auscultation
Rales	Pleural Effusion
Dyspnea	Tachypnea

b. Respiratory rates were not recorded for any patient. Sputum production was not characterized with regard to quantity, quality or relationship to baseline. In patients with chronic respiratory disease, a change in sputum production and/or cough was also not noted.

c. The IDSA states that leukocytosis and pyrexia should be present to support the diagnosis of a lower respiratory tract infection. In this indication, many patients were afebrile and without a significant elevation of the white count. The study was not designed to capture information with respect to chronic administration of steroids and/or the use of acetaminophen or aspirin products. Therefore, this information could not be used as diagnostic criteria.

d. For a reviewer to validate the diagnosis of a specific respiratory illness, certain minimal clinical and laboratory information is necessary. In some instances, this includes baseline respiratory conditions and/or recent medications. Other helpful supporting data are respiratory rates or arterial oxygen content. This study as others in this indication had limited information to precisely characterize the respiratory condition; however, there was sufficient data to determine that a pulmonary process was present. To the reviewer, the minimum clinical observations required to support the diagnosis of pneumonia were cough, sputum production, and/or abnormal auscultatory sounds.

3. a culture documented pathogen susceptible to cefepime.

NOTE:

a. A gram stain was requested by the applicant. However, a written description was provided at the discretion of the investigator.

b. For the most part, the type of specimen was not identified, e.g. transtracheal aspirate, deep expectorated sputum, etc., nor was the quality described e.g. mucoid, voluminous, blood tinged, etc.

c. Those patients with a documented, valid gram stain and/or positive blood culture constituted the "strictly evaluable" reviewer population.

4. received 24 hours or less of pre-study antimicrobial drug with activity against the identified pathogen or a demonstration of a pathogen resistant to the pre-study antimicrobial drug.

NOTE:

The reviewer believes that this criterion is critical in this study; because treatment by applicant definition could be short (i.e. 3.5 days) and the influence of the pre-study antibiotic is unknown. Second, because validated gram stains were not a study requirement, sputum samples could not always differentiate between a colonization organism and a true pathogen. The applicant did not address the issue of pre-study antimicrobials in their protocol or study report. The reviewer refers the reader to the published IDSA general guideline which states that: "Patients may be enrolled if they have received < 24 hours of treatment with a presumably effective anti-infective drug for an infectious process thought (on the basis of published reference material) to require a standard duration of therapy of ≥ 7 days." The only extenuating circumstances where a patient may exceed the suggested 24 hour limit of pre-study therapy are illnesses which require lengthy therapy e.g. osteomyelitis and endocarditis or patients infected with a pathogen

resistant to the initial anti-infective drug and sensitive to the study drug. (pp. S17-18)

Exceptions to this requirement were those patients who had an acceptable interval (five half-lives) between the administration of alternative systemic antimicrobials and study drug.

5. received a minimum of 4.5 days of therapy (i.e. 9 doses of cefepime) for success. This requirement is consistent with the general IDSA guidelines which recommends a minimum 5 days of therapy for pneumonia (However, a patient could be classified as a failure after only five cefepime doses.)
6. received a maximum of 18 days therapy. (The protocol specified a maximum of 14 days of therapy.)
7. had neither concomitant nor post-study antimicrobial therapy with activity against the identified pathogen in excess of a single dose.
8. had the minimum of three clinical evaluations: pre-therapy visit, during therapy visit and the follow-up visit (5-21 days).

NOTE:

In instances when an in-person test-of cure visit was not possible: The reviewer accepted telephone follow-up information provided by the patient (not a third party, e.g. relative), because this mechanism was mutually accepted during the development program. However, the reviewer would like to state his opinion that this information is of dubious value. There was no standard questionnaire to provide consistent data collection and documentation of these telephone conversations. Therefore, each investigator could ask a different battery of questions.

9. had evidence of bacterial clearance ("sputum production resolved") or a statement with regard to "No source to culture" at the follow-up visit (5-21 days).
10. had a pre-treatment chest X-ray and a post-treatment (either end of treatment or follow-up) chest x-ray. The IDSA guideline recommends that: "A chest radiograph will be obtained 3 days after the initiation of therapy, within 72 hours of completion of therapy, and at any other time the investigator deems necessary." (p. S85) It should be noted that the post-treatment X-ray was a requirement in the original protocol.

Clinical Response:

Satisfactory: Improvement and/or resolution of all pre-treatment signs and symptoms diagnostic of pneumonia/ at the test of cure visit (5-21 days). The end of treatment/follow-up chest X-ray had to show either improvement or lack of progression of the pneumonic process.

Unsatisfactory: Persistence or worsening of any clinical signs or symptoms associated with pneumonia during treatment or at the time of the follow-up evaluation (5-21 days). The end of treatment/follow-up chest X-ray showed no improvement or worsening.

Unevaluable: Assessment of the clinical outcome could not be determined e.g. the patient did not return for follow-up evaluation.

Bacteriologic Response:

Eradication - Either the causative pathogen(s) was not isolated from the follow-up culture or there was a presumptive eradication because there was no material available for culture.

Persistence - The original pathogen(s) was isolated from the follow-up culture or the patient was a clinical failure with a presumed pathogen persistence.

Unevaluable - It was not possible to determine a bacteriological response, e.g. because the patient did not return for follow-up.

The reviewer conducted an assessment of the "strictly evaluable" population based on the criteria described above. However, the reviewer feels that the design of this study was severely deficient. Problematic areas were as follows:

- a. Inadequate gram stain assessments/documentation
- b. The lack of description with respect to quality and quantity of sputum samples
- c. The lack of description of the method in which a sputum sample was collected
- d. The absence of characterization of "change" of described signs and symptoms from baseline (especially in the patient with chronic lung disease)
- e. The lack of a gradation system with respect to the improvement of signs and symptoms
- f. The lack of assessments with respect to pre-treatment antibiotics on selected patients
- g. The absence of correlation with white blood cell counts (elevations and/or bandemia) and temperature
- h. The absence of definition and attempts to clarify the setting of the pneumonic processes for either pneumonia (i.e. not all pneumonias; infections are alike.)
- i. The absence of pre-determined format or questionnaire to gather telephone follow-up data

Not unexpectedly, there were few "strictly evaluable" patients. However, a secondary analysis of a "clinically evaluable" patient population was conducted. The "clinically evaluable" population met all the criteria described above with the exception of the valid pathogen requirement. These patients fell into four categories: a) those patients with an inadequate gram stain, b) those patients whose organism did not have sensitivities done, c) those patients with an inadequate gram stain and a resistant organism and d) those patients in which no organism was isolated. Obviously, this population subset contained patients whose respiratory illness was viral/other and not necessarily bacterial in origin. The reviewer believes that the outcome results of this population are more reflective of the "real world" clinical situation and are more consistent with how the drug will perform when used empirically.

Safety Assessments

All patients who received one dose of cefepime were evaluable for safety. All adverse clinical events were reported on the CRF along with the investigator's judgement of the relationship of the reaction to cefepime. Also recorded were the date of onset, duration, and severity of each ACE, and any change in a patient's treatment. If serious or alarming adverse experience(s) occurred that seemed related to cefepime investigators were to stop administering cefepime and notify Bristol-Myers Squibb Company.

Investigators recorded on the CRF whether cefepime was well or poorly tolerated at the infusion site. The occurrence of phlebitis, hematoma, infiltration or other conditions was noted.

Laboratory assessments were required before, during, and after treatment. In addition, a patient with abnormal laboratory results was to be retested until the values returned to approximately the baseline levels for that patient. These assessments were not always done. However, all available laboratory test results were evaluated with respect to normal ranges by the investigators, who recorded on the CRF the relationship of any abnormal or unusual result to cefepime. Data from all study sites were reviewed and analyzed at Bristol-Myers Squibb.

For safety analyses, the laboratory tests listed below were selected as the most appropriate indicators of toxicity. To identify clinical abnormalities, "direction of toxicity" was defined for each of the selected tests as follows (clinically relevant levels are also provided for each unit):

Decrease below the lower limit of normal:

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Hematocrit :	< 24 vol%
Neutrophil :	≤ 500/cmm
WBC :	≤ 2000/cmm
Platelet :	≤ 50,000/cmm
Prothrombin Ratio :	< 50%

Increase above the upper limit of normal:

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Alkaline phosphatase :	≥ 3 x UNL
AST, ALT :	≥ 3 x UNL
Total Bilirubin :	≥ 3.0 mg/dL
BUN :	≥ 50.0 mg/dL
BUR :	≥ 100.0 mg/d
Creatinine :	≥ 3.0 mg/dL
Prothrombin Time :	> 25 sec.
PTT :	> 90 sec.
Eosinophil :	≥ 1000/cmm

Outside normal limits :

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Sodium :	≤ 119 or ≥ 160 mEq/dL
Potassium :	≤ 2.4 or ≥ 6.5 mEq/dL
Calcium :	≤ 7.0 or ≥ 12.0 mg/dL
Phosphorus :	≤ 1.7 or ≥ 6.1 mg/dL

Additional criteria were implemented in testing for neutropenia and eosinophilia.

The following definitions apply to laboratory values :

Abnormal : Outside the normal range limit in the direction of toxicity.

Normal : All other laboratory values were defined to be normal.

Standard conversion factors were applied as needed to both test results and normal range values in order to express data in units as in the table above so that the data could be grouped and analyzed by a minimal number of algorithms.

Discontinuations

The protocol stated that any of the following conditions could justify the early discontinuation of a patient from cefepime treatment. However, investigators sometimes continued cefepime therapy for patients who improved clinically.

1. No pathogen isolated from the pre-treatment culture.
2. *In vitro* testing revealed that the causative pathogen was resistant to cefepime. (MIC $\geq$ 32 mcg/mL; zone size $\leq$ 14 mm for 30 mcg disc).
3. A poor clinical response was evident after 72 hours of therapy.
4. A serious or alarming adverse event.
5. Intercurrent illness.
6. Patient's decision not to participate further.
7. Investigator's decision that it was in the best interest of the patient to discontinue cefepime treatment.
8. Administrative reasons.

Deaths and discontinuations were included in the analysis.

RESULTS:

There were a total of 37 patients enrolled in this study which was conducted at a single site from February 27, 1989 to February 7, 1990. Of these 37 patients, 11 patients were enrolled with pneumonia and 13 patients were enrolled with

STUDY 115
PNEUMONIA
Center 001, Dr. Lode, West Germany

INDICATION	INVESTIGATOR /COUNTRY	CEFEPIME ENROLLED	BMS EVALUABLE	MO CLIN EVALUABLE	MO STRICT EVALUABLE
PNEUMONIA	LODE/W.GERM	11	0	4	0

¹Clinically evaluable patients were those patients who were enrolled with a infection, who did not have a valid pathogen, but who met all other reviewer evaluability criteria.

²The strictly evaluable population included those patients who were followed clinically and whose identified pathogen was microbiologically evaluable. These patients had either a good gram stain recorded (i.e. $\geq$ 25 PMNs and $\leq$ 10 epithelial cells under low power magnification) or had a positive blood culture.

The following table shows the breakdown of bacteriological specimen validation and provides insight into why the number of strictly (clinically and microbiologically) evaluable patients is so small.

GRAM STAIN INFORMATION AVAILABLE

TYPE OF GRAM STAIN	PNEUMONIA N = 11	
GOOD ≤ 10 EPIs, ≥ 25 PMNs	0	
SOME INFO (MANY WBCs)	0	
NONE OR INADEQUATE	10	
RESPIRATOR	0	
POSITIVE BLOOD CULTURE	1	

The clinically evaluable population is essentially a modified-intent-to-treat analysis. It includes all patients with bacterial pneumonias, viral pneumonias, aspiration pneumonias, chlamydial and/or mycoplasma infections.

The strictly evaluable population is also not truly representative of the enrolled patient population. By definition, this population has a larger percentage of patients with positive blood cultures. And, although patients with many types of infections were studied; individual centers tended to enroll patients with similar infection types (e.g. community acquired pneumonia infections in patients with underlying neoplasia). However, patients with "good" gram stains were found in only a few centers.

Finally, it should be recognized that the bulk of patients studied under this indication are in the clinically evaluable population. Because investigators did not anticipate a clinically evaluable population; they often elected to prematurely terminate patients, who did not have a valid pathogen, from the study. Since fewer days of observation are required to detect a failure, there were potentially more patients with negative outcomes that were evaluable.

REASONS PATIENTS COULD BE CONSIDERED NON-EVALUABLE BY THE REVIEWER:

1. The patient did not have the minimally required three clinical evaluations: a) pre-therapy, b) during/end of therapy and c) post-therapy.
2. The isolated pathogen was resistant to study drug.
3. No pathogen was isolated. There was always an additional reason why a patient in this category was unevaluable or he/she is listed in parentheses as a patient considered for the clinically evaluable category.
4. There were antimicrobials administered for greater than twenty-four hours prior to study start. Usually there was insufficient information to determine whether the antimicrobial administered did not impact on the clinical and/or microbiological outcome of the infection.
5. Additional antimicrobial therapy was prescribed between the end of treatment and follow-up assessments.
6. The patient received concomitant antimicrobial therapy.
7. There was no follow-up assessment made at the test of cure visit (5-21 days post-therapy).
8. The patient did not receive the minimum number of doses required for an assessment of cure (9 doses) or failure (5 doses).
9. Therapy exceeded 18 days.
10. The patient did not have either pneumonia indicated and it was not performed. Or, an initial chest X-ray was indicated and it was not performed.
11. A pathogen was isolated and identified. However, no sensitivity testing (no zone sizes or MICs) was completed.
12. The dosage of the study drug administered was other than 2g BID or renal equivalent dosing.
13. The patient was also receiving another investigational drug.
14. No end-of treatment or follow-up chest X-ray was performed. Radiological assessments were acceptable after end of treatment ($\pm$ 1 day).
15. There was either no gram stain available, an inadequate gram stain was recorded and/or a blood culture was negative.

The above lists the possible reasons a patient could be classified as non-evaluable. The tabulation below serves only an indicator of the reasons patients were excluded from the efficacy analysis. Many patients had more than one reason; however, only one reason per patient was listed.

HOW TO READ THE FOLLOWING TABLE:

The table below is a composite of two tables (reasons patients were not clinically evaluable and reasons patients were not strictly evaluable). The gray shaded area labelled "subtotal" is the number of patients who were not clinically evaluable. The gray shaded area labelled "total" is the number patients who were excluded from the strictly evaluable population. The patients in the parentheses are those patients whose only reason for being excluded from the strictly evaluable population was an inappropriate pathogen (i.e. no gram stain documentation, a resistant organism identified, no sensitivities done or no pathogen at all was isolated). For example, listed under no pathogen/pneumonia patients, what does "6 + (4)" mean? This means that 10 patients had no pathogen identified and were excluded from the strictly evaluable population. Of these 10, there were 4 patients who met all other evaluability save for an appropriate pathogen. The other 6 patients were not eligible for the clinically evaluable population, because they had a second reason (not identified here) that made them non-evaluable. For example: Often, when an investigator determined that a patient's culture was negative; the patient was removed from the study. Because the patient was not followed to study completion, the patient could not be considered clinically evaluable.

REASONS PATIENTS WERE EXCLUDED FROM EFFICACY ANALYSIS
Dr. Lode - 2g BID

REASONS NOT EVALUABLE	PNEUMONIA N = 11
3. No Pathogen ¹	6 + (4)
5. Antibiotics between EOT & FUp	1
8. Patient received incomplete Rx	-
9. Therapy > 18 days	-
10. Not pre-study X-ray	-
11. No Sensitivities (MICs) ¹	-
SUBTOTAL (Total excluded from the clinically evaluable population)	7
15. Inadequate pathogen substantiation	(0)
TOTAL (Total excluded from the strictly evaluable population)	7 + (4) = 11

Summary:

Pneumonia:

Total enrollment	11
Total excluded from clinically evaluable population	7
Clinically evaluable	4
Total excluded from strictly evaluable population	11
Strictly evaluable	0

DEMOGRAPHICS:

The following table lists the demographic characteristics of the APPLICANT'S evaluable population for pneumonia.

**DEMOGRAPHICS TABLE
APPLICANT EVALUABLE POPULATION**

PARAMETER	PNEUMONIA N = 0	
SEX FEMALE MALE	0 (0%) 0 (0%)	
RACE WHITE BLACK		
AGE (yr) N MEAN MEDIAN RANGE		
AGE DISTRIBUTION 45-54 65-84		
WEIGHT (kg) N MEAN MEDIAN RANGE		
HEIGHT (cm) N MEAN MEDIAN RANGE		

Below is a table with the demographic information with regard to the reviewer's CLINICALLY evaluable populations.

DEMOGRAPHIC TABLE
MO CLINICALLY EVALUABLE

PARAMETER	PNEUMONIA N = 4
SEX FEMALE MALE	4 (100%)
RACE WHITE BLACK	4 (100%)
AGE (yr) N MEAN MEDIAN RANGE	4 72.3 72
AGE DISTRIBUTION 45-64 65-84	4 (100%)
WEIGHT (kg) N MEAN MEDIAN RANGE	4 60.38 62.0
HEIGHT (cm) N MEAN MEDIAN RANGE	4 160.50 161.0

Below is a table with the demographic information with regard to the reviewer's STRICTLY evaluable populations.

DEMOGRAPHICS TABLE
 NO STRICTLY EVALUABLE

PARAMETER	PNEUMONIA N = 0
SEX FEMALE MALE	0 (0%) 0 (0%)
RACE WHITE BLACK	
AGE (yr) N MEAN MEDIAN RANGE	
AGE DISTRIBUTION 45-64 65-84	
WEIGHT (kg) N MEAN MEDIAN RANGE	
HEIGHT (cm) N MEAN MEDIAN RANGE	

CLINICAL EFFICACY

PNEUMONIA (N = 11)

CLINICAL RESPONSE	BMS	MO CLINICALLY EVAL	MO STRICTLY EVAL
SATISFACTORY	0 (0%)	2 (50%)	0 (0%)
UNSATISFACTORY	0	2 (50%)	0
UNEVALUABLE	11	7	11
TOTALS (N)	11	11	11

The BACTERIOLOGICAL response for pneumonia based on the strictly evaluable patient is:
NONE

The following tables examine efficacy related to various demographic variable to determine if there are intrapopulation variables which would require labelling modifications.

CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
PNEUMONIA N = 11

VARIABLE	BMS	MO CLINICALLY EVAL.	MO STRICTLY EVAL
ALL	0 (0%)	2/4 (50%)	0 (0%)
WOMEN	-	2/4 (50%)	-
MEN	-	-	-
WHITE	-	2/4 (50%)	-
BLACK	-	-	-
OTHER	-	-	-
< 65 YEARS	-	-	-
≥ 65 YEARS	-	2/4 (50%)	-

The following table evaluates the effect of underlying lung disease and/or smoking. In the data collection, the information provided included the presence or absence of disease. The specific disease process or length of its existence was not usually recorded. Further information was sometimes available in the investigator's note.

EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS
PNEUMONIA N = 11

RESPIRATORY STATUS	BMS	MO CLINICAL EVAL.	MO STRICTLY EVAL.
ALL	0/0 (0%)	2/4 (50%)	0/0 (0%)
SMOKER	-	-	-
LUNG DISEASE	-	-	-
SMOKER & LUNG DISEASE	-	2/3 (67%)	-
NONSMOKER	-	0/1 (0%)	-

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SAFETY EVALUATION:

Of the 24 patients enrolled in this study, there were three patients (1/11 = 9% with pneumonia who died.

PNEUMONIA:

The patient was a 49 year old white man with a history of non-Hodgkin's lymphoma who was admitted for treatment of a right middle lobe pneumonia. Treatment began with cefepime, but the investigator switched antimicrobial therapy after only three doses of study drug. *L. pneumophila* was isolated. The patient continued to decline and expired 13 days after cefepime was discontinued. At autopsy, pneumonia was determined to be the cause of death.

Discontinuation

There was one pneumonia (1/11 = 9%) and no bronchitis (0/13 = 0%) patient who discontinued cefepime as the result of an adverse clinical event.

<u>Patient</u>	<u>Adverse Event</u>	<u>Severity</u>	<u>Total dose (g)</u>	<u>Rel.</u>	<u>Outcome</u>
	Rash	Moderate	18g	Prob	Resolved

There were NO discontinuations as a result of a laboratory abnormality nor infusion intolerance.

ADVERSE EVENTS:

Of the 37 patients enrolled in this study, there were five patients who experience 9 clinical events. There were three events of diarrhea, 2 episodes of nausea, and 1 case of rash, 1 case of scaling hands, 1 incident of sweating and 1 case of dysgeusia.

LOCAL TOLERANCE:

All 37 patients tolerated the infusion well.

LABORATORY ABNORMALITIES:

They are recorded from the applicant as follows:

Overall Changes in Laboratory Test Values
for Patients with Normal Pre-Treatment Values
Study 411-115

	Number (%) Patients		
	Normal Pre-Rx Test Results *	Abnormal During-or Post-Rx Test Results	Clinically Relevant Test Results
<u>Hematology</u>			
Hematocrit	28	5 (17.9)	0 (0.0)
Leukocyte count	36	1 (2.8)	0 (0.0)
Neutrophil count	21	1 (4.8)	0 (0.0)
Eosinophil count	19	6 (31.6)	0 (0.0)
Platelet count	33	0 (0.0)	0 (0.0)
<u>Coagulation</u>			
Prothrombin Time	0	0 (0.0)	0 (0.0)
Prothrombin Ratio	30	0 (0.0)	0 (0.0)
PTT	27	2 (7.4)	0 (0.0)
<u>Renal Function</u>			
Creatinine	30	1 (3.3)	0 (0.0)
BUN	0	0 (0.0)	0 (0.0)
Blood Urea	0	0 (0.0)	0 (0.0)
<u>Liver function</u>			
ALT (SGPT)	34	2 (5.9)	0 (0.0)
AST (SGOT)	25	2 (8.0)	0 (0.0)
Alkaline Phosphatase	24	1 (4.2)	0 (0.0)
Total Bilirubin	27	0 (0.0)	0 (0.0)
<u>Electrolytes</u>			
Sodium	32	1 (3.1)	0 (0.0)
Potassium	30	7 (23.3)	0 (0.0)
Calcium	16	10 (62.5)	0 (0.0)
Phosphorus	22	6 (27.3)	0 (0.0)

* Includes all patients with pre-treatment values within investigator's normal range limits and with at least one during- or post-therapy value obtained.

**Overall Changes in Laboratory Test Values
for Patients with Abnormal Pre-Treatment Values
Study 411-115**

	Number Patients					
	Abnormal Pre-Rx	CR ^b	Improved ^a or Unchanged (%)	CR ^b	Worsened (%)	N
<u>Hematology</u>						
Hematocrit	7	0	5 (71.4)	0	2 (28.6)	0
Leukocyte count	0	0	0 (0.0)	0	0 (0.0)	0
Neutrophil count	0	0	0 (0.0)	0	0 (0.0)	0
Eosinophil count	2	0	2 (100)	0	0 (0.0)	0
Platelet count	2	1	2 (100)	1	0 (0.0)	0
<u>Coagulation</u>						
Prothrombin Time	0	0	0 (0.0)	0	0 (0.0)	0
Prothrombin Ratio	1	1	1 (100)	1	0 (0.0)	0
PTT	6	0	5 (83.3)	0	1 (16.7)	1
<u>Renal Function</u>						
Creatinine	4	0	4 (100)	0	0 (0.0)	0
BUN	0	0	0 (0.0)	0	0 (0.0)	0
Blood Urea	0	0	0 (0.0)	0	0 (0.0)	0
<u>Liver function</u>						
ALT (SGPT)	1	0	1 (100)	0	0 (0.0)	0
AST (SGOT)	1	0	1 (100)	0	0 (0.0)	0
Alkaline phosphatase	1	0	1 (100)	0	0 (0.0)	0
Total Bilirubin	4	4	4 (100)	4	0 (0.0)	0
<u>Electrolytes</u>						
Sodium	3	2	2 (66.7)	1	1 (33.3)	0
Potassium	5	0	4 (80.0)	0	1 (20.0)	0
Calcium	10	0	10 (100)	0	0 (0.0)	0
Phosphorus	6	2	3 (50.0)	1	3 (50.0)	1

- ^a During- or post-Rx as compared to pre-treatment. Changes are between relative classes of abnormalities (Appendix E-3.2), not only in the absolute values.
^b Patients with clinically relevant test results.

SUSCEPTIBILITY

Determination of susceptibility was made by disc susceptibility and/or MIC methods. The criteria for the sensitivity to cefepime that have been used are:

Disc sensitivity :	Susceptible	≥ 18 mm
	Intermediate	> 14 and < 18 mm
	Resistant	≤ 14 mm
MIC sensitivity :	Susceptible	≤ 8 mcg/ml
	Intermediate	> 8 and < 32 mcg/ml
	Resistant	≥ 32 mcg/ml

Susceptibility data were requested for all patients with a causative pathogen.

**Susceptibility of Causative Organisms Isolated
Pre-Treatment
All Patients
Study 411-115-001/US**

Pathogen	Number of Isolates		Total
	Susceptible	Not done	
<i>P. vulgaris</i>	3		3
<i>P. aeruginosa</i>	2		2
<i>H. influenzae</i>	1	1	2
<i>H. parainfluenzae</i>	1	1	2
<i>K. pneumoniae</i>	2		2
<i>E. cloacae</i>	1		1
<i>K. oxytoca</i>	1		1
<i>P. mirabilis</i>	1		1
<i>S. marcescens</i>	1		1
<i>S. pneumoniae</i>	1		1
<i>S. viridans</i>	1		1
Total	15	2	17

All tested organisms were susceptible to cefepime.

CONCLUSIONS FOR

INFECTIONS

STUDY AI411-115

1. This study was a single center, noncomparative trial of cefepime conducted in West Germany. The study was to include the study of several types of serious infections including skin and skin structure, urinary tract. Twenty-four of the thirty-seven patients enrolled were diagnosed with infections. Of these patients 11 were diagnosed with pneumonia and 13 were diagnosed with Differentiation with regard to pneumonia, ... and/or more specifically exacerbation of chronic obstructive pulmonary disease was not addressed. All patients were treated with 2 grams of cefepime twice daily.
2. The most common reason patients were not evaluable for the applicant was the lack of an identifiable pathogen. The reviewer included a clinically evaluable population; these were patients for whom treatment was completed, but in whom a pathogen was not identified. In the clinically evaluable population, the success rates were (2/4) 50% and (4/6) 67% for pneumonia.
3. With regard to safety, the drug was apparently well tolerated. There were three deaths and one discontinuation due to an adverse event (rash). The deaths did not appear related to the administration of cefepime. The infusion of cefepime was well tolerated. Laboratory abnormalities were few and not significant.

PNEUMONIAPROTOCOL A411-140 North American Investigators (NDA volumes 1.225-237)

TITLE: A Study of Cefepime in the Treatment of Serious Bacterial Infections, Particularly Those Caused by Staphylococci *Pseudomonas* and Other Less Common Gram-Negative Bacilli

MEDICAL OFFICER'S COMMENTS:

The following protocol description was excerpted from the applicant's study report (volume 1.225); the reviewer has made minor editorial changes. The protocol was designed to study patients with many infections; however, the discussion that follows will be limited to the infections included patients with pneumonia and occasionally other infections. For this review, pneumonia were analyzed separately for safety and efficacy; patients with other respiratory diagnoses were analyzed for safety only. It should also be noted that the protocol did not make any separate provisions to distinguish patients versus patients with pneumonia.

STUDY DESIGN:

This trial was a multi-investigator, non-comparative study of cefepime in the treatment of serious infections of the urinary tract, skin and skin structures. There were a total of seventeen centers who enrolled patients in the United States. (There were 3 amendments.)

Inclusion Criteria

1. Be male or female, 12 years of age or older.
2. Female patients of childbearing potential were to have a negative pregnancy test immediately prior to enrollment, were to be taking oral contraceptives in the prescribed manner, or were to be postmenopausal, premenarcheal, or surgically sterilized.
3. Had signs and symptoms consistent with infections.
4. Had a proven or suspected infection caused by a pathogen(s) which was susceptible to the study drug.
5. Provided informed consent.
6. Although the usual dose for this Protocol was 2 g BID, any patient meeting any of the following criteria for severe, life-threatening infections was to be treated with cefepime at a dose of 2 g TID:
 - a. Patients with signs or symptoms of shock defined by systolic BP < 80 mm Hg or need for intravenous pressure therapy to maintain blood pressure > 80 mm Hg for > 4 hours.

- b. Patients with granulocytopenia (PMN < 500 cells/cmm) which was expected to persist seven days or less.
- c. Multilobar, or necrotizing pneumonia caused by *S. aureus* or *P. aeruginosa* particularly if accompanied
- d. Patients with failure of two or more organ systems defined as follows: 1) cardiac: pulmonary edema or need for two or more medications to treat congestive heart failure; 2) respiratory: requiring mechanical ventilation; 3) hepatic: in clinical jaundice or bilirubin $\geq$ 4.0 mg/dL; 4) renal: calculated creatinine clearance $\leq$ 30 ml/min; 5) neurologic: coma.

Exclusion Criteria

1. Previous enrollment in the study.
2. History of a serious hypersensitivity reaction to a penicillin or a cephalosporin.
3. Pregnancy or lactating.
4. Anuric patients, patients with creatinine clearance < 11 ml/min or those receiving peritoneal dialysis or hemodialysis.
5. Granulocyte count < 500 cmm or expected to become < 500 cmm as a result of underlying disease or cytotoxic therapy, and is expected to persist longer than seven days.
6. Treatment regimen likely to include other antimicrobial drugs during therapy with the study medication or during a period two weeks post-treatment.
7. Drug therapy constituting empiric management of a contaminated body site.
8. Patients who have been placed on "do not resuscitate (DNR)" or "No Code" status.
9. Patients with signs and symptoms of Central Nervous System infection.
10. Patients with suspected bacteremia were excluded if *Bacteroides fragilis* infection was suspected.
11. Patients with serious _____ were excluded if there was cystic fibrosis, pneumonia distal to obstructive carcinoma, or empyema unless definitive surgical management or placement of a chest tube occurs within three days of start of therapy.
12. Presence of medically significant disease or disorder that may have a bearing on the outcome of the study.

Procedures and Observations Outlined in the Protocol and Amendments

The table below lists the procedures and observations that were specified in the Protocol and Amendments for infections.

Study Schedule
Study 411-140

Procedure	Pre-Rx	During-Rx	End-of-Rx	Post-Rx
	Within 48 hrs	Day 3-5	Day 0-4	Day 10-14
Informed Consent	X	-	-	-
Medical History	X	-	-	-
Physical Examination	X	X	X	-
Clinical Evaluation	X	X	X	X
Chest X-ray (LRTI only)	X	X ^a	X ^a	-
Bacteriologic Tests	X	X ^b	X ^b	X ^b
Laboratory Tests	X	X	X	-

- a Applies only to patients with a diagnosis of pneumonia. During-treatment X-ray as clinically indicated. End-of-treatment X-ray within 48 hours of completion of treatment or at the time of the post-treatment evaluation.
- b During- and post-treatment cultures will be obtained if there is a source to culture. If there is no source to culture due to diminished sputum, lack of purulent material or healing of the infection, the date of this observation should be documented in the CRF with the notation "No Source to Culture." Subcultures were obtained only if a causative pathogen was present.

Pretreatment Procedures

1. Within 48 hours before treatment began, a medical history was recorded and a physical examination was completed.
2. Clinical signs and symptoms of infection were to be evaluated.
3. Bacteriologic confirmation of the infectious process was to be made by a positive culture from the infected site or blood. Cultures taken up to 72 hours prior to start of therapy were accepted provided no antimicrobial therapy was administered between the time of the culture and initiation of study therapy.
4. Each pathogen(s) was to be tested *in-vitro* and found susceptible to cefepime. Subcultures of pathogens were prepared and shipped to Bristol-Myers Squibb Company.
5. A chest X-ray and radiologic interpretation was required for patients with _____ A chest X-ray was to be obtained within two days prior to or one day following initiation of study therapy.
6. Laboratory studies were requested within 48 hours before treatment. The assessments performed were:

HEMATOLOGY

Hemoglobin
 Hematocrit
 WBC count, total and differential
 Platelet count or estimate from smear
 Prothrombin time
 Partial thromboplastin time (PTT)
 Direct Coombs' test

SERUM CHEMISTRY

Aspartate aminotransferase (AST/SGOT)
 Alanine aminotransferase (ALT/SGPT)
 Total bilirubin
 Alkaline phosphatase
 Blood urea nitrogen (BUN)
 Creatinine
 Glucose
 Electrolytes (sodium, potassium, calcium, and phosphorus)
 Albumin

URINALYSIS

Specific gravity
 pH
 Albumin
 Glucose
 Microscopic examination (WBC, RBC, casts, crystals, epithelial cells).

7. For patients hospitalized in an Intensive Care Unit (ICU), the patient's severity of illness was to be assessed by the APACHE II classification system.

During-Treatment Procedures

The following procedures were to be performed by investigators during treatment and weekly if the patient was treated for more than 10 days:

1. An abbreviated physical examination.
2. Assessment of clinical signs and symptoms of infection.
3. A culture was to be obtained from the infected site and/or blood (if the pretreatment blood culture was positive) between Day 3-5 of therapy:
 - a. All pathogens from a positive culture were to be isolated and identified. After testing each pathogen's susceptibility, the investigator subcultured it for shipment to Bristol-Myers Squibb.
 - b. At the same time, the investigator was to determine whether a patient with a positive culture should be discontinued and placed on other therapy.
 - c. For patients with _____ if there is no source to culture due to diminished sputum production or healing of the infected site, the date of the attempted culture was recorded in the patient's record and on the CRF with the statement "No Source to Culture".
4. Laboratory tests were to be repeated weekly and at the discretion of the investigator.
5. Patients whose pretreatment culture revealed a causative pathogen resistant to cefepime were removed from the study and placed on other appropriate antimicrobial therapy except for patients with a polymicrobial infection with at least one pathogen susceptible to cefepime, and an anaerobic organism considered to be a pathogen was the only organism not susceptible to cefepime. These patients could receive metronidazole 500 mg QID IV or orally.
6. Patients from whom a causative pathogen was not obtained in the pretreatment culture were removed from the study.
7. Chest X-rays were to be repeated as needed.

End-of-Treatment Procedures

The following procedures were to be performed between the last day of therapy and four days after completion of therapy:

1. A physical examination.
2. Assessment of clinical signs and symptoms of infection.
3. If an end-of-treatment culture was positive, the organism was identified and *in vitro* susceptibility testing was performed with cefepime.
4. For bacteremia, an end-of-treatment blood culture was to be obtained.
5. For patients with _____ a culture was obtained if there was a source to culture. If there was no source to culture due to lack of sputum, then the date of attempted culture was documented

in the patient's records and on the bacteriologic data section of the CRF.

6. A chest X-ray and radiologic interpretation was performed on all patients with confirmed pneumonia. This was done within 48 hours of completion of therapy or at the time of the evaluation.
7. Laboratory studies were to be repeated.

Post-Treatment Procedures

Investigators were requested to complete the procedures listed below between 10-14 days after completion of therapy.

1. Assessment of clinical signs and symptoms of infection.
2. If material was available to culture from the original site of infection or a new site, then a specimen for the culture was to be obtained.

Drug Information and Dose Selection

Cefepime was supplied by Bristol-Myers Squibb Company in vials containing 1 or 2 grams of a dry-powder blend of cefepime dihydrochloride and L-arginine. Investigators were to administer cefepime by intravenous infusion over 30 minutes or by intramuscular injection if necessary to continue or complete a therapeutic course of treatment. Patients were administered 2 g doses every 12 hours (or every 8 hours for very severe, life-threatening infections) to be given for a period of up to 28 days.

Cefepime patients with renal impairment had doses adjusted as follows:

<u>Creatinine Clearance</u>	<u>Cefepime Regimen</u>
> 50	2 g BID or TID*
31 - 50	2 g BID
11 - 30	2 g QD

* For very serious, life-threatening infections.

Microbiology Assessments

Bacterial isolates were tested for susceptibility to cefepime by disc sensitivity or Minimum Inhibitory Concentration (MIC) method. Based on the disc sensitivity method, isolates were defined as susceptible if the zone diameter was 18 mm or greater, resistant if the zone diameter was 14 mm or less, and intermediate if the zone diameter was 15 mm to 17 mm. Based on results of MIC testing, isolates were defined as susceptible if the MIC was 8 mcg/ml or less, resistant if the MIC was 32 mcg/ml or greater, and intermediate if the MIC was 16 mcg/ml.

The identity of each isolate was recorded on the microbiology page of the CRF. Based on the investigator's clinical judgment, each isolate was assigned to one of the following categories: causative pathogen, colonizer, contaminant, normal flora, or other. Isolates assigned to the category of other by the investigators were reassigned by Bristol-Myers Squibb personnel to one of the other four categories.

MEDICAL OFFICER'S COMMENTS:

The protocol gave the following recommendations for sputum collection and documentation: "Specimens should be obtained by sterile suctioning (trans-tracheal aspirate, endotracheal or bronchoscopy) or deep cough purulent expectorated sputum as demonstrated by the presence of leukocytes. (gram stain of sputum should be recorded) A second pretreatment specimen should be attempted if large numbers of squamous epithelial cells are present suggesting contamination with oral secretions."

It was unclear how the classification as indicated above was accomplished without defined guidelines for the investigator with regard to the adequacy of a sputum culture and gram stain. It was also unclear how the applicant re-evaluated the specimen's without the benefit of consistent sputum characterization, either qualitatively or quantitatively.

New Infections

According to the Protocol, a new infection occurred if a different pathogen was cultured from the original infection site after the pretreatment culture. Patients were also considered to have a new infection if either the original pathogen or a new pathogen caused an infection at a body site unrelated to the original site of infection. New infections were diagnosed based on the culture results; associated clinical signs and symptoms were not necessarily present. However, patients also could have a new infection diagnosed solely on the basis of clinical signs and symptoms.

Concomitant Therapy

Medications, except for antimicrobial agents, could be administered as indicated to enrolled patients. Metronidazole 500 mg QID IV or orally, was allowed if a polymicrobial infection was present, at least one pathogen was susceptible to cefepime, and if an anaerobic organism considered to be a pathogen was the only organism not susceptible to cefepime. Use of any non-study medication was to be recorded on the CRF.

Applicant Criteria for Evaluability

A patient was considered evaluable for efficacy only if the following criteria were met.

1. The patient had documented pretreatment signs and/or symptoms of a [redacted] th. [redacted] was confirmed by positive pretreatment culture.
2. Pretreatment clinical and bacteriologic assessments were conducted within 72 hours before beginning treatment and after termination of any previous antimicrobial therapy.
3. Any causative pathogen isolated in the pretreatment culture was identified and shown to be susceptible to cefepime.
4. Post-treatment clinical assessment was conducted on post-treatment Day 5-14.

MEDICAL OFFICER'S COMMENTS:

This is a modification of the time interval for follow-up specified in the Protocol.

5. Post-treatment bacteriologic assessment was conducted on post-treatment Day 3-14. If there was no source available for the bacteriologic assessment, "NO SOURCE TO CULTURE" was documented on the CRF for that date.

6. Patients diagnosed as having pneumonia had a pretreatment chest X-ray that confirmed the diagnosis. The X-ray was performed within 72 hours before beginning treatment and 48 hours after starting treatment. A follow-up X-ray was required for pneumonia patients on Day 3 to the last day of therapy or at the time of the post-treatment evaluation.

MEDICAL OFFICER'S COMMENTS:

This is a modification of the post-therapy chest X-ray requirement stipulated in the Protocol.

7. After the pretreatment clinical assessment and culture, no concomitant systemic antimicrobial agent (that, according to official labeling published in the 1990 PDR, had activity against the genus of pathogen being treated) was allowed before the during- or post-treatment clinical and bacteriologic assessments with the exception of metronidazole.
8. Cefepime was administered intravenously or intramuscularly at the dose, frequency, and duration specified in the appropriate Protocol or amendment; except for treatment failures, a minimum of 7 doses was received within a 96-hour period for the BID administration, 11 doses within 96 hours for TID administration, or 4 doses within 96 hours for QD administration (for renally impaired patients).

MEDICAL OFFICER'S COMMENTS:

The minimum number of required doses to be evaluable for a cure seems too modest, especially in light of the applicant's recommendation that "Because of the serious nature of the infections treated the majority of patients will require at least 14 days of therapy."

Applicant Efficacy Criteria Definitions

Patients were to be examined and assigned a Clinical Response category at their final acceptable visit. Cultures obtained both during and after therapy were used to determine Bacteriologic Response.

Clinical Response

Satisfactory:

Cured: All clinical signs and symptoms of the infection that were present prior to therapy were resolved, and no new signs or symptoms of the infection were present at the post-treatment follow-up evaluation.

Improved: Clinical signs and symptoms of the infection that were present prior to therapy were improved, and no new signs or symptoms of the infection were present at the post-treatment follow-up evaluation.

MEDICAL OFFICER'S COMMENTS:

In the CANDA as well as in the patient profiles, the applicant's assessment was always listed in terms of satisfactory or unsatisfactory. Distinctions between improvement and cure were not made.

Unsatisfactory:

Persistence or worsening of clinical signs or symptoms relevant to the original infection for 72 hours or more after the start of therapy with the study drug and a clinical decision

was made to change antimicrobial agents; or any clinical signs or symptoms relevant to the original site of infection increased, persisted, or worsened following initial improvement by the time of post-treatment follow-up.

Undetermined: All cases where a response could not be determined (e.g., no follow-up evaluation).

Bacteriologic Response

Eradicated: Pretreatment causative pathogen was not present in the post-treatment culture ($\geq$ 3 days post-treatment), or there is no source to culture approaching two weeks following therapy due to diminished sputum production.

Persisted: The pretreatment causative pathogen was present in the post-treatment culture. If the patient was removed from the study and the last culture obtained was positive, then the Bacteriologic Response was considered persisted.

Undetermined: Unable to determine the Bacteriologic Response (e.g., inappropriate cultures, patient is lost to follow-up).

NOTE: For evaluable patients only, if the investigator's assessment of Clinical Response or Bacteriologic Response did not conform to the Protocol definitions, Bristol-Myers Squibb corrected the response to the Protocol specifications.

MEDICAL OFFICER'S COMMENTS:

To be strictly evaluable by the reviewer, a patient had to have:

1. met the inclusion and exclusion criteria established by the applicant.
2. at least two signs and/or symptoms consistent with a *Pneumonia* infection. *Pneumonia* was differentiated by the presence of an infiltrate on chest X-ray.

NOTE:

a. To support the observed diagnosis, the investigator could document the presence of signs and symptoms from a list of pre-selected terms. They were as follows:

Fever	Chills
Chest Pain	Cough
Melaise	Lethargy
Sputum	Circumoral Cyanosis
Rales	Pleural Effusion
Chest Retractions	Tachypnee
Diminished Breath Sounds	Dyspnea

b. Respiratory rates were not recorded for any patient. Sputum production was not characterized with regard to quantity, quality or relationship to baseline. In patients with chronic respiratory disease, a change in sputum production and/or cough was also not noted.

c. The IDSA states that leukocytosis and pyrexia should be present to support the diagnosis of a *Pneumonia* infection. In this indication, many patients were afebrile and without a significant elevation of the white count. The study was not designed to capture information with respect to chronic administration of steroids and/or the use of acetaminophen or aspirin products. Therefore, this information could not be used as diagnostic criteria.

d. For a reviewer to validate the diagnosis of a specific respiratory illness, certain minimal clinical and laboratory information is necessary. In some instances, this includes baseline respiratory conditions and/or recent medications. Other helpful supporting data are respiratory rates or arterial oxygen content. This study as others in this indication had limited information to precisely characterize the respiratory condition; however, there was sufficient data to determine that a pulmonary process was present. To the reviewer, the minimum clinical observations required to support the diagnosis of pneumonia/bronchitis were cough, sputum production, and/or abnormal auscultatory sounds.

3. a culture documented pathogen susceptible to cefepime.

NOTE:

a. A gram stain was requested by the applicant. However, a written description was provided at the discretion of the investigator.

b. For the most part, the type of specimen was not identified, e.g. transtracheal aspirate, deep expectorated sputum, etc., nor was the quality described e.g. mucoid, voluminous, blood tinged, etc.

c. Those patients with a documented, valid gram stain and/or positive blood culture constituted the "strictly evaluable" reviewer population.

4. received 24 hours or less of pre-study antimicrobial drug with activity against the identified pathogen or a demonstration of a pathogen resistant to the pre-study antimicrobial drug.

NOTE:

The reviewer believes that this criterion is critical in this study; because treatment by applicant definition could be short (i.e. 3.5 days) and the influence of the pre-study antibiotic is unknown. Second, because validated gram stains were not a study requirement, sputum samples could not always differentiate between a colonizing organism and a true pathogen. The applicant did not address the issue of pre-study antimicrobials in their protocol or study report. The reviewer refers the reader to the published IDSA general guideline which states that: "Patients may be enrolled if they have received < 24 hours of treatment with a presumably effective anti-infective drug for an infectious process thought (on the basis of published reference material) to require a standard duration of therapy of ≥ 7 days." The only extenuating circumstances where a patient may exceed the suggested 24 hour limit of pre-study therapy are illnesses which require

lengthy therapy e.g. osteomyelitis and endocarditis or patients infected with a pathogen resistant to the initial anti-infective drug and sensitive to the study drug. (pp. S17-18)

Exceptions to this requirement were those patients who had an acceptable interval (five half-lives) between the administration of alternative systemic antimicrobials and study drug.

5. received a minimum of 4.5 days of therapy (i.e. 9 doses of cefepime) for success. This requirement is consistent with the general IDSA guidelines which recommends a minimum 5 days of therapy for pneumonia (However, a patient could be classified as a failure after only five cefepime doses.)
6. received a maximum of 18 days therapy. (The protocol specified a maximum of 28 days of therapy with cefepime/arginine.)
7. had neither concomitant nor post-study antimicrobial therapy with activity against the identified pathogen in excess of a single dose.
8. had the minimum of three clinical evaluations: pre-therapy visit, during therapy visit and the follow-up visit (5-21 days).

NOTE:

In instances when an in-person test-of cure visit was not possible: The reviewer accepted telephone follow-up information provided by the patient (not a third party, e.g. relative), because this mechanism was mutually accepted during the development program. However, the reviewer would like to state her opinion that this information is of dubious value. There was no standard questionnaire to provide consistent data collection and documentation of these telephone conversations. Therefore, each investigator could ask a different battery of questions.

9. had evidence of bacterial clearance ("sputum production resolved") or a statement with regard to "No source to culture" at the follow-up visit (5-21 days).
10. had a pre-treatment chest X-ray and a post-treatment (either end of treatment or follow-up) chest x-ray. The IDSA guideline recommends that: "A chest radiograph will be obtained 3 days after the initiation of therapy, within 72 hours of completion of therapy, and at any other time the investigator deems necessary." (p. S85) It should be noted that the post-treatment X-ray was a requirement in the original protocol.

Clinical Response:

Satisfactory: Improvement and/or resolution of all pre-treatment signs and symptoms diagnostic of pneumonia/ at the test of cure visit (5-21 days). The end of treatment/follow-up chest X-ray had to show either improvement or lack of progression of the pneumonic process.

Unsatisfactory: Persistence or worsening of any clinical signs or symptoms associated with pneumonia during treatment or at the time of the follow-up evaluation (5-21 days). The end of treatment/follow-up chest X-ray showed no improvement or worsening.

Unevaluable: Assessment of the clinical outcome could not be determined e.g. the patient did not return for follow-up evaluation.

Bacteriologic Response:

Eradication - Either the causative pathogen(s) was not isolated from the follow-up culture or there was a presumptive eradication because there was no material available for culture.

Persistence - The original pathogen(s) was isolated from the follow-up culture or the patient was a clinical failure with a presumed pathogen persistence.

Unevaluable - It was not possible to determine a bacteriological response, e.g. because the patient did not return for follow-up.

The reviewer conducted an assessment of the "strictly evaluable" population based on the criteria described above. However, the reviewer feels that the design of this study was severely deficient. Problematic areas were as follows:

- a. Inadequate gram stain assessments/documentation*
- b. The lack of description with respect to quality and quantity of sputum samples*
- c. The lack of description of the method in which a sputum sample was collected*
- d. The absence of characterization of "change" of described signs and symptoms from baseline (especially in the patient with chronic lung disease)*
- e. The lack of a gradation system with respect to the improvement of signs and symptoms*
- f. The lack of assessments with respect to pre-treatment antibiotics on selected patients*
- g. The absence of correlation with white blood cell counts (elevations and/or bandemia) and temperature*
- h. The absence of definition and attempts to clarify the setting of the pneumonic processes for either pneumonia (i.e. not all pneumonias infections are alike.)*
- i. The absence of pre-determined format or questionnaire to gather telephone follow-up data*

Not unexpectedly, there were few "strictly evaluable" patients. However, a secondary analysis of a "clinically evaluable" patient population was conducted. The "clinically evaluable" population met all the criteria described above with the exception of the valid pathogen requirement. These patients fell into four categories: a) those patients with an inadequate gram stain, b) those patients whose organism did not have sensitivities done, c) those patients with an inadequate gram stain and a resistant organism and d) those patients in which no organism was isolated. Obviously, this population subset contained patients whose respiratory illness was viral/other and not necessarily bacterial in origin. The reviewer believes that the outcome results of this population are more reflective of the "real world" clinical situation and are more consistent with how the drug will perform when used empirically.

New Infections

According to the Protocol, a new infection occurred if a different pathogen was cultured from the original infection site after the pretreatment culture. Patients were also considered to have a new infection if either the original pathogen or a new pathogen caused an infection at a body site unrelated to the original site of infection.

Safety Assessments

All patients who received one dose of cefepime were evaluable for safety. All adverse clinical events were reported on the CRF along with the investigator's judgement of the relationship of the reaction to cefepime. Also recorded were the date of onset, duration, and severity of each ACE, and any change in a patient's treatment. If serious or alarming adverse experience(s) occurred that seemed related to cefepime investigators were to stop administering cefepime and notify Bristol-Myers Squibb Company.

Investigators recorded on the CRF whether cefepime was well or poorly tolerated at the infusion site. The occurrence of phlebitis, hematoma, infiltration or other conditions was noted.

Laboratory assessments were required before, during, and after treatment. In addition, a patient with abnormal laboratory results was to be retested until the values returned to approximately the baseline levels for that patient. These assessments were not always done. However, all available laboratory test results were evaluated with respect to normal ranges by the investigators, who recorded on the CRF the relationship of any abnormal or unusual result to cefepime. Data from all study sites were reviewed and analyzed at Bristol-Myers Squibb.

For safety analyses, the laboratory tests listed below were selected as the most appropriate indicators of toxicity. To identify clinical abnormalities, "direction of toxicity" was defined for each of the selected tests as follows (clinically relevant levels are also provided for each unit):

Decrease below the lower limit of normal:

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Hematocrit :	< 24 vol%
Neutrophil :	≤ 500/cmm
WBC :	≤ 2000/cmm
Platelet :	≤ 50,000/cmm
Prothrombin Ratio :	< 50%

Increase above the upper limit of normal:

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Alkaline phosphatase :	≥ 3 x UNL
AST, ALT :	≥ 3 x UNL
Total Bilirubin :	≥ 3.0 mg/dL
BUN :	≥ 50.0 mg/dL
BUR :	≥ 100.0 mg/d
Creatinine :	≥ 3.0 mg/dL
Prothrombin Time :	> 25 sec.
PTT :	> 90 sec.
Eosinophil :	≥ 1000/cmm

Outside normal limits :

<u>Parameter</u>	<u>Clinically Relevant Level</u>
Sodium :	≤ 119 or ≥ 160 mEq/dL
Potassium :	≤ 2.4 or ≥ 6.5 mEq/dL
Calcium :	≤ 7.0 or ≥ 12.0 mg/dL
Phosphorus :	≤ 1.7 or ≥ 6.1 mg/dL

Additional criteria were implemented in testing for neutropenia and eosinophilia.

The following definitions apply to laboratory values :

Abnormal : Outside the normal range limit in the direction of toxicity.

Normal : All other laboratory values were defined to be normal.

Standard conversion factors were applied as needed to both test results and normal range values in order to express data in units as in the table above so that the data could be grouped and analyzed by a minimal number of algorithms.

Discontinuations

The protocol stated that any of the following conditions could justify the early discontinuation of a patient from cefepime treatment. However, investigators sometimes continued cefepime therapy for patients who improved clinically.

1. No pathogen isolated from the pre-treatment culture.
2. *In vitro* testing revealed that the causative pathogen was resistant to cefepime.
3. A poor clinical response was evident after 72 hours of therapy.

4. A serious or alarming adverse event.
5. Intercurrent illness.
6. Patient's decision not to participate further.
7. Investigator's decision that it was in the best interest of the patient to discontinue cefepime treatment.
8. Administrative reasons.

Deaths and discontinuations were included in the analysis.

RESULTS:

There were 321 patients enrolled in this study which was conducted from November 6, 1989 to September 26, 1991. There were 122 patients enrolled with pneumonia and 8 patients enrolled with

One of the Centers (021) was disqualified by the applicant for data inconsistencies; this center enrolled only one pneumonia patient which is not evaluable by either the reviewer or the applicant.

Seventeen investigators enrolled the total of 130 patients.

STUDY 140 - ALL PNEUMONIA PATIENTS^{1,2} N = 122

CENTER	INVESTIG./ STATE	CEFEPIME ENROLLED	BMS EVALUABLE	NO CLIN EVALUABLE	NO STRICT EVALUABLE
003	HOOKER/MO	10	0	0	0
006	MCCABE/CA	3	1	0	0
008	IVERSON/MO	2	1	0	0
009	TAN/OH	3	1	1	0
011	VANWAY/MO	3	0	0	0
012	YANGCO/FL	10	4	4	0
014	BUTLER/TX	17	5	5	2
017	BOYLEN/CA	20	13	11	0
019	NEU/NY	1	0	0	0
020	BROOKS/FL	26	8	5	1
021	(GENTRY/TX*)	(1)	0	0	0
023	MCCLOSKEY/PA	5	2	0	0
024	GELFAND/TN	3	0	1	0
030	JAUREGUI/OH	11	6	3	0
031	SMITH/MO	5	0	0	0
032	SARUBBI/TN	2	1	1	0
033	WAGNER	1	1	1	1
TOTALS		122 + (1)*	43	32	4

*Data Disqualified by the Applicant

PATIENTS WHO RECEIVED TID DOSING

Protocol 140 allowed investigators to enroll severely ill patients at high doses. These patients were treated with 2g thrice daily instead of twice daily. Of the total 122 pneumonia patients, there were 10 pneumonia patients enrolled at the TID dosage; Of the 10 patients enrolled, 3 (30%) were clinically and strictly evaluable by the reviewer. Five (50%) of ten were evaluable by the applicant.

**STUDY 140 - SUBSET OF TID PNEUMONIA PATIENTS
N = 10**

CENTER	INVESTIG. / STATE	CEFEPIME ENROLLED	BMS EVALUABLE	NO CLIN EVALUABLE	NO STRICT EVALUABLE
006	McCABE/CA	2	1	1	1
017	BOYLEN/CA	1	1	1	1
020	BROOKS/FL	6	3	1	1
023	McCLOSKEY/PA	1	0	0	0
TOTALS		10	5	3	3

The following table shows the breakdown of bacteriological specimen validation and provides insight into why the number of strictly (clinically and microbiologically) evaluable patients is so small.

GRAM STAIN INFORMATION AVAILABLE

TYPE OF GRAM STAIN	PNEUMONIA N = 122	
GOOD ≤ 10 EPis, ≥ 25 PMNs	1	
SOME INFO (MANY WBCs)	9	
NONE OR INADEQUATE	76	
RESPIRATOR	22	
POSITIVE BLOOD CULTURE	14	

The clinically evaluable population is essentially a modified-intent-to-treat analysis. It includes all patients with bacterial pneumonias, viral pneumonias, aspiration pneumonias, chlamydial and/or mycoplasma infections.

The strictly evaluable population is also not truly representative of the enrolled patient population. By definition, this population has a larger percentage of patients with positive blood cultures. And, although patients with many types of infections were studied; individual centers tended to enroll patients with similar infection types (e.g. community acquired pneumonia or infections in patients with underlying neoplasia). However, patients with "good" gram stains were found in only a few centers.

Finally, it should be recognized that the bulk of patients studied under this indication are in the clinically evaluable population. Because investigators did not anticipate a clinically evaluable population; they often elected to prematurely terminate patients, who did not have a valid pathogen, from the study. Since fewer days of observation are required to detect a failure, there were potentially more patients with negative outcomes that were evaluable.

REASONS PATIENTS COULD BE CONSIDERED NON-EVALUABLE BY THE REVIEWER:

1. The patient did not have the *minimally required three clinical evaluations*: a) pre-therapy, b) during/end of therapy and c) post-therapy.
2. The isolated pathogen was resistant to study drug.
3. No pathogen was isolated. There was always an additional reason why a patient in this category was unevaluable or he/she is listed in parentheses as a patient considered for the clinically evaluable category.
4. There were antimicrobials administered for greater than twenty-four hours prior to study start. Usually there was insufficient information to determine whether the antimicrobial administered did not impact on the clinical and/or microbiological outcome of the infection.
5. Additional antimicrobial therapy was prescribed between the end of treatment and follow-up assessments.
6. The patient received concomitant antimicrobial therapy.
7. There was no follow-up assessment made at the test of cure visit (5-21 days post-therapy).
8. The patient did not receive the minimum number of doses required for an assessment of cure (9 doses) or failure (5 doses).
9. Therapy exceeded 18 days.
10. The patient did not have either pneumonia Or, an initial chest X-ray was indicated and it was not performed.
11. A pathogen was isolated and identified. However, no sensitivity testing (no zone sizes or MICs) was completed.
12. The dosage of the study drug administered was other than 2g BID or renal equivalent dosing. (This will include the TID dosing for this table, although this was acceptable by the protocol.)
13. The patient was also receiving another investigational drug.
14. No end-of treatment or follow-up chest X-ray was performed. Radiological assessments were acceptable after end of treatment ($\pm$ 1 day).
15. There was either no gram stain available, an inadequate gram stain was recorded and/or a blood culture was negative.

The above lists the possible reasons a patient could be classified as non-evaluable. The tabulation below serves only an indicator of the reasons patients were excluded from the efficacy analysis. Many patients had more than one reason; however, only one reason per patient was listed.

HOW TO READ THE FOLLOWING TABLE:

The table below is a composite of two tables (reasons patients were not clinically evaluable and reasons patients were not strictly evaluable). The gray shaded area labelled "subtotal" is the number of patients who were not clinically evaluable. The gray shaded area labelled "total" is the number patients who were excluded from the strictly evaluable population. The patients in the parentheses are those patients whose only reason for being excluded from the strictly evaluable population was an inappropriate pathogen (i.e. no gram stain documentation, a resistant organism identified, no sensitivities done or no pathogen at all was isolated). For example, listed under no pathogen/pneumonia patients, what does "32 + (1)" mean? This means that 33 patients had no pathogen identified and were excluded from the strictly evaluable population. Of these 33, there was 1 patients who met all other evaluability save for an appropriate pathogen. The other 32 patients were not eligible for the clinically evaluable population, because they had a second reason (not identified here) that made them non-evaluable. For example: Often, when an investigator determined that a patient's culture was negative; the patient was removed from the study. Because the patient was not followed to study completion, the patient could not be considered clinically evaluable.

REASONS PATIENTS WERE EXCLUDED FROM EFFICACY ANALYSIS
All Investigators - 2g BID

REASONS NOT EVALUABLE	ALL PNEUMONIA N = 122
2. Resistant organism	2 + (1)
3. No Pathogen	32 + (1)
4. Pre-antibiotics >24 hours	13
5. Antibiotics between EOT & FUp	5
7. No Test of Cure visit (5-21 days)	10
8. Patient received incomplete Rx	10
9. Treatment exceeded 18 days	1
10. Not pre-study X-ray	3
11. No Sensitivities (MICs)	2 + (1)
12. Inappropriate Dosage	10
14. No EOT or FUp Chest-Xray	1
SUBTOTAL (Total excluded from the clinically evaluable population)	90
15. Inadequate pathogen substantiation	(25)
TOTAL (Total excluded from the strictly evaluable population)	90 + (28) = 118

Summary:

Pneumonia:

Total enrollment	122
Total excluded from clinically evaluable population	90
Clinically evaluable	32
Total excluded from strictly evaluable population	118
Strictly evaluable	4

NOTE: The data from Center 021 was disqualified by the applicant. This center enrolled a single patient with (pneumonia) infection.

DEMOGRAPHICS:

The following table lists the demographic characteristics of the APPLICANT'S evaluable population for pneumonia.

DEMOGRAPHICS TABLE
APPLICANT EVALUABLE POPULATION

PARAMETER	PNEUMONIA N = 43
SEX	
FEMALE	13 (30%)
MALE	30 (70%)
RACE	
WHITE	28 (65%)
BLACK	10 (28%)
HISPANIC	3 (7%)
AGE (yr)	
N	42
MEAN	53.5
MEDIAN	54
RANGE	
AGE DISTRIBUTION	
< 18	2 (5%)
18-24	4 (10%)
25-44	5 (12%)
45-64	16 (38%)
65-84	13 (31%)
85+	2 (5%)
not reported	1
WEIGHT (kg)	
N	36
MEAN	68.81
MEDIAN	68.2
RANGE	
HEIGHT (cm)	
N	34
MEAN	173.82
MEDIAN	175.3
RANGE	

Below is a table with the demographic information with regard to the reviewer's CLINICALLY evaluable populations.

DEMOGRAPHIC TABLE
MO CLINICALLY EVALUABLE

PARAMETER	PNEUMONIA N = 32
SEX	
FEMALE	8 (25%)
MALE	24 (75%)
RACE	
WHITE	16 (50%)
BLACK	10 (31%)
HISPANIC	6 (19%)
AGE (yr)	
N	32
MEAN	51.4
MEDIAN	50
RANGE	
AGE DISTRIBUTION	
18-24	4 (13%)
25-44	7 (22%)
45-64	13 (41%)
65-84	6 (19%)
85+	2 (6%)
WEIGHT (kg)	
N	25
MEAN	74.42
MEDIAN	74.8
RANGE	
HEIGHT (cm)	
N	25
MEAN	175.70
MEDIAN	177.8
RANGE	

Below is a table with the demographic information with regard to the reviewer's STRICTLY evaluable populations.

DEMOGRAPHICS TABLE
MO STRICTLY EVALUABLE

PARAMETER	PNEUMONIA N = 4	
SEX FEMALE MALE	4 (100%)	
RACE WHITE BLACK HISPANIC	2 (50%) 2 (50%)	
AGE (yr) N MEAN MEDIAN RANGE	4 49.8 52	
AGE DISTRIBUTION 18-24 25-44 45-64 65-84 85+	2 (50%) 1 (25%) 1 (25%)	
WEIGHT (kg) N MEAN MEDIAN RANGE	3 80.27 75.3	
HEIGHT (cm) N MEAN MEDIAN RANGE	4 177.15 177.8	

CLINICAL EFFICACY

PNEUMONIA (N = 122)

CLINICAL RESPONSE	BMS	NO CLINICALLY EVAL	NO STRICTLY EVAL
SATISFACTORY	34 (79%)	22 (69%)	3 (75%)
UNSATISFACTORY	9 (21%)	10 (31%)	1 (25%)
UNEVALUABLE	99	90	118
TOTALS (N)	122	122	122

The BACTERIOLOGICAL responses for pneumonia based on patients that were strictly evaluable are as follows:

<u>Diphtheroid</u>	0/1 (0%)
<u>S. pneumoniae</u>	3/3 (100%)
<u>S. viridans</u>	0/1 (0%)

PNEUMONIA (N = 10)

TID DOSING

CLINICAL RESPONSE	BMS	NO CLINICALLY EVAL	NO STRICTLY EVAL
SATISFACTORY	3 (60%)	1 (33%)	1 (33%)
UNSATISFACTORY	2 (40%)	2 (67%)	2 (67%)
UNEVALUABLE	5	7	7
TOTALS (N)	10	10	10

The BACTERIOLOGICAL responses for pneumonia based on patients that were strictly evaluable are as follows:

<u>E. aeroviae</u>	1/1 (100%)
<u>P. aeruginosa</u>	1/1 (100%)
<u>S. pneumoniae</u>	0/2 (0%)

The following tables examine efficacy related to various demographic variable to determine if there are intrapopulation variables which would require labelling modifications.

CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
PNEUMONIA N = 122

VARIABLE	BMS	MO CLINICALLY EVAL.	MO STRICTLY EVAL.
ALL	34/43 (79%)	22/32 (69%)	3/4 (75%)
WOMEN	10/13 (77%)	6/8 (75%)	-
MEN	24/30 (80%)	16/24 (67%)	3/4 (75%)
WHITE	20/28 (71%)	9/16 (56%)	2/2 (100%)
BLACK	11/12 (92%)	9/10 (90%)	-
OTHER	3/3 (100%)	4/6 (67%)	1/2 (50%)
< 65 YEARS	23/27 (85%)	19/24 (79%)	2/3 (67%)
≥ 65 YEARS	10/15 (67%)	3/8 (38%)	1/1 (100%)

The following table evaluates the effect of underlying lung disease and/or smoking. In the data collection, the information provided included the presence or absence of disease. The specific disease process or length of its existence was not usually recorded. Further information was sometimes available in the investigator's note.

EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS
PNEUMONIA N = 122

RESPIRATORY STATUS	BMS	MO CLINICAL EVAL.	MO STRICTLY EVAL.
ALL	34/43 (79%)	22/32 (69%)	3/4 (75%)
SMOKER	14/16 (88%)	10/12 (83%)	1/1 (100%)
LUNG DISEASE	6/9 (67%)	1/4 (25%)	-
SMOKER & LUNG DISEASE	12/12 (100%)	10/11 (91%)	2/2 (100%)
NONSMOKER	2/6 (33%)	1/5 (20%)	0/1 (0%)

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SAFETY EVALUATION:

Of the 130 patients (and one disqualified pneumonia patient) enrolled with a infection, there were twelve (12/131 = 9%) death. All patients who died had the diagnosis of pneumonia.

The patient was a 68 year old man with multiple medical problems who was admitted for treatment of bilateral pneumonia, a urinary tract infection and abdominal distension. The patient received a single dose of cefepime. The patient was subsequently given a "do not resuscitate" order and died shortly thereafter. The investigator listed the cause of death as "sepsis."

The patient was an 84 year old patient with multiple decubiti and chronic debility who developed signs of fever and lethargy. On the admission roentgenogram, a new infiltrate was identified. An admission urine culture was also positive. The patient received two doses of study drug and expired. Blood cultures were positive for *E. coli*. The investigator attributed death to overwhelming "sepsis."

The patient was an 81 year old white with a history of laryngeal carcinoma treated with radiation who was admitted for diffuse alveolar and interstitial infiltrates. He started cefepime therapy. The patient's hypoxia worsened. Because the pulmonary process was so atypical, the cefepime was discontinued after only two doses. Alternative antimicrobials were instituted. The patient developed ARDS, hepatic and renal failure. The patient succumbed to multi-organ failure eleven days after study drug therapy was discontinued.

The patient was a 21 year old man, a victim of a self-inflicted gunshot wound to the head, who was admitted to the hospital for treatment of right lower lobe pneumonia. He received cefepime and was responding. An chest X-ray taken three days after admission showed improvement. The patient expired on the evening of the third day of treatment. The investigator believed that death was a respiratory arrest related to the pneumonia which was superimposed on the patient's vegetative state.

The patient was a 23 year old man who was admitted to the hospital for treatment of a gunshot wound to the abdomen. The patient was taken to the operating room to repair his abdominal injuries. Due to voluminous blood loss and shock, the patient developed acute respiratory distress. Post-operatively, the pulmonary failure progressed rapidly. The patient developed fever and worsening pulmonary infiltrates. He was begun on study drug therapy. The patient received twelve days of study drug and six days of metronidazole. During that time, the patient required additional surgery for persistent drainage. Thereafter, therapy with imipenem was instituted. The patient died 20 days after cefepime was discontinued of progressive respiratory failure.

The patient was a 76 year old man with a history of chronic lymphoblastic lymphoma and multiple

other medical problems for treatment of a multilobar pneumonia. Cefepime therapy was instituted; however, patient did not improve after five days of therapy. Alternative antimicrobial products were begun. He improved and was discharged from the hospital after 8 days of alternative therapy. However, the patient was readmitted four days after discharge for recurrence of his pulmonary symptoms. The patient died 14 days after discontinuation of study drug. A needle aspirate at autopsy revealed an adenocarcinoma of the lung.

The patient was a 73 year old diabetic man admitted to the hospital for the treatment of pneumonia and a urinary tract infection. Cefepime was instituted. The patient deteriorated rapidly shortly after admission. The patient was transferred to the intensive care unit; study drug was discontinued. The patient was placed on alternative triple antibiotic therapy after a single dose of cefepime. The patient died of pneumonia and sepsis; cefepime had been discontinued thirteen days earlier.

The patient was a 79 year old woman with multiple medical problems including decubiti admitted for bilateral lower lobe pneumonia. Shortly after admission, the patient required ventilator assistance. The patient was started on study drug at 2g twice daily; the following day, therapy was increased to thrice daily. The patient continued to decline, was removed from the study and placed on alternative antimicrobial therapy. The patient expired 18 days after study drug was discontinued of multi-organ failure.

The patient was a 49 year old man who suffered from respiratory problems associated with his morbid obesity. He was admitted to the hospital for pneumonia and treated with multiple antibiotics. He was subsequently treated with study drug. However, the patient continued to have a poor clinical response. The patient's treatment with study drug was discontinued after 15 days of therapy. Treatment was then instituted with ciprofloxacin. The patient expired from a cardiac arrest nine days after cefepime was discontinued.

The patient was a 57 year old hypertensive woman who was admitted to the hospital for treatment of cough, dyspnea, and shock. The chest X-ray demonstrated congestive heart failure and bilateral infiltrates. The patient was enrolled in the study. A single dose of cefepime was administered. The patient deteriorated rapidly and suffered a cardiac arrest.

The patient was an 86 year old woman with multiple medical problems admitted from a rehabilitation facility for treatment of pulmonary edema. The patient arrested and was successfully revived. Days later, the patient developed symptoms of pneumonia with fever, dyspnea and sputum production. A chest X-ray showed infiltrates in addition to evidence of congestive heart failure. A urine culture was also positive. Cefepime therapy was begun. The patient deteriorated developing hemoptysis and coma; she expired on the third day of therapy. The investigator listed the cause of death as the result of underlying heart disease.

The patient was an 85 year old white man with a history of atherosclerotic heart disease and chronic pulmonary disease who was admitted to the hospital for treatment of bilateral pneumonia. Cefepime therapy was stated. Essentially, the patient's condition did not improve and the patient expired on the fourth day of therapy.

Discontinuations:

There were eight patients that discontinued treatment due to an adverse event. Seven (7/123 = 6%) of these patients were diagnosed with pneumonia.

Patients Who Discontinued Due to Adverse Clinical Events
Study 411-140
Adapted from Volume 225, p. 144

Patient	Adverse Event ^a	Severity	Total Dose ^b (g)	Rel ^c	Outcome ^d
	Itching	Mild	6	Unk	T/R
	Rash	Moderate	8	Prob	T/R
	Rash	Mild	56	Prob	T/R
	Diarrhea	Severe	34	Prob	NT/R
	Fever	Moderate	6	Prob	T/R
	Constipation	Mild	14	Not	T/NF
	Rales	Moderate	14	Not	NT/R
	Rhonchi	Moderate	14	Not	NT/R
	Headache	Mild	38	Prob	NT/NF
	Itching rash	Mild	38	Prob	T/NF
	Stiff neck	Mild	38	Prob	NT/NF
	Weakness	Mild	38	Unk	NT/NF
	Pain	Moderate	8	Unk	T/R
	Headache	Moderate	12	Unk	T/R
	Diarrhea	Moderate	16	Prob	NT/R
	Low grade fever	Mild	2	Prob	NT/R

a Investigator term.

b Total dose at onset.

c Rel = Relationship to cefepime, where Prob is probably related, and Unk is of unknown relationship, and Not = Not related.

d Indicates outcome of adverse event, whether it was treated (T), not treated (NT), whether patient recovered (R), was hospitalized (H), died (D), or sequelae occurred (S) or no follow-up (NF).

There were NO discontinuations due to a laboratory abnormality or local infusion tolerance in infections.

ADVERSE EVENTS:

There were 90 (28%) of the 321 patients enrolled in this study who experienced a total of 185 adverse clinical events. The most common events, i.e. affecting more than 1% of all patients, were as follows: diarrhea (16 cases), vomiting (12 cases), headaches (11 cases), nausea (11 cases), rash (9 cases), chest pain (7 cases), dizziness (5 cases), pruritus (5 cases), and abdominal pain, confusion and pain (4 cases each). Of the 16 cases of diarrhea, 6 (6/16 = 35%) were reported to be associated with *C. difficile*.

MEDICAL OFFICER'S COMMENTS:

The applicant did not subset adverse clinical events or laboratory abnormalities with respect to the indication studied i.e. urinary tract infection, skin and skin structure infection,

Therefore, the reviewer requested that applicant present this information for the the applicant responded by submitting NDA amendment, number 71. Although the information per study was not itemized, the data with respect to the entire indication was presented. This information is tabulated in the summary section of this report.

LOCAL TOLERANCE:

Seven percent (23) of the 313 patients who received cefepime intravenously expressed intolerance to the infusion. One of four (25%) complained of discomfort related to intramuscular injection. No patients discontinued therapy due to intolerance.

LABORATORY ABNORMALITIES:

No patient discontinued therapy due to abnormal during- or post-treatment laboratory results.

SUSCEPTIBILITY
Baseline Sensitivity to Cefepime
for All Causative Pathogens
Study 411-140

Infection Type/ Pathogen	Number (%) of Pathogens			Total
	----- Type of Sensitivity -----			
	Susceptible	Intermediate	Resistant	
Strep. (Group A)	2 (100)			2
Strep. (alpha hemo.)	1 (100)			1
S. viridans	2 (100)			2
Strep. (beta hemo.)	3 (100)			3
S. agalactiae	1 (100)			1
Strep. (Group G)	1 (100)			1
Strep. (Group B)	4 (100)			4
S. milleri	1 (100)			1
S. aureus	7 (100)			7
S. aureus (MS)	8 (89)	1 (11)		9
S. pneumoniae	29 (100)			29
B. corrodens	1 (100)			1
P. aeruginosa	10 (91)	1 (9)		11
P. maltophilia			2 (100)	2
P. cepacia			1 (100)	1
E. coli	1 (100)			1
K. pneumoniae	7 (100)			7
E. cloacae	2 (100)			2
E. aerogenes	3 (100)			3
E. geroviae	1 (100)			1
S. marcescens	2 (100)			2
P. mirabilis	3 (100)			3
P. rettgeri	1 (100)			1
H. influenzae	2 (100)			2
H. influenzae (p+)	3 (100)			3
H. influenzae (p-)	11 (100)			11
N. meningitidis	1 (100)			1
Diphtheroids	1 (100)			1
Total	108 (96)	2 (2)	3 (3)	113

EFFICACY SUMMARY

This report has been a concurrent review of pneumonia. The applicant studied "infections" as they had been defined in the past. The applicant separated these entities based primarily on the presence or absence of an infiltrate on chest X-ray. The protocols did not specifically address differences between these two disease entities e.g. with respect to physical signs and symptoms and/or underlying disease states.

At the barest minimum, bacterial pneumonia may be subdivided into community acquired and nosocomial pneumonia. Ideally, enrolled patients should demonstrate signs and symptoms consistent with pneumonia (chest pain, cough and/or auscultatory findings supportive of pulmonary consolidation) with or without fever ($> 38\text{ }^{\circ}\text{C}$) and/or leukocytosis (WBCs $\geq 10,000/\text{cc}$ or 10-15% juvenile neutrophilic cells). Radiological evidence should also be provided to support the diagnosis. Specimens for culture should be screened for the suitability of culture. The method of sample collection and the suitability of the specimen should be documented for later review and evaluation. Appropriate sputum specimens should be cultured aerobically; blood culture or pleural fluid should be cultured aerobically and anaerobically.

For pneumonia the patient should receive adequate treatment courses and appropriate follow-up. For more specific information with regard to procedural information and documentation, the reader is referred to the excellent suggestions set forth by the Infectious Disease Society of America (IDSA) (*CID* 1992; 15 (Suppl. 1), S77-S88.)

Although there is often blurring between the diagnosis of community acquired and nosocomially acquired pneumonia and there are difficulties in assessing bacterial versus viral etiologies in patients; it should be understood that "the greater the homogeneity of the randomized population of patients as trial candidates, the greater the likelihood the trial results will have clinical import." (p. S83)

The applicant enrolled 1808 patients with abnormal processes. Of these 1808 patients, the applicant classified 1510 as having pneumonia on the basis of an infiltrate demonstrated on a chest radiograph. There was little attempt to further define these patients with respect to the pathogenesis of their respiratory process. Theoretically, patients could have been characterized more based on supplemental information provided in the investigator notes. Because notes were not obligatory, the depth of available information was investigator dependent. The applicant suggests a classification based on the pathogenicity of the organism recovered from sputum/blood specimens. For pneumonia patients, there is some value in this endeavor. This, of course, requires a valid bacteriological specimen.

From the reviewer's perspective, there was inadequate information with regard to specimen suitability. No protocol *required* gram stain documentation. Gram stain acceptability was not clearly stated. In the best of circumstances (see individual protocol reviews), the investigator was asked to examine the specimen for epithelial contamination; if unacceptable the investigator was asked to repeat the examination. It should be noted that at no time did the applicant assess a patient as "unevaluable" on the basis of an inadequate gram stain. Based on the information provided in most cases, the reviewer could not assess the suitability/validity of the pathogen. The available information is summarized in the table below.

GRAM STAIN STATISTICS
N = 1808

TYPE OF GRAM	PNEUMONIA
GOOD (< 10 EPIs/ > 25 WBCs)	115 (8%)
MINIMAL TO NO INFORMATION	933 (62%)
SOME INFORMATION (e.g. "2+ GPC")	143 (9%)
SAMPLE FROM RESPIRATOR	182 (12%)
BLOOD CULTURE POSITIVE	137 (9%)
TOTAL	1510

There was also no descriptive information provided with regard to the quality, the quantity of the sputum i.e. blood tinged, mucoid etc. or the changes from baseline. Nor, for the most part, was there information with regard to the method of specimen collection.

In this submission, documentation would have been enhanced by the addition of more clinical data, e.g. evidence of dullness to percussion, E to A changes, respiratory rates, levels of hypoxia and so forth.

Protocols for these indications had similar designs. Thus, it was theoretically possible to combine outcome results from all trials. All patients that were evaluable had the following minimum requirements: they had a respiratory illness; they were classified as pneumonia based on radiographical evidence; they received a minimum course of therapy; and they had a follow-up assessment within five to twenty-one days.

ENROLLMENT AND EVALUABILITY:

The results of 1510 patients enrolled with pneumonia were submitted by the applicant in support of efficacy claims for "nosocomial and community acquired pneumonia,"

There were 1114 pneumonia patients who received treatment with cefepime and 396 patients who received treatment with control drug.

With the exception of one study, all controlled trials used ceftazidime as the control drug. Study AI411-106 employed cefotaxime as the control drug. Because cefotaxime and ceftazidime have similarities as third generation cephalosporins, the reviewer felt it appropriate to group the few cefotaxime patients with the other control patients. In the following tables, the reviewer has catalogued all patients into three groups - applicant evaluable, MO clinically evaluable and MO strictly evaluable populations. The reason for the two reviewer populations is that the documentation of the validity of the sputum specimens, e.g. gram stain and other qualitative information, was considered insufficient (*vide supra*). Strictly evaluable patients are those with positive blood cultures and/or acceptable gram stain information. (See the following enrollment/evaluability charts.)

There was one center disqualified by the applicant on the basis of data discrepancies. This center enrolled a total of four patients in two studies: In study there were three pneumonia patients that were disqualified; one was treated with cefepime and two were treated with ceftazidime. The cefepime patient died. In study there was a single pneumonia patient treated with cefepime. These patients are mentioned here for completeness; however, they are NOT accounted for in the following efficacy tables in which the enrollment (N) totals 1808.

Cefepime:

Pneumonia
1114 + (2) disqualified

Ceftazidime:

396 + (2) disqualified
1510 + (4) disqualified

ENROLLMENT AND EVALUABILITY
PER APPLICANT AND REVIEWER
PNEUMONIA

INFECTIONS

STUDY	DOSE	ENROLLMENT		BMS EVALUABLE		NO CLINICALLY EVALUABLE		NO STRICTLY EVALUABLE	
		CEFEPIME	CONTROL	CEFEPIME	CONTROL	CEFEPIME	CONTROL	CEFEPIME	CONTROL
061	1 g	221	NA	92	NA	48	NA	3	NA
067 LC, E	1 g	85	NA	27	NA	37	NA	2	NA
067 HD, E	2 g	83	NA	9	NA	30	NA	3	NA
115 E	2 g	11	NA	0	NA	4	NA	0	NA
140	2 g	122 (+1)	NA	43	NA	32	NA	4	NA
SUBTOTAL NC		522	NA	174	NA	151	NA	12	NA
070	1 g	180	89	68	29	61	33	30	16
070 E	1 g	83	39	12	16	40	27	4	3
070 B	1 g	39	21	15	8	10	8	1	3
097	2 g	143 (+1)	138 (+2)	53	49	53	51	6	6
097 B	2 g	46	34	7	8	9	8	1	1
106 LD, E	1 g	2	2	0	0	0	2	0	1
106 HD, E	2 g	34	14	14	2	28	11	0	0
111 E	2 g	65	59	12	15	27	23	2	5
SUBTOTAL C		592	396	181	127	228	163	44	35
TOTAL		1114 (+2)	396 (+2)	352	127	379	163	56	35

KEY:

- DOSES ARE LISTED AS 1 g OR 2 g. THIS REFERS TO 1 OR 2 GRAM BID DOSING FOR CEFEPIME OR 1 OR 2 GRAM DOSING FOR THE CONTROL
- THE CONTROL DRUG IS CEFTAZIDIME FOR ALL STUDIES EXCEPT 106 WHICH USED CEFOTAXIME.
- THE FOLLOWING ABBREVIATIONS ARE USED IN THE TABLE ABOVE - C = COMPARATIVE STUDIES, NC = NON-COMPARATIVE STUDIES, B = BLINDED STUDIES, E = EUROPE, g = GRAM, LD = LOW DOSE, HD = DOSE, () NUMBER OF DISQUALIFIED PATIENTS, NOT IN THE EFFICACY ANALYSIS

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DEMOGRAPHICS

The majority of the enrolled patients in all treatment groups were older, white males. This was especially true in the European trials. There were no significant enrollment differences between the experimental and control study groups. The following two tables document the demographic characteristics of the two indications.

DEMOGRAPHIC CHARACTERISTICS
PNEUMONIA N = 1510

PARAMETER	ENROLLED		BMS EVALUABLE		MO CLINICALLY EVALUABLE		MO STRICTLY EVALUABLE	
	CEFEPIME	CONTROL	CEFEPIME	CONTROL	CEFEPIME	CONTROL	CEFEPIME	CONTROL
WOMEN	317 (28%)	119 (30%)	86 (24%)	32 (25%)	106 (28%)	40 (25%)	11 (20%)	8 (23%)
MEN	797 (72%)	277 (70%)	266 (76%)	95 (75%)	273 (72%)	123 (75%)	45 (80%)	27 (77%)
WHITE	841 (75%)	303 (76%)	278 (79%)	107 (84%)	315 (83%)	139 (85%)	43 (77%)	28 (80%)
BLACK	212 (19%)	76 (19%)	58 (16%)	15 (12%)	48 (13%)	17 (11%)	9 (16%)	4 (11%)
OTHER	61 (5%)	17 (4%)	16 (5%)	5 (4%)	16 (4%)	7 (4%)	4 (7%)	3 (9%)
MEAN AGE	59.5	61.0	61.7	64.2	62.5	64.0	61.2	59.9
MEDIAN AGE	64	65	65	67	66	66	64	63
AGE RANGE								
< 65 YEARS	586 (53%) ¹	191 (48%)	175 (50%) ¹	52 (41%)	177 (47%)	71 (46%)	32 (57%)	18 (51%)
≥ 65 YEARS	527 (47%) ¹	205 (52%)	176 (50%) ¹	75 (59%)	202 (53%)	92 (54%)	24 (43%)	17 (49%)
MEAN WEIGHT (kg)	68.68	68.78	68.28	68.06	68.57	68.80	66.59	71.37
MEAN HEIGHT (cm)	170.55	170.85	170.33	169.90	170.63	170.05	171.62	169.72

¹ One patient's age was not reported.

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CLINICAL EFFICACY SUMMARIZED

On the next few pages, there are several tables which examine the final data in various subsets. The most important information are the absolute numbers which are presented. The remarks that follow below reflect the reviewer's interpretation of overall trends based on the clinically evaluable populations. The strictly evaluable populations were too small to assess.

A. *Tables based on demographic variables - age, race, sex*

1. CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE, LOW DOSE, PNEUMONIA

3. CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE, HIGH DOSE, PNEUMONIA

There do not appear to be any obvious differences between the sexes, old and young ages or races for patients treated with either cefepime or control drugs.

B. *Clinical efficacy by study type - blinding*

1. CLINICAL EFFICACY BY STUDY TYPE - BLINDING - PNEUMONIA

There were too few patients evaluable in the blinded studies to make a meaningful comparison between comparative and non-comparative trials.

C. *Clinical efficacy by dosage*

1. CLINICAL EFFICACY BY DOSAGE - PNEUMONIA

In both clinically and strictly evaluable pneumonia populations, the success rates are lower for patients treated with cefepime than for patients treated with control drug. This is not true for the clinically evaluable population; the strictly evaluable population is too small to comment.

D. *Clinical efficacy by study location*

1. CLINICAL EFFICACY BY STUDY LOCATION - PNEUMONIA

For the clinically evaluable pneumonia patients, there are no significant difference between the patients treated with cefepime/comparator in North America or Europe.

E. *Clinical efficacy by study type - comparative or non-comparative*

1. CLINICAL EFFICACY BY STUDY TYPE - COMPARATIVE OR NONCOMPARATIVE - PNEUMONIA

Of the clinically evaluable cefepime patients, patients in the comparative trials had better outcomes than those in the non-comparative trials.

F. *Efficacy based on underlying respiratory status*

1. EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS - PNEUMONIA

Neither smoking, underlying lung disease nor steroids made any significant difference to the outcome of either treatment group.

G. *Summary tables*

1. SUMMARY TABLE - PNEUMONIA

All studies and comparative studies are presented with their confidence intervals. The clinically evaluable pneumonia population showed no difference between the experimental and control groups.

However, when looking at the strictly evaluable populations, the success rates for cefepime are worse than those of the comparator drug. Examining clinically evaluable patients, there appears to be essentially no difference between the two treatment groups. There were too few patients evaluable in the strictly evaluable comparator group to draw a meaningful conclusion.

H. *Bacteriological response by pathogen per applicant*

1.	BACTERIOLOGICAL RESPONSE BY PATHOGEN	PNEUMONIA
2.	BACTERIOLOGICAL RESPONSE BY PATHOGEN	PNEUMONIA

These tables were prepared by the applicant. According to the applicant, "in order to provide the most meaningful summary of bacteriological eradication, results were pooled for evaluable patients at all dose levels in all trials both comparative and non-comparative. ... Pathogens are grouped by those which characteristically cause nosocomial pneumonia (especially *S. aureus*, various Enterobacteriaceae, and *P. aeruginosa*) and those implicated in community-acquired pneumonia (*S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*).

I. *Bacteriological efficacy - all studies, all doses*

1. MICROBIOLOGICAL EFFICACY - PNEUMONIA

With regard to pneumonia, cefepime appears to be adequately effective against *S. pneumoniae*. The cefepime eradication rate for *H. influenzae* (4/5 = 80%) is acceptable and equal to that of control (5/6 = 83%) drug. However, the number of evaluable organisms is small. The same is true for the eradication rate of *M. catarrhalis* (2/2 and 3/3 for cefepime and control, respectively). Although the numbers are small, the efficacy against *Pseudomonas aeruginosa* (1/3 = 33%) is not promising. Although the eradication rates for *H. influenzae*, *M. catarrhalis* and *S. pneumoniae* the numbers are small and there is essentially no information for the comparator drug.

J. *Bacteriological efficacy - LOW DOSE*

1. MICROBIOLOGICAL EFFICACY - PNEUMONIA

These patients received either 1 gram cefepime BID or 1 gram comparator drug TID.

K. *Bacteriological efficacy - HIGH DOSE*

1. MICROBIOLOGICAL EFFICACY - PNEUMONIA

These patients received either 2 grams cefepime BID or 2 grams comparator drug TID.

L. *Pathogens identified from respirator aspirations*

1. ISOLATES OF EVALUABLE RESPIRATOR PATIENTS - PNEUMONIA

Aspirates obtained from an endotracheal tube, for the most part, do not convey meaningful microbiological information. The reviewer refers the reader to the reviews by Meduri and Baselski in the *Infectious Disease Clinics of North America*, June, 1993. A quote from Dr. Baselski is as follows: "Endotracheal specimens are easy to obtain, but many studies have shown them to be unreliable specimens. The aspirates may or may not show the true pathogen but almost certainly contain multiple potential pathogens when compared with tissue or bronchoscopic samples. ... This generally results in unnecessary or inappropriate antimicrobial therapy. The routine endotracheal aspirate culture for the diagnosis of VAP [ventilator assisted patient] may therefore be considered yet another 'sacred cow,' with the potential for serious patient mismanagement and excessive non-productive laboratory workload." The reviewer concurs that attention to these specimens (in which it is often not even

known if they were purulent) is unwise and may lead to mismanagement. For *interest and completeness only*, the reviewer presents non-validated pathogens from mechanically ventilated patients. The IDSA guideline suggests that a gram stain may be helpful in these patients; however, only two patients had a good gram stain submitted. Therefore, these tables are prepared from the clinically evaluable patient populations. It should be understood, therefore, that patients whose pathogens were identified as resistant and/or did not have sensitivities completed are also included.

M. Bacteriological Efficacy - Bacteremia patients - all studies, all doses

1. MICROBIOLOGICAL EFFICACY - PNEUMONIA

N. Duration of Therapy

1. CLINICALLY EVALUABLE POPULATIONS FOR PNEUMONIA

2. STRICTLY EVALUABLE POPULATIONS FOR PNEUMONIA

The average duration of therapy for a satisfactory outcome with ceftazidime therapy for treatment of pneumonia ranges from 6.2 to 14 days. The average duration of therapy for a satisfactory outcome with control drug for the treatment of infections ranges from 7.3 to 10.2 days.

AI. CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
 LOW DOSE (1g BID); STUDIES 061, 067LD, 070, 106LD
 PNEUMONIA

PARAMETER	BMS EVALUABLE		NO CLINICALLY EVALUABLE		NO STRICTLY EVALUABLE	
	CEFEPINE	CONTROL	CEFEPINE	CONTROL	CEFEPINE	CONTROL
ALL	178/214 (83%)	43/53 (81%)	130/196 (66%)	52/70 (74%)	29/40 (73%)	20/23 (87%)
WOMEN	39/44 (89%)	6/9 (67%)	37/49 (76%)	8/12 (67%)	9/9 (100%)	3/4 (75%)
MEN	139/170 (82%)	37/44 (84%)	93/147 (63%)	44/58 (76%)	20/31 (65%)	17/19 (89%)
WHITE	146/175 (83%)	40/46 (87%)	113/169 (67%)	46/61 (75%)	24/31 (77%)	18/19 (95%)
BLACK	25/31 (81%)	3/6 (50%)	14/22 (64%)	6/8 (75%)	4/7 (57%)	2/3 (67%)
OTHER	7/8 (88%)	0/1 (0%)	3/5 (60%)	0/1 (0%)	1/2 (50%)	0/1 (0%)
< 65 YEARS	92/107 (86%)	18/20 (90%)	60/90 (67%)	21/27 (78%)	15/20 (80%)	9/11 (82%)
> 65 YEARS	86/107 (80%)	25/33 (76%)	70/106 (66%)	31/43 (72%)	14/20 (70%)	11/12 (92%)

A3. CLINICAL EFFICACY BY DEMOGRAPHIC VARIABLE
HIGH DOSE (2g BID); STUDIES 067ND, 097, 106ND, 111, 115, 140
PNEUMONIA

PARAMETER	BMS EVALUABLE		MO CLINICALLY EVALUABLE		MO STRICTLY EVALUABLE	
	CEFEPIME	CONTROL	CEFEPIME	CONTROL	CEFEPIME	CONTROL
ALL	101/138 (73%)	53/74 (72%)	115/183 (63%)	59/93 (63%)	10/16 (63%)	8/12 (67%)
WOMEN	36/42 (86%)	15/23 (65%)	41/57 (72%)	19/28 (68%)	1/2 (50%)	3/4 (75%)
MEN	65/96 (68%)	38/51 (75%)	74/126 (59%)	40/65 (62%)	7/14 (64%)	5/8 (63%)
WHITE	71/103 (69%)	43/61 (70%)	89/146 (61%)	51/78 (73%)	8/12 (67%)	6/9 (67%)
BLACK	22/27 (81%)	7/9 (78%)	17/26 (65%)	4/9 (44%)	1/2 (50%)	0/1 (0%)
OTHER	8/8 (100%)	3/4 (75%)	9/11 (82%)	4/6 (67%)	1/2 (50%)	2/2 (100%)
< 65 YEARS	50/68 (74%) ¹	26/32 (81%)	53/87 (61%)	25/44 (57%)	8/12 (67%)	5/7 (71%)
≥ 65 YEARS	50/69 (72%) ¹	27/42 (64%)	62/96 (65%)	34/49 (69%)	2/4 (50%)	3/5 (60%)

¹One patient's age was not reported

B1. CLINICAL EFFICACY BY STUDY TYPE - BLINDING
PNEUMONIA

TYPE	BMS EVALUABLE		NO CLINICALLY EVALUABLE		NO STRICTLY EVALUABLE	
	CEFEPIME	CONTROL	CEFEPIME	CONTROL	CEFEPIME	CONTROL
NON-BLIND	262/330 (79%)	82/111 (74%)	236/360 (66%)	100/147 (68%)	38/54 (70%)	26/31 (84%)
BLIND	17/22 (77%)	14/16 (88%)	9/19 (47%)	11/16 (69%)	1/2 (50%)	2/4 (50%)
ALL	279/352 (79%)	96/127 (76%)	245/379 (65%)	111/163 (68%)	39/56 (70%)	28/35 (80%)

KEY:

NON-BLIND STUDIES: 061, 067, 070, 097, 106, 111, 140
BLINDED STUDIES: 0708, 0978

C1. CLINICAL EFFICACY BY DOSAGE
PNEUMONIA

TYPE	BMS EVALUABLE		NO CLINICALLY EVALUABLE		NO STRICTLY EVALUABLE	
	CEFEPIME	CONTROL	CEFEPIME	CONTROL	CEFEPIME	CONTROL
LOW DOSE	178/214 (83%)	43/53 (81%)	130/196 (66%)	52/70 (74%)	29/40 (73%)	20/23 (87%)
HIGH DOSE	101/138 (73%)	53/74 (72%)	115/183 (63%)	59/93 (63%)	10/16 (63%)	8/12 (67%)
ALL	279/352 (79%)	96/127 (76%)	245/379 (65%)	111/163 (68%)	39/56 (70%)	28/35 (80%)

KEY:

LOW DOSE STUDIES: 061, 067LD, 70, 106LD
 HIGH DOSE STUDIES: 067HD, 97, 106HD, 111, 115, 140

D1. CLINICAL EFFICACY BY STUDY LOCATION
PNEUMONIA

LOCATION	BMS EVALUABLE		MO CLINICALLY EVALUABLE		MO STRICTLY EVALUABLE	
	CEFEPIME	CONTROL	CEFEPIME	CONTROL	CEFEPIME	CONTROL
NORTH AMERICA	215/278 (77%)	66/94 (70%)	133/213 (62%)	68/100 (68%)	30/45 (67%)	22/26 (85%)
EUROPE	64/74 (86%)	30/33 (91%)	112/166 (67%)	43/63 (68%)	9/11 (82%)	6/9 (67%)
ALL	279/352 (79%)	96/127 (76%)	245/379 (65%)	111/163 (68%)	39/56 (70%)	28/35 (80%)

KEY:

NORTH AMERICAN STUDIES: 061, 070, 097, 140
 EUROPEAN STUDIES: 067, 070E, 106, 111, 115

E1. CLINICAL EFFICACY BY STUDY TYPE - COMPARATIVE OR NONCOMPARATIVE
PNEUMONIA

TYPE	BMS EVALUABLE		NO CLINICALLY EVALUABLE		NO STRICTLY EVALUABLE	
	CEFEPIME	CONTROL	CEFEPIME	CONTROL	CEFEPIME	CONTROL
NON-COMPARATIVE	163/171 (84%)	-	88/151 (58%)	-	8/12 (67%)	-
COMPARATIVE	136/181 (75%)	96/127 (76%)	157/228 (69%)	111/163 (68%)	31/44 (70%)	28/35 (80%)
ALL	279/352 (79%)	96/127 (76%)	245/379 (65%)	111/163 (68%)	39/56 (70%)	28/35 (80%)

KEY:

NON-COMPARATIVE STUDIES: 061, 067, 115, 140
 COMPARATIVE STUDIES: 070, 097, 106, 111

F1. EFFICACY BASED ON UNDERLYING RESPIRATORY STATUS
 PNEUMONIA
 N = 1510

RESPIRATORY STATUS	BMS EVALUABLE		MO CLINICALLY EVALUABLE		MO STRICTLY EVALUABLE	
	CEFEPIME	CONTROL	CEFEPIME	CONTROL	CEFEPIME	CONTROL
ALL	279/352 (79%)	96/127 (76%)	245/379 (65%)	111/163 (68%)	39/56 (70%)	28/35 (80%)
SMOKER	48/55 (87%)	15/20 (75%)	41/59 (69%)	22/35 (63%)	8/10 (80%)	5/6 (83%)
LUNG DISEASE	68/85 (80%)	22/36 (61%)	70/100 (70%)	30/46 (65%)	9/12 (75%)	6/7 (86%)
SMOKER & LUNG DISEASE	116/150 (77%)	39/46 (85%)	80/137 (58%)	38/50 (76%)	17/25 (68%)	12/14 (86%)
NONSMOKER	47/62 (75%)	20/25 (80%)	54/83 (65%)	21/32 (66%)	5/9 (56%)	5/8 (63%)

* The totals for steroids do not add into the total (ALL), because a patient could have two categories i.e. a smoker treated with steroid medication.

G1. SUMMARY TABLE
PNEUMONIA

	BMS EVALUABLE		NO CLINICALLY EVALUABLE		NO STRICTLY EVALUABLE	
	CEFEPINE	CONTROL	CEFEPINE	CONTROL	CEFEPINE	CONTROL
ALL STUDIES	279/352 (79%)	96/127 (76%)	245/379 (65%)	111/163 (68%)	39/56 (70%)	28/35 (80%)
CONFIDENCE INTERVALS	-0.061, 0.121		-0.121, 0.061		-0.301, 0.102	

	BMS EVALUABLE		NO CLINICALLY EVALUABLE		NO STRICTLY EVALUABLE	
	CEFEPINE	CONTROL	CEFEPINE	CONTROL	CEFEPINE	CONTROL
COMPARATIVE STUDIES ONLY	136/181 (75%)	96/127 (76%)	157/228 (69%)	111/163 (68%)	31/44 (70%)	28/35 (80%)
CONFIDENCE INTERVALS	-0.114, 0.094		-0.089, 0.109		-0.315, 0.115	

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**III. PNEUMONIA - BACTERIOLOGIC RESPONSE BY PATHOGEN
PER APPLICANT**
By Pathogen Type and Pathogen
For Evaluable Patients

PATHOGEN TYPE/ Pathogen	No. of Pathogens Eradicated/ Total Pathogens (%)			
	Cefepime		Comparators	
<u>S. aureus (All)</u>	31/38	(86)	7/9	(78)
<u>S. aureus (nt)</u>	25/29	(86)	7/9	(78)
<u>S. aureus (ms)</u>	6/7	(86)		
<u>Pseudomonas (All)</u>	21/39	(54)	7/14	(50)
<u>P. aeruginosa</u>	19/36	(53)	6/13	(46)
<u>P. fluorescens</u>	2/2	(100)	1/1	(100)
<u>P. putida</u>	0/1			
<u>Klebsiella (All)</u>	22/24	(92)	8/8	(100)
<u>K. pneumoniae</u>	16/18	(89)	5/5	(100)
<u>K. ozaenae</u>	1/1	(100)		
<u>K. oxytoca</u>	5/5	(100)	2/2	(100)
<u>Klebsiella sp.</u>			1/1	(100)
<u>Enterobacter (All)</u>	14/18	(88)	1/4	(25)
<u>E. cloacae</u>	8/8	(100)	1/2	(50)
<u>E. aerogenes</u>	6/8	(75)	0/2	
<u>Escherichia coli</u>	15/18	(84)	9/11	(82)
<u>PROTEAE (All)</u>	10/10	(100)	5/5	(100)
<u>P. mirabilis</u>	6/6	(100)	5/5	(100)
<u>P. vulgaris</u>	1/1	(100)		
<u>H. morgani</u>	3/3	(100)		
<u>Serratia (All)</u>	6/8	(75)	1/3	(33)
<u>S. marcescens</u>	5/7	(71)	1/3	(33)
<u>S. liquefaciens</u>	1/1	(100)		
<u>Citrobacter (All)</u>	2/2	(100)	1/1	(100)
<u>C. freundii</u>	2/2	(100)		
<u>C. diversus</u>			1/1	(100)
<u>Acinetobacter (All)</u>	2/2	(100)	0/1	
<u>A. anitratus</u>			0/1	
<u>A. lwoffii</u>	1/1	(100)		
<u>Acinetobacter sp.</u>	1/1	(100)		
<u>Veillonella sp.</u>	1/1	(100)		
TOTAL (Nosocomial)	124/154	(81)	39/56	(70)

(Based on 179 evaluable pneumonias with nosocomial pathogens)

*The comparative agent for study 411-106 was cefotaxime; the comparative agent for all other studies was ceftazidime.

NOTE: nt = not tested for methicillin susceptibility
ms = methicillin susceptible

**H2. PNEUMONIA - BACTERIOLOGIC RESPONSE BY PATHOGEN
PER APPLICANT**

By Pathogen Type and Pathogen
For Evaluable Patients

PATHOGEN TYPE/ Pathogen	No. of Pathogens Eradicated/ Total Pathogens (%)	
	Cefepime	Comparators
<u>S. pneumoniae</u>	115/116 (99)	47/49 (96)
<u>Haemophilus (All)</u>	104/107 (97)	37/38 (97)
<u>H. influenzae (All)</u>	91/94 (97)	33/34 (97)
<u>H. influenzae (NP)</u>	57/57 (100)	15/15 (100)
<u>H. influenzae (P+)</u>	7/9 (78)	3/3 (100)
<u>H. influenzae (P-)</u>	27/28 (96)	15/16 (94)
<u>H. parainfluenzae</u>	10/10 (100)	3/3 (100)
<u>H. parahaemolyticus</u>	1/1 (100)	
<u>Haemophilus sp.</u>	2/2 (100)	1/1 (100)
<u>M. catarrhalis (All)</u>	10/12 (83)	10/10 (100)
<u>M. catarrhalis (NP)</u>	6/7 (86)	3/3 (100)
<u>M. catarrhalis (P+)</u>	3/4 (75)	7/7 (100)
<u>M. catarrhalis (P-)</u>	1/1 (100)	
<u>Streptococci (Beta-hemo.)</u>	10/11 (91)	1/1 (100)
Group A	1/2 (50)	
Group B	6/6 (100)	1/1 (100)
Group G	1/1 (100)	
Ungrouped	2/2 (100)	
<u>Streptococci (Alpha-hemo.)</u>	13/13 (100)	1/1 (100)
<u>Neisseria sp.</u>	5/5 (100)	
<u>N. meningitidis</u>	6/6 (100)	3/3 (100)
<u>Corynebacterium sp.</u>	1/1 (100)	
<u>Staph. Coag. (neg.)</u>	2/2 (100)	2/2 (100)
<u>Bacteroides sp.</u>	5/5 (100)	
<u>Eikenella sp.</u>	1/1 (100)	
<u>Kluyvera sp.</u>		1/1 (100)
TOTAL (Community-Acquired)	272/279 (97)	104/107 (97)

(Based on 300 evaluable pneumonias with community-acquired pathogens)

*The comparative agent for study 411-106 was cefotaxime; the comparative agent for all other studies was ceftazidime.

NOTE: NP = not tested for beta-lactamase
P+ = produced beta-lactamase
P- = did not produce beta-lactamase

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11. MICROBIOLOGICAL RESPONSE TABLE - PNEUMONIA
PER REVIEWER - ALL DOSES

Parameter	CEFEPINE	CONTROL
NO. OF EVALUABLE PATIENTS	56	35
BACTERIOLOGIC ERADICATION		
DIPHtheroids	0/ 1 (0%)	0
E. COLI	0/ 3 (0%)	1/ 2 (50%)
H. INFLUENZAE	0/ 1 (0%)	1/ 1 (100%)
H. INFLUENZAE (P+)	1/ 1 (100%)	1/ 1 (100%)
H. INFLUENZAE (P-)	3/ 3 (100%)	3/ 4 (75%)
H. PARANAEMOLYTICUS	1/ 1 (100%)	0
H. PARAINFLUENZAE (P-)	1/ 1 (100%)	2/ 2 (100%)
K. OXYTOCA	1/ 1 (100%)	0
K. PNEUMONIAE	3/ 5 (60%)	0
M. CATARRHALIS	0	1/ 1 (100%)
M. CATARRHALIS (P+)	2/ 2 (100%)	1/ 1 (100%)
M. CATARRHALIS (P-)	0	1/ 1 (100%)
N. MENINGITIDIS	0/ 1 (0%)	1/ 1 (100%)
NEISSERIA SP.	1/ 1 (100%)	0
P. AERUGINOSA	1/ 3 (33%)	0/ 1 (0%)
P. MIRABILIS	1/ 1 (100%)	0
P. PUTIDA	0/ 1 (0%)	0
S. AUREUS	1/ 1 (100%)	0/ 1 (0%)
S. EPIDERMIDIS	1/ 1 (100%)	0
S. HAEMOLYTICUS	0/ 1 (0%)	0
S. MARCESCENS	1/ 1 (100%)	0
S. MITIS	0/ 1 (0%)	1/ 1 (100%)
S. PNEUMONIAE	24/ 29 (83%)	16/ 20 (80%)
S. SANGUIS	1/ 1 (100%)	0
S. VIRIDANS	0/ 1 (0%)	1/ 1 (100%)
STREP. (GROUP A)	1/ 1 (100%)	0
STREP. (GROUP B)	0/ 1 (0%)	0
	44/ 64 (69%)	30/ 38 (79%)

J1. MICROBIOLOGICAL RESPONSE TABLE - PNEUMONIA
PER REVIEWER - LOW DOSE

Parameter	CEFEPIME	CONTROL
NO. OF EVALUABLE PATIENTS	40	23
BACTERIOLOGIC ERADICATION		
E. COLI	0/ 1 (0%)	0
H. INFLUENZAE	0/ 1 (0%)	1/ 1 (100%)
H. INFLUENZAE (P+)	1/ 1 (100%)	1/ 1 (100%)
H. INFLUENZAE (P-)	3/ 3 (100%)	3/ 4 (75%)
H. PARAHAEVOLYTICUS	1/ 1 (100%)	0
H. PARAINFLUENZAE (P-)	1/ 1 (100%)	2/ 2 (100%)
K. OXYTOCA	1/ 1 (100%)	0
K. PNEUMONIAE	1/ 2 (50%)	0
M. CATARRHALIS	0	1/ 1 (100%)
M. CATARRHALIS (P+)	2/ 2 (100%)	1/ 1 (100%)
M. CATARRHALIS (P-)	0	1/ 1 (100%)
N. MENINGITIDIS	0/ 1 (0%)	1/ 1 (100%)
NEISSERIA SP.	1/ 1 (100%)	0
P. AERUGINOSA	1/ 3 (33%)	0
P. MIRABILIS	1/ 1 (100%)	0
P. PUTIDA	0/ 1 (0%)	0
S. AUREUS	1/ 1 (100%)	0/ 1 (0%)
S. EPIDERMIDIS	1/ 1 (100%)	0
S. MARCESCENS	1/ 1 (100%)	0
S. MITIS	0/ 1 (0%)	1/ 1 (100%)
S. PNEUMONIAE	17/ 20 (85%)	9/ 11 (82%)
S. SANGUIS	1/ 1 (100%)	0
S. VIRIDANS	0	1/ 1 (100%)
STREP. (GROUP B)	0/ 1 (0%)	0
	34/ 46 (74%)	22/ 26 (85%)

**K1. MICROBIOLOGICAL RESPONSE TABLE - PNEUMONIA
PER REVIEWER - HIGH DOSE**

Parameter	CEFEPIME	CONTROL
NO. OF EVALUABLE PATIENTS	16	12
BACTERIOLOGIC ERADICATION		
DIPHTHEROIDS	0/ 1 (0%)	0
E. COLI	0/ 2 (0%)	1/ 2 (50%)
K. PNEUMONIAE	2/ 3 (67%)	0
P. AERUGINOSA	0	0/ 1 (0%)
S. HAEMOLYTICUS	0/ 1 (0%)	0
S. PNEUMONIAE	7/ 9 (78%)	7/ 9 (78%)
S. VIRIDANS	0/ 1 (0%)	0
STREP. (GROUP A)	1/ 1 (100%)	0
	10/ 18 (56%)	8/ 12 (67%)

L1. MICROBIOLOGICAL RESPONSE TABLE - RESPIRATOR PATHOGENS - PNEUMONIA

Parameter	CEFEPIME	CONTROL
NO. OF EVALUABLE PATIENTS	40	22
BACTERIOLOGIC ERADICATION		
A. ANITRATUS	0	0/ 1 (0%)
ACINETOBACTER SP.	0/ 1 (0%)	0
C. DIVERSUS	1/ 1 (100%)	0
C. FREUNDII	0/ 1 (0%)	0
E. AEROGENES	2/ 2 (100%)	0
E. AGGLOMERANS	0/ 1 (100%)	0
E. CLOACAE	0/ 1 (0%)	0/ 2 (0%)
E. COLI	0/ 1 (0%)	2/ 3 (67%)
H. INFLUENZAE	3/ 6 (50%)	0/ 1 (0%)
H. INFLUENZAE (P+)	1/ 1 (100%)	0
H. INFLUENZAE (P-)	1/ 1 (100%)	0/ 1 (0%)
K. OXYTOCA	1/ 1 (100%)	0
K. PNEUMONIAE	0	1/ 1 (100%)
KLEBSTELLA SP.	0	0/ 2 (0%)
M. CATARRHALIS (P+)	0	0/ 1 (0%)
P. AERUGINOSA	2/ 8 (25%)	1/ 6 (17%)
P. MALTOPHILIA	0/ 2 (0%)	0
P. MIRABILIS	2/ 2 (100%)	1/ 5 (20%)
P. VULGARIS	0/ 1 (100%)	0
S. AUREUS	10/ 16 (63%)	3/ 6 (50%)
S. AUREUS (MR)	0	0/ 1 (0%)
S. LIQUIFACIENS	1/ 1 (100%)	0
S. MARCESCENS	1/ 2 (50%)	0/ 2 (0%)
S. PNEUMONIAE	1/ 5 (20%)	0/ 2 (0%)
STREP. (ALPHA HEMOLYTIC)	0/ 1 (0%)	0
STREP. SP.	1/ 2 (50%)	0
	27/ 57 (47%)	8/ 34 (24%)

BACTERIOLOGICAL EFFICACY -

PATIENTS - ALL STUDIES, ALL DOSES

**M1. MICROBIOLOGICAL RESPONSE TABLE - PNEUMONIA - BACTEREMIA
PER REVIEWER - ALL DOSES**

<i>Parameter</i>	CEFEPIME	CONTROL
NO. OF EVALUABLE PATIENTS	31	20
BACTERIOLOGIC ERADICATION		
DIPHTHEROIDS	0/ 1 (0%)	0
E. COLI	0/ 2 (0%)	1/ 2 (50%)
K. PNEUMONIAE	2/ 4 (50%)	0
P. AERUGINOSA	0/ 1 (0%)	0
S. AUREUS	0	0/ 1 (0%)
S. HAEMOLYTICUS	0/ 1 (0%)	0
S. PNEUMONIAE	18/ 22 (82%)	13/ 17 (76%)
S. SANGUIS	1/ 1 (100%)	0
S. VIRIDANS	0/ 1 (0%)	1/ 1 (100%)
STREP. (GROUP A)	1/ 1 (100%)	0
	22/ 34 (65%)	15/ 21 (71%)

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N1. DURATION OF TREATMENT

Clinically Evaluable Population

PNEUMONIA:Low Dose:

Cefepime - Satisfactory Outcome (N = 130), Range = 5 - 15 days of therapy
Average = 8.9 days

Cefepime - Unsatisfactory Outcome (N = 66), Range = 3 - 16 days of therapy
Average = 7.2 days

Control - Satisfactory Outcome (N = 52), Range = 5 - 15 days of therapy
Average = 9.2 days

Control - Unsatisfactory Outcome (N = 18), Range = 3 - 12 days of therapy
Average = 6.3 days

High Dose:

Cefepime - Satisfactory Outcome (N = 115), Range = 5 - 15 days of therapy
Average = 8.8 days

Cefepime - Unsatisfactory Outcome (N = 67), Range = 3 - 15 days of therapy
Average = 8.1 days

Control - Satisfactory Outcome (N = 60), Range = 5 - 15 days of therapy
Average = 8.3 days

Control - Unsatisfactory Outcome (N = 34), Range = 3 - 15 days of therapy
Average = 8.0 days

N2. DURATION OF TREATMENT

Strictly Evaluable Population

PNEUMONIA:

Low Dose:

Cefepime - Satisfactory Outcome (N = 29), Range = 6 - 14 days of therapy
Average = 8.6 days

Cefepime - Unsatisfactory Outcome (N = 11), Range = 3 - 10 days of therapy
Average = 7.0 days

Control - Satisfactory Outcome (N = 19), Range = 5 - 12 days of therapy
Average = 8.6 days

Control - Unsatisfactory Outcome (N = 4), Range = 3 - 10 days of therapy
Average = 7.0 days

High Dose:

Cefepime - Satisfactory Outcome (N = 10), Range = 7 - 12 days of therapy
Average = 9.7 days

Cefepime - Unsatisfactory Outcome (N = 6), Range = 6 - 15 days of therapy
Average = 7.3 days

Control - Satisfactory Outcome (N = 8), Range = 5 - 18 days of therapy
Average = 10.2 days

Control - Unsatisfactory Outcome (N = 4), Range = 5 - 15 days of therapy
Average = 12.2 days

The following three pages were prepared by the applicant to demonstrate the susceptibility patterns of the clinical isolates.

PNEUMONIA - SUSCEPTIBILITY OF INITIAL PATHOGENS

Susceptibility to Cefepime
By Pathogen Type and Pathogen
For All Trials and All Patients

Pathogen Type/ Pathogen	Number of Pathogens (%)						ND	All
	S	I	SI	R	T			
<i>S. aureus</i> (nt)	57 (75)	12 (16)	69 (91)	7 (9)	76	8	84	
<i>S. aureus</i> (ms)	10 (100)		10 (100)		10	1	11	
<i>S. aureus</i> (mr)	1		1	1	2		2	
<i>P. aeruginosa</i>	74 (81)	11 (12)	85 (93)	6 (7)	91	8	99	
<i>P. maltophilia</i>	1 (14)		1 (14)	6 (86)	7		7	
<i>P. fluorescens</i>	4		4		4		4	
<i>P. putida</i>	1		1		1	1	2	
<i>P. cepacia</i>				2	2		2	
<i>E. coli</i>	44 (100)		44 (100)		44	3	47	
<i>Citrobacter</i> sp.	2		2		2		2	
<i>C. freundii</i>	2		2		2		2	
<i>C. diversus</i>	1	1	2		2		2	
<i>Klebsiella</i> sp.	3		3		3		3	
<i>K. pneumoniae</i>	46 (98)	1 (2)	47 (100)		47	3	50	
<i>K. ozaenae</i>	1		1		1		1	
<i>K. oxytoca</i>	12 (100)		12 (100)		12	2	14	
<i>E. cloacae</i>	23 (88)	2 (8)	25 (96)	1 (4)	26	1	27	
<i>E. aerogenes</i>	16 (100)		16 (100)		16		16	
<i>E. geroviae</i>	1		1		1		1	
<i>E. intermedium</i>		1	1		1	1	2	
<i>E. agglomerans</i>	1	1	2		2		2	
<i>Serratia</i> sp.	1		1		1		1	
<i>S. marcescens</i>	17 (94)	1 (6)	18 (100)		18	2	20	
<i>S. liquefaciens</i>	1		1		1		1	
<i>P. mirabilis</i>	19 (86)	3 (14)	22 (100)		22	2	24	
<i>P. vulgaris</i>	2		2		2	1	3	
<i>M. morgani</i>	5 (100)		5 (100)		5	2	7	
<i>P. rettgeri</i>	1		1		1	1	2	
<i>P. stuartii</i>	1		1		1		1	
<i>Acinetobacter</i> sp.	1		1	3	4		4	
<i>A. calcoaceticus</i>	2		2		2	1	3	
<i>A. anitratus</i>	1	1	2	1	3		3	
<i>A. lwoffii</i>	1		1		1		1	
<i>Veillonella</i> sp.		1	1		1		1	

NOTE: S = Susceptible; I = Intermediate; SI = Sum of S + I; R = Resistant; T = Total;
ND = Not Done; nt = Not methicillin typed; ms = methicillin susceptible;
mr = methicillin resistant

PNEUMONIA - SUSCEPTIBILITY OF INITIAL PATHOGENS
Susceptibility to Cefepime
By Pathogen Type and Pathogen
For All Trials and All Patients

Pathogen Type/ Pathogen	----- Number of Pathogens (%) -----						All
	S	I	SI	R	T	ND	
<i>S. pneumoniae</i>	260 (100)		260 (100)		260	35	295
<i>H. influenzae</i> (NP)	122 (99)	1 (1)	123 (100)		123	18	141
<i>H. influenzae</i> (P+)	15 (100)		15 (100)		15		15
<i>H. influenzae</i> (P-)	70 (100)		70 (100)		70	5	75
<i>H. parainfluenzae</i> (NP)	24 (92)		24 (92)	2 (8)	26	3	29
<i>H. parainfluenzae</i> (P-)	8 (100)		8 (100)		8		8
<i>H. parahaemolyticus</i>	3		3		3		3
<i>H. aphrophilus</i>	1		1		1		1
<i>Hemophilus</i> sp. (NP)	3		3		3	1	4
<i>Hemophilus</i> sp. (P-)	2		2		2		2
<i>Branhamella</i> sp.	1		1		1		1
<i>M. catarrhalis</i> (NP)	20 (100)		20 (100)		20	1	21
<i>M. catarrhalis</i> (P+)	15 (100)		15 (100)		15	1	16
<i>M. catarrhalis</i> (P-)	3		3		3		3

NOTE: S = Susceptible; I = Intermediate; SI = Sum of S + I; R = Resistant; T = Total;
 ND = Not Done; NP = Not tested for beta-lactamase; P+ = Produced beta-lactamase;
 P - = did not produce beta-lactamase.

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EFFICACY FINAL COMMENTS

1. This study was difficult to evaluate, because it was originally designed to study a more generalized entity entitled _____ infections." Later, it was determined that two indications would be sought, namely pneumonia _____ However, the applicant did not expand on existing protocols to differentiate these two entities. It was stated that to be evaluable for pneumonia, it was necessary to have radiographic evidence of an infiltrate. The deficiencies were more significant for _____ for which there was essentially no definition. *There were no requirements for gram stain documentation and no requirements for recording underlying symptomatology.*

2. To have more meaning in terms of what is being evaluated, it is recommended that the following be included:
 - a. Gram stain information - number of PMNs, number of epithelial cells and predominant organism per low power microscopic field
 - b. How the specimen was obtained - sputum, transtracheal aspirate (which is NOT an aspirate from an endotracheal tube), endotracheal tube aspirate, protected _____ specimens, surrogate markers and so forth.
 - c. Definitions - what signs/symptoms are required to qualify as _____ because cough, sputum production and rales/rattles can describe a _____ at baseline
 - d. Designation of the clinical entity studied - was the pneumonia nosocomial, community acquired, previously treated relapse, aspiration pneumonia, bacterial infection superimposed on a viral _____
 - e. Assessment with regard to previous antimicrobial therapy - two doses of drug A and then switching to study drug does not necessarily constitute a clinical failure. In fact, in some instances of short term therapy, two days of an effective alternative drug can be significant with regard to outcome.
 - f. Provision of baseline assessments - this is particularly important in the _____ to document evidence change and/or infection.
 - g. Provision of qualitative and quantitative descriptions of sputum - mucoid, blood tinged, foamy pink froth
 - h. Provision of minimum signs and symptoms so that the disease entity being studied can be verified and followed. In patients with pneumonia _____ it would be helpful to have respiratory rates recorded! Arterial blood gases, especially in patients with chronic obstructive pulmonary disease, should also be included. Additional suggestions include E to A changes, dullness at bases, decreased breath sounds, fremitus etc. These clinical signs can be followed during the course of therapy.
 - i. Standardized battery of information to be provided at the time of follow-up - this is particularly relevant in patients contacted by telephone. A standardized battery of questions and data (e.g. temperature) is to be collected and documented in the case report form. This reviewer is generally not in favor of the telephone evaluation, because responses depend on the patient's medical sophistication and cultural background. Certainly, third party evaluators are not acceptable. ("My wife is not home, but she is fine.")
 - j. Length of therapy must be addressed - in the current protocols, a patient could be applicant evaluable if he/she had a minimum of 3.5 days of study drug therapy. However, conventional therapy for *S. pneumoniae* pneumonia is generally seven to ten days. Nosocomial infections are usually treated longer. If the applicant decides that 3.5 days is adequate, it must address the point that this is inadequate for conventional

therapy in its comparative trials.

- k. Radiological follow-up - Chest X-rays should be required post-therapy (either at the end of therapy or follow-up examination) as originally required in the applicant protocol and as recommended in the IDSA guidelines.
- l. Additional information with regard to deaths - information that was collected later i.e. autopsy reports should be included in patient profiles and case report forms, not just in the final study report narratives.

3. In general, this reviewer has reviewed 1808 patients most of whom had a cough, sputum production and some auscultatory findings, 1510 $\pm$ of these patients had evidence of consolidation on chest X-ray. Very few (10%) had adequate information documenting the validity of the isolated pathogens. Some patients had nosocomial pneumonia; some had community acquired pneumonia; some had aspiration pneumonia; some had cancer related obstructive pneumonia;

With the information provided, these patients were grouped by investigator diagnosis of pneumonia, by dosage and by study drug therapy. The results have been presented on the previous pages. Information with regard to pathogen eradication was derived from those strictly evaluable patients who had documented complete gram stains and/or positive blood cultures.

4. With regard to pneumonia, the clinically evaluable population demonstrates that "all comers" i.e. those with bacterial, viral, aspiration pneumonia, mycoplasma pneumonia etc. respond as well to cefepime as to the comparator drug ceftazidime. The clinical import of this statement is that the physician in the emergency room who has tentatively diagnosed that his/her patient has pneumonia can expect an equal outcome whether he chooses cefepime or ceftazidime. Underlying lung disease need not be a factor in his/her selection.

The reviewer believes that the clinically evaluable population is the more relevant population when assessing a new drug in the treatment of pneumonia.

5. Examining the strictly evaluable pneumonia population, there are differences between the two drug treatments and the meaning of this fact is unclear. The overall clinical cure rates for the strictly evaluable patients are 39/56 (70%) for cefepime and 28/35 (80%) for the comparator. The pathogen eradication rate for the cefepime group is 44/64 (69%) and for the control group is 30/38 (79%). When examining the limited number of strictly evaluable pathogens, it appears that cefepime is effective against *S. pneumoniae* (24/29 = 83% for cefepime and 16/20 = 80% for control drug). It also appears to be effective against *H. influenzae* and *M. catarrhalis*; however, the numbers are small. The efficacy against the *Pseudomonas* species is less encouraging. In general, there were so few gram negative organisms that were evaluable that the clinical spectrum of the test drug is difficult to assess. Although the reviewer does not know if the respirator pathogens are valid, giving the data the benefit of the doubt, nosocomial pathogens such as *Pseudomonas* or *Enterobacter* do not seem to be eradicated easily.

A subset of this strictly evaluable population is the bacteremic patient. Of the patients with pneumonia, there were 31 cefepime patients and 20 control patients with bacteremia, (i.e. a pathogen isolated from the bloodstream). The bacteremic patients' clinical cure rates for the two drug groups are equivalent: 22/31 = 71% for the cefepime group and 14/20 = 70% for the control group. The eradication rates for the 34 blood pathogens treated with cefepime and the 21 blood pathogens treated with control drug were (22/34) 65% and (15/21) 71%,

respectively. The majority of blood pathogens were *S. pneumoniae* i.e. eighteen (18/34) of the cefepime isolates and seventeen (13/21) of the control isolates. The eradication rates for the latter two groups are 18/22 (82%) and 13/17 (76%), respectively. In conclusion, cefepime is effective against the major respiratory pathogen; the efficacy of cefepime against nosocomial pathogens is less clear.

6.

Without knowing baseline conditions (e.g. baseline cough and sputum production) and without adequate gram stain information to follow, it is impossible to reach a meaningful conclusion. Even the slightest clinical parameter such as change in respiratory rates or a change in arterial oxygen content would have been helpful. The reviewer evaluated all 298 patients who had cough, sputum production and negative chest X-rays. Once again, for all comers in the clinically evaluable population; the data suggests that treatment with cefepime is equivalent to treatment with the control drug. In the very few strictly evaluable patients, it appears that cefepime may even be more effective. In contrast to pneumonia in which at least an infiltrate defines the disease; in this mixed population of coughing, sputum producers; it is impossible to know what disease, if any, was studied. Therefore, the reviewer would recommend that the applicant return to the investigators and secure more information i.e. with regard to gram stains and/or baseline conditions (e.g. pO₂) and resubmit the amended information.

7.

Finally, when examining the 1 gram BID dosage groups in the treatment of pneumonia, the success rates for both the clinically evaluable and strictly evaluable populations were lower than those of the control drug. In two gram twice daily dosage group, the two drugs appeared to perform equivalently. Therefore, it would be the reviewer's conclusion that cefepime should be recommended for the treatment of pneumonia at the 2 gram BID dosage level.

SAFETY SUMMARY

DEATHS

Deaths were discussed individually in each study report. Each patient was reviewed by examining the patient profile, investigator's comment, pertinent portions of the case report form and the applicant narrative. It should be noted that sometimes there was additional information in the applicant narrative that was not available in the CRF or patient profile. It is unclear from where this additional information was secured. For individual patient synopses, the reader is referred to the individual study reports. The table below is a summary of deaths per study.

STUDY	PNEUMONIA	
	CEFEPIME	CONTROL
061	16	NA
067		
Low Dose	5	NA
High Dose	8	NA
070		
NonBlind	16	8
Blind	3	3
Europe	7	3
097		
NonBlind	13	16
Blind	1	1
106		
Low Dose	0	1
High Dose	11	3
111	18	8
115	1	NA
140	12	NA
TOTALS	111/1114 (10%)	43/396 (11%)

DISCONTINUATIONS DUE TO AN ADVERSE EVENT

Each individual study report has tallied how many patients and what adverse clinical event caused an individual patient to discontinue treatment with study drug. The reader is referred to these individual reports for these findings. Below is a tabulation by study to demonstrate the distribution of discontinued patients.

STUDY	PNEUMONIA	
	CEFEPIME	CONTROL
061	4	NA
067		
Low Dose	3	NA
High Dose	2	NA
070		
NonBlind	6	1
Blind	1	1
Europe	3	0
097		
NonBlind	3	2
Blind	1	2
106		
Low Dose	0	0
High Dose	0	0
111	1	0
115	1	NA
140	7	NA
TOTALS	32/1114 (3%)	6/396 (2%)

INFUSION TOLERANCE

The applicant did not tabulate local tolerance for each indication per study. In the multi-indication studies, data with regard to infusion tolerance was given for the entire study; but it was not subdivided per indication. In general, infusions were well tolerated in over 90 percent of patients. There were occasional complaints of infiltration, phlebitis and hematoma. These complaints were similar in the control groups. These findings were detailed in each individual study report.

With regard to treatment of lower respiratory tract infection with intramuscular injection, there were only 10 cefepime patients and five cefotaxime patients that were treated in this manner. All intramuscularly administered doses were well tolerated except one pneumonia patient treated with cefepime. The complaint was listed as infiltration.

Clinical Adverse Events
Incidence
PER APPLICANT

Group	Cefepime					Ceftazidime				
	N	Prob.	Unk.	Not	Total	N	Prob	Unk	Not	Total
Comparative Studies -All	792	30 (4%)	71 (9%)	48 (6%)	150 (19%)	516	21 (4%)	47 (9%)	43 (8%)	111 (22%)
No. American Studies (C)	500	24 (5%)	69 (14%)	43 (9%)	137 (28%)	336	16 (5%)	45 (13%)	42 (13%)	103 (31%)
European (C)	292	6 (2%)	2 (1%)	5 (2%)	13 (5%)	180	5 (3%)	2 (1%)	1 (1%)	8 (4%)
Low Dose ^{1,3} (C & NC)	878	36 (4%)	44 (5%)	38 (4%)	119 (14%)	251	8 (3%)	18 (7%)	20 (8%)	46 (18%)
High Dose ^{2,3} (C & NC)	689	35 (5%)	63 (9%)	39 (6%)	137 (20%)	240	12 (5%)	28 (12%)	18 (8%)	58 (24%)
Renally Impaired (C/NC) ³	29	1 (3%)	4 (14%)	2 (7%)	7 (24%)	25	1 (4%)	1 (4%)	5 (20%)	7 (28%)
All Studies ³	1596	72 (5%)	111 (7%)	79 (5%)	263 (17%)	NA	NA	NA	NA	NA

¹ ≤ 2 grams per day of cefepime.

² > 2 grams per day of cefepime.

³ All cefepime listings include comparative and non-comparative studies.

MEDICAL OFFICER'S COMMENTS:

The reviewer is unclear why the denominators for cefepime and ceftazidime are 1596 and 516, respectively. There were additional patients with "other" infections, but not enough to account for the difference.

Modified APPLICANT Table - Clinical Adverse Events - Listed by Body System and Relatedness

BODY SYSTEM	ALL COURSES CEFEPIME N = 1596				ALL COURSES CEFTAZIDIME N = 516			
	PROBABLY RELATED		TOTAL		PROBABLY RELATED		TOTAL	
	N	%	N	%	N	%	N	%
BODY AS WHOLE	14	0.9	71	4.4	4	0.8	28	5.4
ACCIDENTAL INJ.	-	-	1	<0.1	-	-	-	-
ASTHENIA	-	-	8	0.5	-	-	4	0.8
CHEST PAIN	-	-	-	-	-	-	1	0.2
CHILLS	-	-	1	<0.1	-	-	-	-
DRAINAGE	-	-	-	-	-	-	1	0.2
EDEMA	-	-	1	0.1	-	-	-	-
FEVER	4	0.3	8	0.5	-	-	2	0.4
HEADACHE	7	0.4	32	2.0	1	0.2	12	2.3
HYDROCEPHALUS	-	-	1	<0.1	-	-	-	-
LESION	-	-	1	<0.1	1	0.2	1	0.2
MALAISE	-	-	1	<0.1	-	-	1	0.2
MUCOSITIS	2	0.1	2	0.1	1	0.2	1	0.2
NECK RIGIDITY	1	<0.1	1	<0.1	-	-	-	-
PAIN	1	<0.1	10	0.6	-	-	-	-
PAIN ARMS	-	-	6	0.4	-	-	1	0.2
PAIN ARTHRITIC	-	-	1	<0.1	-	-	-	-
PAIN BACK	-	-	4	0.3	-	-	1	0.2
PAIN BODY	-	-	1	<0.1	-	-	1	0.2
PAIN CHEST	-	-	2	0.1	-	-	-	-
PAIN CHEST TUBE	-	-	1	<0.1	-	-	-	-
PAIN FACIAL	-	-	2	0.1	-	-	-	-
PAIN FEET	-	-	2	0.1	-	-	-	-
PAIN HIPS	-	-	2	0.1	-	-	1	0.2
PAIN JOINTS	-	-	1	<0.1	-	-	1	0.2
PAIN LEGS	-	-	-	-	-	-	1	0.2
PAIN NECK	-	-	-	-	1	0.2	4	0.8
PAIN RIBS	-	-	1	<0.1	-	-	-	-
PAIN SHOULDERS	-	-	1	<0.1	-	-	-	-
PAIN STUMP	-	-	1	<0.1	-	-	-	-
TOXIC REACTION	-	-	-	-	-	-	1	0.2
HEAT SENSATION	-	-	1	<0.1	-	-	-	-

BODY SYSTEM	ALL COURSES CEFEPIME N = 1596				ALL COURSES CEFTAZIDIME N = 516			
	PROBABLY RELATED		TOTAL		PROBABLY RELATED		TOTAL	
	N	%	N	%	N	%	N	%
CARDIOVASCULR	2	0.1	40	2.5	-	-	22	4.3
ANGINA	-	-	1	<0.1	-	-	-	-
ARRHYTHMIA	-	-	2	0.1	-	-	1	0.2
ATRIAL FIB	-	-	3	0.2	-	-	1	0.2
ATRIAL FLUTTER	-	-	2	0.1	-	-	-	-
AV 2 ^o BLOCK	-	-	1	<0.1	-	-	-	-
BRADYCARDIA	-	-	2	0.1	-	-	-	-
CARDIAC ARREST	-	-	1	<0.1	-	-	4	0.8
CARDIAC DISORDER	-	-	1	<0.1	-	-	-	-
CVA	-	-	2	0.1	-	-	1	0.2
CHEST PAIN	-	-	1	0.1	-	-	-	-
CHEST PRESSURE	-	-	1	<0.1	-	-	-	-
CHF	-	-	1	<0.1	-	-	1	0.2
EMBOLISM	-	-	1	<0.1	-	-	1	0.2
HEART ARREST	-	-	1	<0.1	-	-	-	-
HYPERTENSION	-	-	2	0.1	1	0.2	2	0.4
HYPOTENSION	-	-	3	0.2	-	-	1	0.2
MYOCARDIAL INFRECT	-	-	1	<0.1	-	-	-	-
NEAR SYNCOPE	-	-	-	-	-	-	1	0.2
PAIN CHEST	-	-	8	0.5	-	-	6	1.2
PHLEBITIS	-	-	1	<0.1	-	-	-	-
SHOCK	-	-	-	-	-	-	1	0.2
SYNCOPE	-	-	1	<0.1	-	-	-	-
TACHYCARDIA	-	-	4	0.3	-	-	1	0.2
THROMBOSIS	-	-	1	<0.1	-	-	-	-
VASODILATION	2	0.1	3	0.2	-	-	-	-
VENT EXTRASYSTOLE	-	-	-	-	-	-	1	0.2
VENTRICULAR TACH	-	-	1	<0.1	-	-	2	0.4
DIGESTIVE SYS	30	1.9	119	7.5	10	1.9	54	10.5
ANOREXIA	-	-	2	0.1	-	-	-	-
BM DISORDER	-	-	1	<0.1	-	-	-	-
COLITIS	-	-	2	0.1	-	-	-	-

BODY SYSTEM	ALL COURSES CEFEPIME N = 1596				ALL COURSES CEFTAZIDIME N = 516			
	PROBABLY RELATED		TOTAL		PROBABLY RELATED		TOTAL	
	N	%	N	%	N	%	N	%
CONSTIPATION	1	<0.1	11	0.7	-	-	5	1.0
COPROSTASIS	-	-	1	<0.1	-	-	-	-
DIARRHEA	17	1.1	41	2.6	6	1.2	20	3.9
DUODENAL ULCER	-	-	-	-	-	-	1	0.2
DYSPEPSIA	-	-	1	0.1	-	-	2	0.4
FECAL INCONTINENT	-	-	2	0.1	-	-	2	0.4
FLATULENCE	-	-	1	<0.1	-	-	4	0.8
HEMATEMESIS	-	-	1	<0.1	-	-	-	-
HEMORRHAGE	-	-	5	0.3	-	-	3	0.6
ILEUS	-	-	1	<0.1	-	-	1	0.2
JAUINDICE	-	-	-	-	-	-	1	0.2
LESION	-	-	1	<0.1	-	-	-	-
LIVER DAMAGE	1	<0.1	1	<0.1	-	-	-	-
MELENA	-	-	1	<0.1	-	-	1	0.2
ORAL MONILIASIS	5	0.3	5	0.3	2	0.4	4	0.8
NAUSEA	6	0.4	32	2.0	1	0.2	9	1.7
PAIN ABDOMEN	-	-	15	0.9	1	0.2	8	1.6
PAIN MOUTH	-	-	2	0.1	-	-	-	-
PSEUDOMEM COLITIS	-	-	-	-	1	0.2	1	0.2
RECTAL DISORDER	-	-	1	<0.1	-	-	-	-
STOMATITIS	-	-	1	<0.1	-	-	-	-
ULCERATION MOUTH	1	<0.1	1	<0.1	-	-	-	-
VOMITING	2	0.1	19	1.2	-	-	7	1.4
HEME & LYMPH	-	-	3	0.2	2	0.4	5	1.0
ANEMIA	-	-	-	-	-	-	1	0.2
CONTUSION	-	-	-	-	-	-	1	0.2
HEMOLYTIC ANEMIA	-	-	-	-	1	0.2	1	0.2
HEMORRHAGE	-	-	-	-	-	-	1	0.2
ECCHYMOSIS	-	-	2	0.1	-	-	-	-
THROMBOCYTOPENIA	-	-	-	-	1	0.2	1	0.2
PETECHIA	-	-	1	<0.1	-	-	-	-
METABOLIC	-	-	5	0.3	-	-	8	1.6

BODY SYSTEM	ALL COURSES CEFEPIME N = 1596				ALL COURSES CEFTAZIDIME N = 516			
	PROBABLY RELATED		TOTAL		PROBABLY RELATED		TOTAL	
	N	%	N	%	N	%	N	%
EDEMA	-	-	5	0.3	-	-	6	1.2
PERIPHERAL EDEMA	-	-	-	-	-	-	1	0.2
WEIGHT GAIN	-	-	-	-	-	-	1	0.2
MUSCULOSKELET	1	<0.1	4	0.3	-	-	1	0.2
ARTHRALGIA	1	<0.1	1	<0.1	-	-	-	-
FRACTURE	-	-	1	<0.1	-	-	-	-
MYALGIA	-	-	2	0.1	-	-	1	0.2
NERVOUS SYSTEM	8	0.5	65	4.1	-	-	21	4.1
AGITATION	-	-	5	0.3	-	-	4	0.8
AMNESIA	-	-	1	<0.1	-	-	-	-
ANXIETY	1	<0.1	11	0.7	-	-	3	0.6
COMA	-	-	-	-	-	-	1	0.2
CONFUSION	1	<0.1	11	0.7	-	-	4	0.8
CONVULSION	-	-	3	0.2	-	-	1	0.2
DELIRIUM	-	-	3	0.2	-	-	-	-
DEPERSONALIZAT'N	-	-	1	<0.1	-	-	-	-
DEPRESSION	-	-	5	0.3	-	-	-	-
DIZZINESS	4	0.3	14	0.9	-	-	1	0.2
DROWSINESS	-	-	4	0.3	-	-	-	-
DRUG WITHDRAWAL	-	-	1	<0.1	-	-	-	-
EMOTIONAL LABILE	-	-	1	<0.1	-	-	-	-
HALLUCINATION	-	-	2	0.1	-	-	1	0.2
INSOMNIA	-	-	11	0.7	-	-	4	0.8
NERVOUSNESS	-	-	5	0.3	-	-	2	0.4
PARANOID RX	-	-	1	<0.1	-	-	-	-
PARESTHESIA	2	0.1	6	0.4	-	-	1	0.2
SENSORY DISORDER	-	-	1	<0.1	-	-	-	-
SOMNOLENCE	-	-	1	<0.1	-	-	-	-
SPEECH DISORDER	-	-	2	0.1	-	-	-	-
STUPOR	-	-	-	-	-	-	1	0.2
TREMOR	-	-	2	0.1	-	-	1	0.2
RESPIRATORY	-	-	30	1.9	-	-	19	3.7

BODY SYSTEM	ALL COURSES CEFEPIME N = 1596				ALL COURSES CEFTAZIDIME N = 516			
	PROBABLY RELATED		TOTAL		PROBABLY RELATED		TOTAL	
	N	%	N	%	N	%	N	%
APNEA	-	-	4	0.3	-	-	3	0.6
ASPIRATION	-	-	1	<0.1	-	-	-	-
ASTHMA	-	-	2	0.1	-	-	1	0.2
COUGH INCREASED	-	-	-	-	-	-	1	0.2
DYSPNEA	-	-	4	0.3	-	-	5	1.0
EDEMA	-	-	-	-	-	-	1	0.2
EPISTAXIS	-	-	4	0.3	-	-	2	0.4
HEMOPTYSIS	-	-	1	<0.1	-	-	-	-
HYPERVENTILATION	-	-	3	0.3	-	-	1	0.2
LUNG CANCER	-	-	1	<0.1	-	-	-	-
LUNG DISORDER	-	-	1	<0.1	-	-	-	-
LUNG EDEMA	-	-	1	<0.1	-	-	2	0.4
PAIN PLEURA	-	-	2	0.1	-	-	-	-
PAIN THROAT	-	-	3	0.2	-	-	1	0.2
PLEURAL EFFUSION	-	-	2	0.1	-	-	1	0.2
PNEUMONIA	-	-	-	-	-	-	1	0.2
PNEUMOTHORAX	-	-	1	<0.1	-	-	-	-
RESP. DISORDER	-	-	1	<0.1	-	-	2	0.4
RHINITIS	-	-	2	0.1	-	-	1	0.2
SKIN/APPENDAGE	25	1.6	54	3.4	7	1.4	18	3.5
BLISTERS	-	-	-	-	-	-	2	0.4
DRY SKIN	-	-	1	<0.1	-	-	-	-
ERYTHEMA	-	-	3	0.2	1	0.2	3	0.6
HERPES SIMPLEX	1	<0.1	1	<0.1	-	-	-	-
PRURITUS	3	0.2	11	0.7	3	0.6	4	0.8
RASH	20	1.3	32	2.0	4	0.8	9	1.7
SEBORRHEA	-	-	1	<0.1	-	-	-	-
SWEATING	-	-	5	0.3	-	-	1	0.2
URTICARIA	3	0.2	3	0.2	-	-	1	0.2
VESTICOBULLOUS R	-	-	1	<0.1	-	-	-	-
SPECIAL SENSES	2	0.1	4	0.3	-	-	2	0.4
BLURRED VISION	1	<0.1	3	0.2	-	-	-	-

BODY SYSTEM	ALL COURSES CEFEPIME N = 1596				ALL COURSES CEFTAZIDIME N = 516			
	PROBABLY RELATED		TOTAL		PROBABLY RELATED		TOTAL	
	N	%	N	%	N	%	N	%
EYE PAIN	-	-	-	-	-	-	1	0.2
PAIN EAR	-	-	-	-	-	-	1	0.2
TASTE PERVERSION	1	<0.1	1	<0.1	-	-	-	-
UROGENITAL SYS	2	0.1	22	1.4	1	0.2	6	1.2
ACUTE RENAL FAIL	-	-	1	<0.1	-	-	-	-
BREAST PAIN	-	-	1	<0.1	-	-	-	-
DYSURIA	-	-	1	<0.1	-	-	1	0.2
GENITAL EDEMA	-	-	1	<0.1	-	-	-	-
HEMATURIA	-	-	4	0.3	-	-	-	-
INFECTION	-	-	1	<0.1	-	-	-	-
KIDNEY FAILURE	-	-	1	<0.1	-	-	1	0.2
KIDNEY FXN ABNORM	-	-	1	<0.1	-	-	-	-
PAIN	-	-	1	<0.1	-	-	-	-
PAIN GENITOURIN	-	-	1	<0.1	-	-	-	-
URINARY FREQ	-	-	1	<0.1	-	-	1	0.2
URINARY INCONT	-	-	5	0.3	-	-	2	0.4
URINARY OBSTRUCT	-	-	1	<0.1	-	-	-	-
URINARY RETENT'N	-	-	1	<0.1	-	-	-	-
VAGINAL MONILIA	2	0.1	2	0.1	1	0.2	1	0.2

The table on the aforementioned pages was taken from safety data presented by the applicant in amendment number 71 (8/11/93). There was an additional patient who experienced a seizure that was not listed by the applicant. This was a 51 year old, white man who was being treated for pneumonia and urinary tract infection. The patient had been receiving phenytoin from at least day -7 of this study; the drug was stopped on day three. The patient also had had a spinal tap on day -7. It is unclear when the seizure occurred. The investigator wrote that the cause for the "epileptic insults was not found." Diagnostic studies, MRI, EEG and CT of the brain, were negative.

On the previous pages, the incidence rates of clinical adverse events were listed for all cefepime patients and for all ceftazidime patients. Clinical adverse events occurred most commonly in the body as a whole, digestive system, nervous system and skin systems. The two drugs appear to be quite comparable. Clinical events occurring in greater than 1% of the population exposed to cefepime include: headache (2%), diarrhea (2.6%), nausea (2.0%), vomiting (1.2%), and rash (2%). The most common events that were probably related to cefepime administration are as follows: fever, headache, diarrhea, oral moniliasis, nausea, dizziness and rash (including urticaria and pruritus.)

As expected, when comparing low dose and high dose cefepime treatment groups, the incidence of adverse clinical events is for the most part greater in the high dose group. For example:

<u>TOTAL INCIDENCE</u>	<u>LOW DOSE (n = 499)</u>	<u>HIGH DOSE (N = 274)</u>
Headache	2.0%	3.3%
Diarrhea	1.4%	3.6%
Oral Monilia	0.2%	0.7%
Nausea	3.4%	0.7%
Dizziness	0.6%	0.7%
Rash	1.8%	2.2%

The two most common body systems affected by cefepime administration are the digestive (7.5%) and the nervous (4.1%) systems. These values are higher than that for the usually most commonly affected system e.g. skin (3.4%). When contrasting low dose and high dose values, the incidence of nervous system events becomes more pronounced. The low dose values for the digestive and nervous systems are 9.4% and 4.8%, respectively whereas the high dose values for these two systems are 8.4% and 5.8%, respectively.

On the following pages are adaptations of tables of laboratory values prepared by the applicant (Amendment 71) for those patients with infections in all trials. The number of patients of tests reported is listed as "N." However, it is important to note the following: a) patients with infections from other studies, not submitted for efficacy are included here; b) not every enrolled patient had complete baseline laboratory testing done; and c) the patients listed here are only those with a normal baseline pretreatment value. Therefore, these tables are not comprehensive and only identify trends.

The most common clinically relevant laboratory abnormalities include eosinophilia, elevations of liver transaminases and changes in phosphorus levels.

NOTE: Applicant's Definition of Clinically Relevant Used in the Tables:

Hematocrit (%)	< 23.9	Alkaline Phosphatase (U/L)	> 300% UNL
Platelet count (cells x 1000/cc)	< 50	AST/SGOT (U/L)	> 300% UNL
WBC (cells x 1000/cc)	< 2	ALT/SGPT (U/L)	> 300% UNL
Absolute Neutrophil Count (cells/cc)	< 500	Total Bilirubin (mg/dL)	> 3
Absolute Eosinophil Count (cells/cc)	< 1000	BUN (mg/dL)	> 50
Prothrombin time (seconds)	> 15	Creatinine (mg/dL)	> 3.0
PTT (seconds)	> 45		
		Sodium (mEq/L)	x < 119 or x > 160
		Potassium (mEq/L)	x < 2.4 or x > 6.5
		Calcium (mg/dL)	x < 7.0 or x > 12.0
		Phosphorus (mg/dL)	x < 1.7 or x > 6.1

During- or Post-Treatment Laboratory Test Abnormalities
for Patients with a Normal Pretreatment Value

LOW DOSE^a

All Cefepime N = 770+

Ceftazidime N = 191+

Laboratory Test	----- Number (%) Patients -----					
	Cefepime			Ceftazidime		
	N ^b	Abnormal ^c	Cl. Rel. ^d	N ^b	Abnormal ^c	Cl. Rel. ^d
HEMATOLOGY						
Hematocrit	443	180 (41)	1	140	47 (36)	2
Platelet count	652	15 (2)	1	198	8 (4)	0
WBC count	766	36 (5)	0	223	8 (4)	0
Neutrophil count	687	35 (5)	0	203	10 (5)	0
Eosinophil count	646	77 (12)	11	198	20 (10)	0
COAGULATION						
Prothrombin time	407	21 (5)	6	121	4 (3)	0
PTT	504	33 (7)	3	144	10 (7)	2
LIVER FUNCTION						
Alkaline phosphatase	518	55 (11)	1	147	13 (9)	1
AST (SGOT)	561	11 (2)	8	143	20 (14)	2
ALT (SGPT)	546	117 (21)	12	130	19 (15)	0
Total bilirubin	585	16 (3)	4	166	3 (2)	1
RENAL FUNCTION						
BUN	521	98 (19)	2	160	9 (6)	1
Creatinine	647	24 (4)	1	188	6 (3)	0
ELECTROLYTES^e						
Na ⁺	522	92 (18)	2	163	28 (17)	0
K ⁺	622	156 (25)	1	180	39 (22)	2
Ca ⁺⁺	233	64 (27)	1	116	34 (29)	0
PO ₄ ⁼	270	62 (23)	11	119	25 (21)	3

a Includes patients from controlled and uncontrolled, North American and European trials

b N indicates number of patients tested (had at least 2 values).

c During- or post-treatment results outside the investigator's normal range limit, in the direction of toxicity.

d Patients with Clinically Relevant values are included in the "Abnormal" column.

e Increased or Decreased Abnormal values were combined by the Applicant

+ Listed values are from the 1808 efficacy patients; (+) and those handful of patients included from 081, 110, 113, 123, 126, 129, 135 and 146.

During- or Post-Treatment Laboratory Test Abnormalities
for Patients with a Normal Pretreatment Value

HIGH DOSE^a

All Cefepime N = 525+

Ceftazidime N = 254+

Laboratory Test	----- Number (%) Patients -----					
	<u>Cefepime</u>			<u>Ceftazidime</u>		
	N ^b	Abnormal ^c	Cl. Rel. ^d	N ^b	Abnormal ^c	Cl. Rel. ^d
HEMATOLOGY						
Hematocrit	290	147 (51)	1	80	34 (43)	2
Platelet count	520	28 (5)	3	187	10 (5)	0
WBC count	614	29 (5)	3	205	13 (6)	2
Neutrophil count	510	26 (5)	0	191	18 (9)	1
Eosinophil count	482	72 (15)	7	180	26 (14)	3
COAGULATION						
Prothrombin time	221	17 (8)	4	96	9 (9)	1
PTT	355	41 (12)	7	110	7 (6)	4
LIVER FUNCTION						
Alkaline phosphatase	350	57 (16)	4	117	28 (24)	2
AST (SGOT)	351	88 (25)	11	107	23 (21)	1
ALT (SGPT)	345	95 (28)	10	75	25 (33)	1
Total bilirubin	382	38 (10)	4	128	6 (5)	2
RENAL FUNCTION						
BUN	296	46 (16)	2	125	21 (17)	0
Creatinine	391	22 (6)	2	173	5 (3)	0
ELECTROLYTES^e						
Na ⁺	394	48 (12)	1	137	34 (25)	0
K ⁺	471	126 (28)	3	166	47 (28)	1
Ca ⁺⁺	229	77 (34)	2	77	24 (31)	1
PO ₄ ⁻	266	22 (8)	10	104	21 (20)	1

a Includes patients from controlled and uncontrolled, North American and European trials

b N indicates number of patients tested (had at least 2 values).

c During- or post-treatment results outside the investigator's normal range limit, in the direction of toxicity.

d Patients with Clinically Relevant values are included in the "Abnormal" column.

e Increased or Decreased Abnormal values were combined by the Applicant

+ Listed values are from the 1808 efficacy patients; (+) and those handful of patients included from 081, 110, 113, 123, 126, 129, 135 and 146.

During- or Post-Treatment Laboratory Test Abnormalities
for Patients with a Normal Pretreatment Value

RENALLY IMPAIRED^a

Laboratory Test	----- Number (%) Patients -----					
	N ^b	Cefepime		N ^b	Ceftazidime	
		Abnormal ^c	Cl. Rel. ^d		Abnormal ^c	Cl. Rel. ^d
HEMATOLOGY						
Hematocrit	7	3 (43)	0	9	7 (78)	0
Platelet count	22	2 (9)	1	22	3 (14)	0
WBC count	25	1 (4)	0	24	0 (0)	0
Neutrophil count	22	1 (5)	0	19	1 (5)	0
Eosinophil count	22	4 (18)	1	19	1 (5)	1
COAGULATION						
Prothrombin time	7	0 (0)	0	11	3 (27)	0
PTT	12	0 (0)	0	11	4 (36)	0
LIVER FUNCTION						
Alkaline phosphatase	8	2 (25)	0	12	4 (33)	0
AST (SGOT)	13	3 (23)	0	13	1 (8)	0
ALT (SGPT)	16	5 (0)	0	14	3 (21)	0
Total bilirubin	18	2 (11)	0	14	1 (7)	0
RENAL FUNCTION						
BUN	4	1 (25)	0	3	0 (0)	0
Creatinine	6	3 (50)	1	8	1 (13)	0
ELECTROLYTES^e						
Na ⁺	19	7 (37)	0	14	3 (21)	0
K ⁺	23	7 (30)	0	18	6 (33)	0
Ca ⁺⁺	10	3 (30)	0	6	4 (33)	0
PO ₄ ⁻	11	4 (36)	0	9	1 (11)	0

a Includes patients from controlled and uncontrolled, North American and European trials

b N indicates number of patients tested (had at least 2 values).

c During- or post-treatment results outside the investigator's normal range limit, in the direction of toxicity.

d Patients with Clinically Relevant (see definition below) values are included in the "Abnormal" column.

e Increased or Decreased Abnormal values were combined by the Applicant

+ Listed values are from the 1808 efficacy patients; (+) and those handful of patients included from 081, 110, 113, 123, 126, 129, 135 and 146.

SAFETY FINAL COMMENTS

1. For the 1808 patients with _____ infections studied in the aforementioned protocols, there were 125/1336 (9%) deaths in the cefepime treatment group and 53/472 (11%) in the control treatment group. Most deaths were related to the patients' underlying diseases. Some were the result of clinical failure. None of the deaths appeared to be related to the direct toxicity of study drugs.
2. The infusions were well tolerated by greater than 90% of all patients. There were very few patients who received cefepime by intramuscular injection. Of the 10 patients who received their treatment by intramuscular injection 90% (9) tolerated the injection.
3. Adverse events described by the patients appeared comparable for both study drug groups. The most frequent complaints in the cefepime group were nausea, vomiting, diarrhea, dizziness, rash, oral moniliasis and headache.
4. Clinically relevant laboratory abnormalities developed in greater than 1% of cefepime patients in the following tests: eosinophil count, prothrombin time, AST, ALT, and phosphorus in the low dose group; eosinophil count, prothrombin time, PTT, alkaline phosphatase, AST, ALT, total bilirubin and phosphorus in the high dose group. Clinically relevant laboratory abnormalities developed in greater than 1% of control patients in the following tests: hematocrit, PTT, AST, potassium and phosphorus in the low dose group; hematocrit, WBC, PTT, alkaline phosphatase, ALT, AST, total bilirubin and phosphorus.
5. It is not unexpected, but a greater number of clinical and laboratory adverse events are associated with the higher dosage for both study groups. However, on the whole, the test drug, cefepime, appears to have a similar safety profile as other cephalosporins.

FINAL RECOMMENDATION

1. Cefepime can be recommended for the treatment of pneumonia caused by *S. pneumoniae*. The 2 gram twice daily (IV) dosage and a treatment length of 7-10 days is recommended. Patients with _____ had similar success rates as those patients without _____ therefore a statement with regard to the treatment of pneumonia _____ is acceptable. There were too few patients treated intramuscularly to confirm the safety and efficacy of this route of administration.
2. With regard to _____ it was difficult to ascertain if the appropriate population was studied without adequate gram stain and baseline clinical information. Preliminary findings suggest that cefepime may be beneficial in the treatment _____. It is recommended that the applicant return to the patients' hospital records to obtain supplemental information that would support this indication.

ADDENDUM

The following addendum was written by the supervisory medical officer, Renata Albrecht, MD. The primary reviewer concurs with this opinion. It re-iterates the information stated in item five of the efficacy final comments on page 359.

The recommendation to approve cefepime in the treatment of pneumonia due to *Streptococcus pneumoniae* is supported by the following data:

- (a) In the treatment of patients with pneumonia, the outcome in the MO clinically evaluable patients was 245/379 (65%) for cefepime and 111/163 (68%) for the control drugs. The 95% confidence interval for the difference was (-0.121, +0.061) indicating no statistical difference between the regimens. (MOR page 334)
- (b) In the treatment of patients with pneumonia, the clinical outcome for MO strictly evaluable patients was 39/56 (70%) for cefepime and 28/35 (80%) for the control regimens. The 95% confidence interval for the difference is (-0.301, +0.102) which fails to demonstrate statistical equivalence. (MOR page 334) The reason for the 10% difference can be explained by the low eradication rates for various organisms other than *S. pneumoniae* (See table 11 on MOR page 348).
- (c) However, since only *S. pneumoniae* is considered approvable, the outcome of patients with this organism is important. Eradication rates (which are essentially extrapolations of clinical responses) are 24/29 (83%) for cefepime and 16/20 (80%) for the control regimens. (MOR page 348) Examining the eradication for *S. pneumoniae* in the subset of patients with bacteremia due to *S. pneumoniae*, the eradication rates are 18/22 (82%) for cefepime and 13/17 (76%) for the control regimens. (MOR page 352) These eradication rates, in context of the drug's overall clinical activity, are adequate for approval of the indication due to *S. pneumoniae*.

SAFETY SUMMARY

CEFEPIME

MAXIPIME®

SAFETY SUMMARY

Cefepime, at the time of the NDA submission, had been administered to 6,646¹ patients in clinical trials in North America, Europe and Japan. These patients have been divided by the applicant into three groups: 4,442¹ patients in the Clinical Efficacy studies; 461 adult and 9 pediatric in the Pharmacokinetic studies; and 4 individual treatment use and 1,730 Japanese patients as additional safety patient information. Of the patients in North America and Europe who were randomized to cefepime, there were 1,054 treatment courses of the _____ with sodium chloride formulation administered; the remaining treatment courses were administered with the dihydrochloride/arginine formulation. There were a total of 1,842 patients who received control drug in comparative studies; 1,456 of these patients received ceftazidime.

MEDICAL OFFICER'S COMMENTS:

The reader should be aware that the numbers/charts that follow were prepared by the APPLICANT, except for the rare reviewer tables which are clearly identified. The applicant used the definition of "N" in two different ways. "N" sometimes referred to the total number of patients in a given population. At other times, "N" referred to the total number of courses of drug administered. A patient who received cefepime on two separate occasions could have been labelled as one (1) patient or two (2) cefepime courses. However, the applicant often used the terms patient and course interchangeably and often did not clarify which type of "N" was being employed. Therefore, the reviewer found the tables confusing and, in many instances, was unable to reconcile totals from subtotals. This theme appears several times throughout the review.

Cephalosporins in General

Cephalosporins are considered to be among the safest of antibiotic drug classes. Beta-lactam antibiotics can produce life-threatening anaphylaxis; but less serious hypersensitivity reactions such as fever, arthralgia, and exanthema are encountered more commonly. Cross-reactivity between penicillins and cephalosporins can occur, but the incidence of cephalosporin reactions in penicillin-allergic patients has been a matter of much debate.

The following lists the most common adverse reactions seen with known cephalosporins:

1. Gastrointestinal side effects of cephalosporins include nausea and/or vomiting, nonspecific diarrhea, and antibiotic-associated diarrhea or colitis, including that associated with *Clostridium difficile* toxin.
2. Cephalosporins containing an N-methyl thiotetrazole side chain in the three position on the cephem nucleus have been associated with disulfiram-like reactions and bleeding diatheses. (NOTE: Cefepime does not contain this side chain configuration.)
3. Skin rashes and rarely serious and potentially fatal skin and mucous membrane reactions (i.e. the Stevens-Johnson syndrome) can occur following cephalosporin usage.
4. In general, cephalosporins have a low potential for neurotoxicity, although such events as convulsions, psychosis, delirium, and confusion have been reported.
5. Abnormal laboratory values may develop during cephalosporin therapy. Increases in the levels of liver transaminases and alkaline phosphatase have been reported with all cephalosporins, with frequencies generally less than 5%. Hematologic effects have included eosinophilia, leukopenia (especially granulocytopenia), and thrombocytopenia. Platelet dysfunction, especially defective platelet aggregation, has also been reported. Positive direct Coombs' tests, usually of little clinical importance, have been reported with all cephalosporins. Rarely, immune-mediated hemolysis has been associated with this class of drugs.
6. Some cephalosporins (e.g., cephaloridine) have nephrotoxic potential; this is sometimes amplified with the concomitant use of a potent diuretic or an aminoglycoside.

¹In the integrated summary of safety, the original patient count was given as 6,649 patients of which 4,445 patients were enrolled in clinical efficacy studies. Three cefepime patients had been counted twice.

The following pages summarize the safety examination for cefepime and how cefepime compares to ceftazidime, another cephalosporin.

The applicant submitted safety information in four segments. Safety data was provided for the NDA; it is summarized in volumes 286, 287 and 288. The NDA cut-off date was May 31, 1991. The first safety update was submitted by the applicant on December 18, 1992. It provided a summary of the safety experience during the period of additional enrollment from May 31, 1991 to June 30, 1992. An amendment was filed to this document on February 12, 1993. This amendment contained omitted European patient narratives. A second safety update was filed on May 28, 1993. The second safety update summarized the entire post-NDA safety experience for all patients who were enrolled after the NDA cut off date but on or before December 31, 1992 and whose case report forms were entered into the applicant's clinical database as of February 28, 1993. The final safety submission was filed on November 24, 1993. This update summarized the safety experience of all patients who were enrolled in clinical trials between January 1, 1993 and October 31, 1993.

The safety data was presented by the applicant in either tabular or narrative format. The reviewer's presentation was therefore dependent on the accuracy of the applicant's presentation. The reviewer could only independently assess the following: 1) Actual case report forms for those patients who died or those patients who discontinued treatment prematurely 2) And, raw laboratory data from the North American comparative trials provided by the applicant in SAS files. Other than these two exceptions, what follows, is a summary of the applicant's data.

DEATHS

NDA

There were a total of 353 patients who died and whose case report forms were listed in the NDA. This includes all patients enrolled in efficacy studies, all pharmacokinetic studies, all pediatric patients and all compassionate use patients. The Japanese patients are not included. Of these 353 patients who died, there were 350 (244/4419 = 6% cefepime; 106/1842 = 6% control) deaths among patients enrolled in clinical trials, two patients (2/4 = 50%) who were enrolled under compassionate use and one patient (1/470 = 0.2%) who was enrolled in a pharmacokinetic study. The 350 deaths within the clinical studies are broken down in the reviewer table below:

DRUG	NORTH AMERICA	EUROPE	LOW DOSE < 2g BID	HIGH DOSE ≥ 2g BID
CEFEPIME	138/3313 (4%)	106/1106 (10%)	83/2070 (4%)	161/2349 (7%)
CONTROL	64/1483 (4%)	42/359 (12%)	28/640 (4%)	78/1202 (6%)

The following pages catalogue all NDA deaths by indication. Those patients that have been previously discussed by the reviewer in the efficacy section of the review are itemized below. The following information is listed for each patient: patient number, dosage, study location and cause of death. For each patient who was not submitted for efficacy, a short narrative is presented.

Patients who were submitted for more than one disease process are listed per indication, but assigned only one number. When a patient is repeated, the number is designated as "***."

Although there were many deaths and many of these deaths were a result of drug failure, there were NO deaths that appeared to be a direct, toxic consequence of the drug.

Pages 3 - 19

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SKIN AND SKIN STRUCTURE INFECTIONS

STUDY AI-411-061

Cefepime

208.	1g cefepime	North America
	Cause of death: Gunshot wound to the heart	
209.	1g cefepime	North America
	Cause of death: Cardiopulmonary arrest	

STUDY AI-411-067

Cefepime

There were no deaths in this protocol.

STUDY AI-411-075Cefepime

210. 0.5g cefepime North America
Cause of death: Myocardial infarct

STUDY AI-411-081Cefepime

211. 1g cefepime North America
Cause of death: Cardiopulmonary arrest

212. 1g cefepime North America
Cause of death: Multi-organ failure and systemic infection

213. 1g cefepime North America
Cause of death: Cardiac arrest

214. 1g cefepime North America
Cause of death: Hypovolemic shock secondary to ischemic bowel and hemorrhage

215. 1g cefepime North America
Cause of death: Acute myocardial infarct and cerebrovascular accident

STUDY AI-411-097Cefepime

216. 2g cefepime North America
Cause of death: Septic shock

217. 2g cefepime North America
Cause of death: Lymphoma

218. 2g cefepime North America
Cause of death: Hemorrhage from esophageal varices

Ceftazidime

219. 2g ceftazidime North America
Cause of death: Congestive heart failure and cardiac arrhythmia

... 2g ceftazidime North America
Cause of death: Septic shock

220. 2g ceftazidime North America
Cause of death: Gastrointestinal hemorrhage

221. 2g ceftazidime North America
Cause of death: Bronchopneumonia and purulent pancreatitis
222. 2g ceftazidime North America
Cause of death: Esophageal hemorrhage and Hodgkin's lymphoma
223. 2g ceftazidime North America
Cause of death: Bronchopneumonia

STUDY AI-411-111

Cefepime

224. 2g cefepime Europe
Cause of death: Metastatic breast carcinoma
- *** 2g cefepime Europe
Cause of death: Metastatic breast carcinoma
225. 2g cefepime Europe
Cause of death: Metastatic lung carcinoma
226. 2g cefepime Europe
Cause of death: Bladder neoplasia and renal failure
- *** 2g cefepime Europe
Cause of death: Renal insufficiency and carcinoma of the larynx (
227. 2g cefepime Europe
Cause of death: Congestive heart failure secondary to chemotherapy for leukemia

Ceftazidime

- *** 2g ceftazidime Europe
Cause of death: Gastrointestinal hemorrhage, neoplasia and shock
- *** 2g ceftazidime Europe
Cause of death: Extensive cervical carcinoma
228. 2g ceftazidime Europe
Cause of death: Metastatic cystadenocarcinoma
229. 2g ceftazidime Europe
Cause of death: Sepsis

STUDY AI-411-140**Cefepime**

230.	2g cefepime	North America
	Cause of death: Multi-organ failure including renal failure and infection	
***	2g cefepime	North America
	Cause of death: Pneumonia and sepsis	
***	2g cefepime	North America
	Cause of death: Multi-organ failure	

URINARY TRACT INFECTIONS**STUDY AI-411-061****Cefepime**

231.	1g cefepime	North America
	Cause of death: Respiratory insufficiency due to adenocarcinoma of the lung	
232.	1g cefepime	North America
	Cause of death: Respiratory arrest	

The patient was a 64 year old white man with a history of neurological disease who was admitted to the hospital for treatment of fever, cough, sputum production and decreased urine output. The patient received two doses of cefepime. He aspirated his stomach contents and clinically worsened. It was decided not to treat the patient aggressively. Cefepime was discontinued. The patient suffered a respiratory arrest nine days after cefepime was discontinued.

233.	1g cefepime	North America
	Cause of death: Respiratory insufficiency due to past cerebrovascular accidents	
234.	1g cefepime	North America
	Cause of death: Acute myocardial infarct	
235.	1g cefepime	North America
	Cause of death: Hypotension, acidosis, leukopenia of unknown etiology	
236.	1g cefepime	North America
	Cause of death: Metastatic breast carcinoma	
237.	1g cefepime	North America
	Cause of death: Squamous cell carcinoma of lung	
***	1g cefepime	North America
	Cause of death: Complications of a cerebrovascular accident	

STUDY AI-411-067

Cefepime

238. 1g cefepime Europe
Cause of death: Renal carcinoma
239. 1g cefepime Europe
Cause of death: Cardiopulmonary arrest secondary to lung carcinoma
240. 2g cefepime Europe
Cause of death: Underlying neurological disease
241. 2g cefepime Europe
Cause of death: Complications of decubitus ulcers and bronchial obstruction

STUDY AI-411-071

Ceftazidime

242. 0.25g ceftazidime North America
Cause of death: Cardiorespiratory arrest

STUDY AI-411-083

Cefepime

243. 0.5g cefepime North America
Cause of death: Unknown, thought to be related to underlying prostate carcinoma
244. 0.5g cefepime North America
Cause of death: Probable pulmonary embolism
245. 0.5g cefepime North America
Cause of death: Cardiorespiratory arrest
246. 0.5g cefepime North America
Cause of death: Subarachnoid hemorrhage
247. 0.5g cefepime North America
Cause of death: Urosepsis
248. 0.5g cefepime North America
Cause of death: Probable myocardial infarct

Ceftazidime

249. 0.5g ceftazidime North America
Cause of death: Sepsis

250. Cause of death: Unknown 0.5g ceftazidime North America
251. Cause of death: Perforated diverticula 0.5g ceftazidime North America

Cefepime

252. Cause of death: Hyponatremia related to metastatic lung carcinoma 0.5g cefepime Europe
253. Cause of death: Urosepsis 0.5g cefepime Europe

Ceftazidime

254. Cause of death: Metastatic cancer of the prostate 0.5g ceftazidime Europe
255. Cause of death: AIDS 0.5g ceftazidime Europe
256. Cause of death: Multi-organ failure 0.5g ceftazidime Europe

STUDY AI-411-097

Cefepime

- ... Cause of death: Respiratory arrest 2g cefepime North America
257. Cause of death: Respiratory failure associated with metastatic lung cancer 2g cefepime North America
258. Cause of death: Pneumonia 2g cefepime North America
- ... Cause of death: Respiratory arrest 2g cefepime North America
259. Cause of death: Sepsis 2g cefepime North America
260. Cause of death: Multi organ failure 2g cefepime North America
261. Cause of death: Complications of brainstem infarct 2g cefepime North America

262.	2g cefepime	North America
	Cause of death: Cardiac arrest	
***	2g cefepime	North America
	Cause of death: Septic shock (***) See SSTI)	
263.	2g cefepime	North America
	Cause of death: Post-surgical complications	
264.	2g cefepime	North America
	Cause of death: Cardiopulmonary arrest	
265.	2g cefepime	North America
	Cause of death: Hypertensive stroke, ?delirium tremens	
***	2g cefepime	North America
	Cause of death: Lymphoma, pneumonia and renal failure	
266.	2g cefepime	North America
	Cause of death: Sepsis and Acute respiratory distress syndrome	
267.	2g cefepime	North America
	Cause of death: Metastatic colonic carcinoma	
268.	2g cefepime	North America
	Cause of death: Large cell carcinoma of unknown etiology	
269.	2g cefepime	North America
	Cause of death: Sepsis	
<u>Ceftazidime</u>		
270.	2g ceftazidime	North America
	Cause of death: Opportunistic infection and sepsis	
***	2g ceftazidime	North America
	Cause of death: Cardiopulmonary arrest	
***	2g ceftazidime	North America
	Cause of death: Cardiac arrhythmia	
271.	2g ceftazidime	North America
	Cause of death: Respiratory arrest, prostate carcinoma	
272.	2g ceftazidime	North America
	Cause of death: Cardiorespiratory arrest	
273.	2g ceftazidime	North America
	Cause of death: Viral encephalitis and aspiration pneumonia	

274.	2g ceftazidime	North America
	Cause of death: Hemorrhagic brainstem infarct	
275.	2g ceftazidime	North America
	Cause of death: Respiratory arrest, bronchopneumonia	
276.	2g ceftazidime	North America
	Cause of death: Cardiac arrhythmia	
277.	2g ceftazidime	North America
	Cause of death: AIDS	
278.	2g ceftazidime	North America
	Cause of death: Multiple myeloma	
***	2g ceftazidime	North America
	Cause of death: Respiratory arrest, cause unclear	
***	2g ceftazidime	North America
	Cause of death: Congestive heart failure	
279.	2g ceftazidime	North America
	Cause of death: Hepatorenal syndrome	

STUDY AI-411-108

Cefepime

280.	0.5g cefepime	North America
	Cause of death: Congestive heart failure secondary to myocardial infarct	
281.	0.5g cefepime	North America
	Cause of death: Bilateral pneumonia	

Ceftazidime

282.	0.5g ceftazidime	North America
	Cause of death: Metastatic prostatic carcinoma	

STUDY AI-411-111

Cefepime

283.	2g cefepime	Europe
	Cause of death: Pulmonary embolism	
***	2g cefepime	Europe
	Cause of death: Ovarian carcinoma	

284.	2g cefepime	Europe
	Cause of death: Unknown	
***	2g cefepime	Europe
	Cause of death: Metastatic lung carcinoma	
***	2g cefepime	Europe
	Cause of death: Bladder neoplasia and renal failure	
285.	2g cefepime	Europe
	Cause of death: Sepsis	
***	2g cefepime	Europe
	Cause of death: Renal insufficiency and carcinoma of the larynx	SSTI)
<u>Ceftazidime</u>		
***	2g ceftazidime	Europe
	Cause of death: Cardiac arrest and infection	
286.	2g ceftazidime	Europe
	Cause of death: Acute cardiac arrest	
287.	2g ceftazidime	Europe
	Cause of death: Intracerebral hemorrhage	
288.	2g ceftazidime	Europe
	Cause of death: Unknown	
289.	2g ceftazidime	Europe
	Cause of death: Metastatic malignant melanoma	
290.	2g ceftazidime	Europe
	Cause of death: Congestive heart failure and ?bronchopneumonia	
291.	2g ceftazidime	Europe
	Cause of death: Carcinomatous peritonitis	
***	2g ceftazidime	Europe
	Cause of death: Extensive cervical carcinoma	SSTI)
***	2g ceftazidime	Europe
	Cause of death: Sepsis (*** See SSTI)	
292.	2g ceftazidime	Europe
	Cause of death: Sepsis related to colonic carcinoma	

STUDY AI-411-140

Cefepime

***		2g cefepime	North America
	Cause of death: Sepsis		
293.		2g cefepime	North America
	Cause of death: Urosepsis		
***		2g cefepime	North America
	Cause of death: Sepsis		
294.		2g cefepime	North America
	Cause of death: Sepsis, renal failure and cardiac failure		
295.		2g cefepime	North America
	Cause of death: Urosepsis		
296.		2g cefepime	North America
	Cause of death: Unknown		
***		2g cefepime	North America
	Cause of death: Pneumonia and sepsis	SSTI)	
***		2g cefepime	North America
	Cause of death: Multi-organ failure	SSTI)	
297.		2g cefepime	North America
	Cause of death: Urosepsis		
298.		2g cefepime	North America
	Cause of death: Congestive heart failure		
299.		2g cefepime	North America
	Cause of death: Septic shock		
300.		2g cefepime	North America
	Cause of death: Squamous cell carcinoma of the head/neck and multi-organ failure		
***		2g cefepime	North America
	Cause of death: Cardiopulmonary arrest and pneumonia		
301.		2g cefepime	North America
	Cause of death: Aspiration pneumonia		

NDA 50-679

SAFETY SUMMARY

STUDY AI-411-999

Cefepime

302. 2g cefepime
Cause of death: Fungal sepsis

North America

Pages 31-63

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FINAL SAFETY UPDATE

Twenty-three clinical trials were conducted in North America and Europe during 1993, and 667 courses of cefepime were administered. This included 187 courses from four blinded trials. The applicant stated that the incidence of death in patients enrolled for the final update was 7%. (The reviewer assumes that the denominator is 967 as stated above.) Seventy patients died within 30 days of cefepime therapy and one patient died 35 days post-treatment. The case report forms for these patients were not submitted. Random narrative comments were listed for each of the 71 patients. A typical example follows:

Patient	"Respiratory arrest secondary to myotonic dystrophy. Patient found in bed without pulse or respirations. Respiratory arrest apparently secondary to myotonic dystrophy."

Seventy-one patients were listed; all were treated with cefepime. There were two patients treated with pediatric dosing; two patients treated with 1g BID; 29 patients treated with 2g BID; and 28 patients treated with 2g TID. Patient number, dosage group and primary cause of death were tabulated by the reviewer below.

ALL CEFEPIME DEATHS:

<u>Patient number</u>	<u>Dose</u>	<u>Cause of Death</u>
1.	Pediatric	Bacterial Meningitis
2.	Pediatric	RSV Pneumonia
3.	1g BID	Pulmonary Embolism
4.	1g BID	Pneumonia
5.	2g BID	Shock, Cardiac Arrest
6.	2g BID	Pulmonary Hemorrhage
7.	2g BID	Respiratory Insufficiency
8.	1g BID	Pneumonia, Sepsis
9.	2g BID	Cerebral Hemorrhage
10.	2g BID	Respiratory failure, RSV
11.	2g BID	Septic Shock
12.	2g BID	Non-Hodgkin's Lymphoma
13.	2g BID	Disseminated Aspergillosis
14.	2g BID	Respiratory Insufficiency, AML
15.	2g BID	Respiratory Insufficiency, Myeloma
16.	2g BID	Leukemia, Cardiac Arrest
17.	2g BID	Disseminated Aspergillosis
18.	2g BID	Multi-organ Failure
19.	2g BID	Multi-organ Failure
20.	2g BID	Septic Shock, Renal Failure
21.	2g BID	Leukemia
22.	2g BID	Leukemia
23.	2g BID	Veno-occlusive Disease of the Liver
24.	2g BID	Bilateral Alveolar Hemorrhage
25.	2g BID	Adult Respiratory Distress Syndrome
26.	2g BID	Respiratory Failure
27.	2g BID	Pneumonia, Cardiogenic Shock
28.	2g BID	Septic Shock
29.	2g BID	Chronic Obstructive Pulmonary Disease
30.	2g BID	Adult Respiratory Distress Syndrome
31.	2g BID	Pulmonary Edema, Sepsis
32.	2g BID	Cardiopulmonary Arrest
33.	2g TID	Pneumonia
34.	2g TID	Renal Failure
35.	2g TID	Traumatic Brain Injury
36.	2g TID	Brain Abscess

<u>Patient number</u>	<u>Dose</u>	<u>Cause of Death</u>
37.	2g TID	Allergic Reaction, Hepatotoxicity
38.	2g TID	Cardiopulmonary Arrest
39.	2g TID	Respiratory Failure
40.	2g TID	Respiratory Failure
41.	2g TID	Respiratory Failure, Myotonic Dystrophy
42.	2g TID	Pancytopenia, Probable Sepsis
43.	2g TID	Cancer
44.	2g TID	Hemorrhage, AML
45.	2g TID	Agranulocytosis
46.	2g TID	Cardiopulmonary Arrest, Aspiration
47.	2g TID	Multi-organ Failure
48.	2g TID	Respiratory Failure
49.	2g TID	Myocardial Infarct
50.	2g TID	Lung Carcinoma
51.	2g TID	Bilateral Pneumonia
52.	2g TID	Pneumonia
53.	2g TID	Cardiorespiratory Arrest
54.	2g TID	Congestive Heart Failure, Aspiration
55.	2g BID	Pneumonia
56.	2g TID	Adult Respiratory Distress Syndrome
57.	2g TID	Leukemia
58.	2g TID	Septic Shock
59.	2g TID	Cerebral Hemorrhage
60.	2g TID	Lung Cancer, Septic Shock
61.	2g TID	Respiratory Failure, Myeloma
62.	2g TID	Chronic Myelogenous Leukemia
63.	2g TID	Metastatic Lacrimal Gland Cancer
64.	2g TID	Disseminated Adenocarcinoma
65.	2g TID	Lymphoma
66.	2g TID	Lung Cancer, Trauma
67.	2g TID	Pneumonia
68.	2g TID	Head Trauma
69.	2g TID	Cardiac Arrest
70.	2g TID	Hepatic Failure, Sepsis
71.	2g TID	Respiratory Failure, Glioblastoma

Summary: From the NDA and three safety updates, the applicant stated that there were a cumulative total of 374 cefepime deaths. All blinded study patients were assumed to have been treated with cefepime. The applicant itemized these patients by dosage as follows:

Pediatric dosage	12 patients
0.5 g BID	11 patients
1g BID	75 patients
2g BID	173 patients
3g TID	102 patients
PK study	<u>1 patient</u>
	374 patients (Note: The reviewer calculated 377.)

In the applicant discussion, the total number of patients are not given. However, the reviewer presumes that the total number of cefepime patients is 8646 (from the NDA) plus 742 (from the first and second safety updates) plus 967 (from the final safety update) or 8355 patients. If this is the correct total, then the overall death rate for cefepime would be $374/8355 = 4.5\%$. This is slightly less than the $247/4419^1 = 5.5\%$ found in the original NDA.

Cefepime, itself, did not appear to be a direct toxin or cause of death. However, there were many deaths that were the result of failure or lack of efficacy of the product.

¹A total of 4,419 patients were treated with cefepime; however there were an additional 23 (N = 4,442) patients who were not initially randomized to cefepime who received cefepime either as a second course of therapy or concomitantly with their randomized treatment of therapy.

Japanese Data

The Japanese enrolled 1734 patients, of whom 1,730 actually received cefepime. Of these 1730 patients, the Japanese chose to exclude 89 patients from their safety evaluation. These were patients in their Phase I trials (N = 45) and a few patients from their clinical efficacy trials (N = 44). There were four (4/89 = 4%) patients who received cefepime who died in this group. Of the 1641 remaining Japanese patients who received cefepime and were submitted for safety review, there were five deaths. The total rate of death for cefepime was 9/1730 or 5%. There were three deaths among the ceftazidime patients in comparative trials. The denominator of ceftazidime patients was unclear to the reviewer. There were no case report forms submitted for the Japanese patients. The applicant provided narrative summaries for all patients who died. The investigator of one patient

thought that death may have been related to cefepime administration. Below are summaries and causes of death of the Japanese patients.

Cefepime

1. 1g cefepime Japan
Cause of death: Cardiorespiratory failure

The patient was a 58 year old woman with a history of emphysema and cardiac dysfunction who was admitted to the hospital for treatment of respiratory distress. She was treated with cefepime for a presumed respiratory tract infection for seven days. The patient did not improve and imipenem was substituted. The patient died of cardiorespiratory failure two days after cefepime was discontinued.

2. 2g cefepime Japan
Cause of death: Multi-organ failure

The patient was a 78 year old man who was admitted for an exacerbation of his asthma. He subsequently developed pneumonia and cardiac failure. Initially, the patient received treatment with moxalactam. The patient received treatment with cefepime and minocycline. The patient's condition continued to decline; he died on the eighth day of study therapy.

3. 2g cefepime Japan
Cause of death: Peritonitis and septic shock

The patient was a 65 year old man who was admitted for treatment of a lower respiratory tract infection. Cefepime therapy was initiated. However, on day three of treatment; it was discovered that he had a ruptured liver abscess. Cefepime was discontinued. He died five days later of septic shock.

4. 1g cefepime Japan
Cause of death: hemorrhage

The patient was a 69 year old man with a history of lung carcinoma who was admitted for treatment of a lower respiratory tract infection. He received cefepime therapy for 10 days. He died on the tenth day of treatment after a hemorrhagic complication of bronchoscopy.

5. **1g cefepime** **Japan**
Cause of death: ?Graft versus host reaction

The patient, an 80 year old man with a history of a recent cystectomy for bladder carcinoma, was admitted for treatment of an impacted ureteral stone. During the hospitalization the patient received several transfusion and intravenous dL-lysine. The stone was removed surgically; the patient was placed on ofloxacin post-operatively. Thirteen days later, the patient was still febrile and cefepime was initiated. Within three days, the patient developed a rash and ileus. Cefepime and dL-lysine were discontinued. The rash became more diffusive. Pancytopenia developed. The patient died of multi-organ failure 12 days after cefepime was discontinued.

Blinded Studies

Cefepime

6. **1g cefepime** **Japan**
Cause of death: Respiratory failure

The patient was an 80 year old Japanese man with a history of lymphoma who was admitted for treatment of a lower respiratory tract infection. He was initially treated with another anti-infective drug and did not respond. He was enrolled in the cefepime trial. He was treated for twelve days and died on the thirteenth day of respiratory failure.

7. **1g cefepime** **Japan**
Cause of death: Respiratory failure

The patient was a 76 year old Japanese man with a history of emphysema who was admitted to the hospital for treatment of pneumonia. The patient was enrolled in the blinded study. After the first dose, the patient experienced an episode of hypotension. The patient was removed from the study after the second dose of cefepime. The patient expired on the following day of respiratory failure.

8. **1g cefepime** **Japan**
Cause of death: Respiratory failure

The patient was a 70 year old Japanese man with history of tuberculosis who was admitted to the hospital for treatment of acute pneumonia. The patient was enrolled in the study; he received treatment for 2.5 days. He died of respiratory failure on the third day of treatment.

9. **2g cefepime** **Japan**
Cause of death: Respiratory failure

The patient was a 43 year old diabetic man who was admitted to the hospital for treatment of lower extremity gas gangrene. Post-surgery, the patient had a cardiopulmonary arrest and remained comatose. Antibiotic therapy was initiated with cefepime. The patient was treated for 14 days. The patient died of respiratory failure one day after study drug was discontinued.

Ceftazidime

10. 1g ceftazidime Japan
Cause of death: Respiratory failure

The patient was a 54 year old woman with a history of chronic pulmonary insufficiency who was admitted to the hospital for treatment of pneumonia. She died of respiratory failure on the fifth day of treatment.

11. 7g ceftazidime Japan
Cause of death: Intracerebral hemorrhage

The patient was a 64 year old man who was hospitalized for treatment of anemia and fever. During the patient's hospital stay, he developed a lower respiratory tract infection. He was enrolled in the study and received treatment for 14 days. The patient died two days after study drug was discontinued. The cause of death was an intracerebral hemorrhage secondary to thrombocytopenia.

12. 1g ceftazidime Japan
Cause of death: Intracerebral hemorrhage

The patient was a 59 year old woman with a history of chronic rheumatoid arthritis who was admitted to the hospital for treatment of an acute pneumonia. The patient was enrolled in the study and was treated with ceftazidime. She had received two doses of the study drug when she experienced an acute respiratory decompensation. Study drug was discontinued. She died the following day of DIC and an intracerebral hemorrhage.

DISCONTINUATIONS**NDA DATA**

In the efficacy section of each indication, patients who discontinued therapy due to an adverse event were presented individually. The reader is referred to the review of each efficacy study for further detail. However, there were many patients who were not submitted for efficacy and they were not addressed until this point. Below are tables presented by the applicant which summarize the main risks for discontinuation in ALL North American and European cefepime patients. In both the North American and European populations, the incidence of discontinuations is higher in the high dose ($\geq 2\text{g BID}$) risk group than in the low dose ($< 2\text{g BID}$) risk group. The following page gives the data for comparative trials.

**NUMBER OF COURSES DISCONTINUED DUE TO ACE,
LABORATORY ABNORMALITIES, OR LOCAL INTOLERANCE,
BY RISK GROUP
ALL NORTH AMERICAN CEFEPIME COURSES
Cefepime Safety Summary**

Risk Group	Number (%) of Cefepime Patients ¹				
	Cefepime (N = 3335)				
	N	ACE	Abn. Labs	Intol.	Total
Low-dose (≤ 2000 mg/day)	1467	22 (1.5)	9 (0.6)	2 (0.1)	33
High-dose (> 2000 mg/day)	1705	53 (3.1)	8 (0.5)	1 (< 0.1)	62
Renally Impaired	73	3 (4.1)	1 (1.4)	0	4
Neutropenic	90	11 (12.2)	0	0	11
TOTAL (North America)	3335	89 (2.7)	18 (0.5)	3 (0.1)	110

NOTE: Abn. = Abnormal; Intol. = Intolerance.

**NUMBER OF COURSES DISCONTINUED DUE TO ACE,
LABORATORY ABNORMALITIES, OR LOCAL INTOLERANCE,
BY RISK GROUP
ALL EUROPEAN CEFEPIME COURSES
Cefepime Safety Summary**

Risk Group	Number (%) of Cefepime Courses ¹				
	Cefepime (N = 1133)				
	N	ACE	Abn. Labs	Intol.	Total
Low-dose (≤ 2000 mg/day)	580	11 (1.9)	2 (0.3)	9 (1.6)	22
High-dose (> 2000 mg/day)	420	10 (2.4)	0	0	10
Renally Impaired	15	1 (6.7)	0	1 (6.7)	2
Neutropenic	119	6 (5.0)	0	1 (0.8)	7
TOTAL (Europe)	1134	28 (2.5)	2 (0.2)	11 (1.0)	41

NOTE: Abn. = Abnormal; Intol. = Intolerance.

¹Is "patients" or "courses" the correct term? In the NDA, it was stated that 4,445 patients received 4,469 courses of cefepime.

DISCONTINUATIONS DUE TO ADVERSE CLINICAL EVENTS

The most frequent reason for discontinuation was an adverse clinical event. Below the applicant has presented a listing of all adverse clinical events which led to discontinuation of study therapy, by relationship to cefepime body system for all cefepime courses. Cefepime was discontinued early due to an adverse clinical event in 2.6% (117/4469) courses of therapy. Adverse clinical events (ACE) of probable or unknown relationship to cefepime were involved in 99 (84.6%) of the 117 courses where therapy was discontinued. Rash (50 episodes) was the event of probable or unknown relationship which most commonly led to discontinuation of cefepime therapy, followed by pruritus (11), fever (9), diarrhea (8), urticaria (6), headache (5), and nausea (4).

**ADVERSE CLINICAL EVENTS WHICH LED TO DISCONTINUATION
OF THERAPY BY RELATIONSHIP TO CEFEPIME AND BODY SYSTEM
ALL PATIENTS
Cefepime Safety Summary**

Body System	Number of Patients ¹			Total
	Prob. Rel.	Unknown	Not Rel.	
Any Body System	77	22	18	117
Body as a Whole				
Anaphylactoid Reaction	1	0	0	1
Chills	2	0	0	2
Fever	6	3	2	11
Headache	4	1	0	5
Malaise	0	1	0	1
Moniliasis	1	0	0	1
Neck Rigidity	1	0	0	1
Pain Facial	1	0	0	1
Pain Joint(s)	0	1	0	1
Pain Leg(s)	1	0	0	1
Sepsis	0	0	1	1
Cardiovascular System				
Cerebral Ischemia	0	0	1	1
Congestive Heart Failure	0	0	1	1
Hypertension	1	0	0	1
Hypotension	1	1	3	5
Syncope	0	1	0	1
Tachycardia	1	0	1	2
Vasodilation	1	1	0	2

continued next page

¹ Again, the reviewer believes that the applicant meant number of courses and not number of patients.

(continued)

**ADVERSE CLINICAL EVENTS WHICH LED TO DISCONTINUATION
OF THERAPY BY RELATIONSHIP TO CEFEPIME AND BODY SYSTEM
ALL PATIENTS**

Cefepime Safety Summary

Body System	----- Number of Patients -----			Total
	Prob. Rel.	Unknown	Not Rel.	
Digestive System				
Diarrhea	6	2	1	9
Dyspepsia	0	2	0	2
Nonlithiasis, Oral	1	0	0	1
Nausea	2	2	1	5
Pain Abdomen	0	1	1	2
Stomatitis	0	1	0	1
Vomiting	1	1	0	2
Hemic & Lymphatic System				
Anemia	0	0	1	1
Cyanosis	1	0	0	1
Musculoskeletal System				
Myalgia	0	1	0	1
Nervous System				
Agitation	0	0	1	1
Confusion	0	1	4	5
Convulsion	1	0	1	2
Dizziness	1	0	0	1
Drowsiness	0	0	1	1
Paresthesia	1	0	0	1
Speech Disorder	0	2	0	2
Stupor	0	0	1	1
Respiratory System				
Asthma	1	1	0	2
Hyperventilation	0	0	1	1
Lung Disorder	0	0	1	1
Pain Throat	0	1	0	1
Respiratory Disorder	0	1	0	1
Skin & Appendages				
Pruritus	10	1	1	12
Rash	46	4	3	53
Urticaria	6	0	0	6
Urogenital System				
Kidney Failure	0	0	3	3
Kidney Function Abnormal	0	0	1	1

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

MEDICAL OFFICER'S COMMENTS:

From the tally given above, the following events with regard to their a) import, b) probability of cause and c) frequency of cause deserve consideration for listing in the label in the section entitled adverse events:

ANAPHYLACTOID REACTION, CHILLS, FEVER, HEADACHE, HYPOTENSION, PAIN, DIARRHEA, DYSPEPSIA, NAUSEA, VOMITING, PRURITUS, RASH, and URTICARIA

Vasodilation was not included because it is a subset, if you will, of hypotension. Dysarthria was not included, because the reviewer felt that this event of unknown relationship is unlikely to be a phenomenon caused by the drug. Asthma was not included, because it is related to "anaphylactoid reactions" which is covered essentially by including the term anaphylaxis. The disease process of asthma, itself, is not caused by a drug.

To provide further insight into discontinuations due to adverse clinical events, the applicant provided tables for the COMPARATIVE studies. The tables given below are extracted from electronically supplied versions of sections of safety summary.

NUMBER OF PATIENTS WHO DISCONTINUED DUE TO ACE, LABORATORY ABNORMALITIES, OR LOCAL INTOLERANCE BY RISK GROUP ALL NORTH AMERICAN PATIENTS Cefepime vs. Ceftazidime Cefepime Safety Summary

Risk Group	----- Number (%) of Patients -----							
	Cefepime (N = 1559)				Ceftazidime (N = 1124)			
	N	ACE	Abn. Labs	Intol.	N	ACE	Abn. Labs	Intol.
Low-dose (≤ 2000 mg/day cefepime) (≤ 3000 mg/day ceftazidime)	910	13(1.4)	4(0.4)	1(0.1)	477	9(1.9)	0	0
High-dose (> 2000 mg/day cefepime) (> 3000 mg/day ceftazidime)	581	17(2.9)	4(0.7)	1(0.2)	540	19(3.5)	2(0.4)	1(0.2)
Renally Impaired	46	1(2.2)	1(2.2)	0	82	0	1(1.2)	0
Neutropenic	22	3(13.6)	0	0	25	1(4.0)	0	0
TOTAL (North America)	1559	34(2.2)	9(0.6)	2(0.1)	1124	29(2.6)	3(0.3)	1(0.1)

NOTE: Abn. = Abnormal; Intol. = Intolerance.

**NUMBER OF PATIENTS WHO DISCONTINUED DUE TO ACE,
LABORATORY ABNORMALITIES, OR LOCAL INTOLERANCE
BY RISK GROUP
ALL EUROPEAN PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Risk Group	----- Number (%) of Patients -----							
	Cefepime (N = 473)				Ceftazidime (N = 332)			
	N	ACE	Abn. Labs	Intol.	N	ACE	Abn. Labs	Intol.
Low-dose (≤ 2000 mg/day cefepime) (≤ 3000 mg/day ceftazidime)	300	4(1.3)	0	1(0.3)	157	0	0	0
High-dose (> 2000 mg/day cefepime) (> 3000 mg/day ceftazidime)	160	3(1.9)	0	0	165	2(1.2)	1(0.6)	0
Renally Impaired	13	1(7.7)	0	1(7.7)	10	0	0	0
TOTAL (Europe)	473	8(1.7)	0	2(0.4)	332	2(0.6)	1(0.3)	0

NOTE: Abn. = Abnormal; Intol. = Intolerance.

NOTE: The totals listed for "Any Body System" below are correct. However, they differ from the totals given in the "paper NDA - volume 286, page 230." The applicant must have corrected these totals on the electronic submission, but inadvertently forgotten to correct the paper copy.

The reasons for discontinuation were similar for both comparative groups.

**ADVERSE CLINICAL EVENTS WHICH LED TO DISCONTINUATION OF STUDY THERAPY
BY RELATIONSHIP TO CEFEPIME AND CEFTAZIDIME AND BODY SYSTEM**

ALL PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary

Body System Primary Term	Number of Patients							
	Cefepime (N=2032)				Ceftazidime (N=1456)			
	Prob. Rel.	Unknown	Not Rel.	Total	Prob. Rel.	Unknown	Not Rel.	Total
Any Body System	25	11	17	53	28	13	3	44
Body as a Whole								
Anaphylactoid Reaction	0	0	0	0	1	0	0	1
Asthenia	0	0	0	0	0	1	0	1
Fever	1	0	1	2	2	0	0	2
Headache	2	0	0	2	0	0	0	0
Nonilliasis	1	0	0	1	1	0	0	1
Pain Leg(s)	1	0	0	1	0	0	0	0
Sepsis	0	0	1	1	0	0	0	0
Cardiovascular System								
Atrial Fibrillation	0	0	0	0	0	0	1	1
Congestive Heart Failure	0	0	1	1	0	0	0	0
Hypotension	0	1	3	4	0	0	0	0
Pericarditis	0	0	0	0	0	1	0	1
Vasodilation	0	1	0	1	0	0	0	0

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

continued next page

(continued)

**ADVERSE CLINICAL EVENTS WHICH LED TO DISCONTINUATION OF STUDY THERAPY
BY RELATIONSHIP TO CEFEPIME AND CEFTAZIDIME AND BODY SYSTEM
ALL PATIENTS**
Cefepime vs. Ceftazidime
Cefepime Safety Summary

Body System Primary Term	Number of Patients							
	Cefepime (N=2032)				Ceftazidime (N=1456)			
	Prob. Rel.	Unknown	Not Rel.	Total	Prob. Rel.	Unknown	Not Rel.	Total
Digestive System								
Diarrhea	0	1	0	1	2	2	0	4
Dyspepsia	0	1	0	1	0	0	0	0
Nausea	1	0	1	2	3	1	0	4
Pain Abdomen	0	0	1	1	1	0	0	1
Vomiting	1	0	0	1	1	0	0	1
Hemic & Lymphatic System								
Hemolytic Anemia	0	0	0	0	1	0	0	1
Nervous System								
Coma	0	0	0	0	0	0	1	1
Confusion	0	1	2	3	0	0	0	0
Convulsion	0	0	1	1	1	0	0	1
Dizziness	0	0	0	0	1	1	0	2
Nervousness	0	0	0	0	1	0	0	1
Speech Disorder	0	2	0	2	0	0	0	0
Respiratory System								
Asthma	0	1	0	1	0	1	0	1
Dyspnea	0	0	0	0	0	2	0	2
Hyperventilation	0	0	0	0	0	1	0	1
Pneumothorax	0	0	0	0	0	0	1	1
Respiratory Disorder	0	1	0	1	0	0	0	0
Skin & Appendages								
Erythema	0	0	0	0	2	0	0	2
Lesion	0	0	0	0	1	0	0	1
Pruritus	4	0	1	5	2	0	0	2
Rash	12	2	3	17	8	3	0	11
Urticaria	2	0	0	2	0	0	0	0
Urogenital System								
Kidney Failure	0	0	2	2	0	0	0	0

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

Pharmacokinetic Studies

Among the subjects that were enrolled in the pharmacokinetic studies, there were 13 patients that discontinued due to adverse clinical events. In the single dose studies, one patient developed hives; one patient developed an allergic reaction including the sensation of tightness around the eyes, nose and mouth; and a third patient developed anaphylaxis. In the multiple dose studies, there were 10 patients who discontinued treatment due to an adverse event. Two patients discontinued due to rash. Eight other patients discontinued due to a "flu-like" reaction. All eight of these patients were enrolled in one center. Investigation into the drug lot did not reveal an explanation.

Japanese Patients

There were 1641 Japanese individuals who were evaluated for safety. There were two individuals who discontinued treatment for severe hypotension (and/or anaphylaxis). One patient developed severe hypotension (from 122/78 mm Hg to 54/28 mm Hg) after drug administration. A second patient experienced a decrease in blood pressure, loss of pulse, loss of consciousness and shock. He responded immediately to corticosteroid treatment. Both these patients had had negative skin tests prior to cefepime administration.

DISCONTINUATIONS DUE TO LABORATORY ABNORMALITIES OR INFUSION TOLERANCE

Cefepime therapy was discontinued due to laboratory abnormalities in 0.4% (20/4,469) of courses and due to local intolerance in 0.3% (14/4,469) of courses. These patients were not summarized by the applicant in the integrated summary of safety. However, further information is given by the reviewer below.

Discontinuations Due to Laboratory Abnormality and Relationship to Drug

<u>Patient Number</u>	<u>Drug</u>	<u>Dose</u>	<u>US/Europe</u>	<u>Abnormality</u>	<u>Related?</u>
<u>Cefepime</u>					
1.	Cefepime	1g	US	Incr. SGOT/SGPT	Not
2.	Cefepime	1g	US	Incr. Eosinophils	Probably
3.	Cefepime	1g	US	Incr. SGOT	Probably
4.	Cefepime	1g	US	Incr. Creatinine	Not
5.	Cefepime	1g	Europe	Incr. SGOT/SGPT	Possibly
6.	Cefepime	1g	Europe	Incr. Eosinophils	Probably
7.	Cefepime	1g	US	Incr. SGOT/SGPT	Possibly
8.	Cefepime	1g	US	Incr. Alk. Phos., Bilirubin Incr. Creatinine, Alk. Phos. Incr. SGOT	Possibly Possibly Not
9.	Cefepime	0.5g	US	Incr. Potassium, Bilirubin	Unknown
10.	Cefepime	2g	US	Neutropenia	Probably
11.	Cefepime	2g	US	Incr. SGOT/SGPT	Probably
12.	Cefepime	2g	US	Incr. SGOT/SGPT, Creatinine	Not
13.	Cefepime	2g	US	Leukocytosis	Not
14.	Cefepime	2g	US	Incr. Creatinine, BUN	Possibly
15.	Cefepime	2g	US	Incr. Prothrombin Time	Possibly
16.	Cefepime	Peds	US	Incr. SGOT/SGPT Leukopenia	Possibly Possibly
17.	Cefepime	2g	US	Leukopenia, Neutropenia	Probably
18.	Cefepime	2g	US	Leukopenia, Neutropenia	Probably
19.	Cefepime	2g	US	Incr. Creatinine, BUN	Not
20.	Cefepime	2g	US	Neutropenia, Positive Coomb's	Possibly

Discontinuations Due to Laboratory Abnormality and Relationship to Drug
continued

<u>Patient Number</u>	<u>Drug</u>	<u>Dose</u>	<u>US/Europe</u>	<u>Abnormality</u>	<u>Related?</u>
<u>Control</u>					
21.	Ceftazidime	2g	US	Incr. SGOT/SGPT	Probably
22.	Ceftazidime	2g	US	Leukopenia	Possibly
23.	Ceftazidime	2g	US	Incr. Creatinine	Not
24.	Ceftazidime	2g	Europe	Neutropenia, Thrombocytopenia	Probably
25.	Pip/Gentamicin	N/A	US	Incr. SGOT/SGPT	Not
				Incr. Bilirubin, Alk. Phos	Not
26.	Pip/Gentamicin	N/A	US	Incr. Creatinine	Possibly
27.	Pip/Gentamicin	N/A	US	Incr. Creatinine	Probably
28.	Pip/Gentamicin	N/A	US	Incr. Creatinine	Possibly
29.	Pip/Gentamicin	N/A	US	Incr. Creatinine, BUN	Probably
30.	Clinda/Gent	N/A	US	Incr. Bilirubin	Possibly
31.	Mez/Gentamicin	N/A	US	Decr. Prothrombin Ratio	Possibly

MEDICAL OFFICER'S COMMENTS:

The reviewer has presented the twenty patients with the investigator's assessment with regard to probability of cause and drug effect. The reviewer believes that those events that occurred twice or more and were either probably or possibly related should appear in the adverse reactions section in the label. These would include the following:

Eosinophilia; elevations in alanine aminotransferase (SGPT) and aspartate aminotransferase (SGOT), alkaline phosphatase, bilirubin, creatinine; neutropenia and leukopenia

FIRST SAFETY UPDATE DATA

The following information was provided by the applicant. A total of 810 patients were enrolled in studies after the NDA cut-off date of May 31, 1991 and on or before June 30, 1992. These 810 patients consisted of 772 patients enrolled in efficacy trials in North America and Europe (503 who received cefepime and 269 who received a comparative study drug); 23 cefepime treated patients enrolled in Individual treatment Protocols; and 15 cefepime treated patients enrolled in clinical pharmacokinetic studies. There were 27 additional patients enrolled in blinded studies.

North America

There were 391 cefepime patients (396 courses of therapy - five patients with neutropenia received two courses of therapy with cefepime) who were enrolled in North American clinical efficacy studies after the NDA cut-off date of May 31, 1991 and on or before June 30, 1992. There an additional 195 patients who received ceftazidime in comparative clinical trials during this period. Below is a table that presents the number of courses of cefepime (since the NDA) that were discontinued due to an adverse clinical event, to a laboratory abnormality or to local intolerance.

Adverse events led to early discontinuations in 5.6% (22/396) of all cefepime courses, and laboratory abnormalities led to early discontinuations in 1.3% (5/396) of cefepime courses.

**NUMBER OF COURSES DISCONTINUED DUE TO ACE,
LABORATORY ABNORMALITIES, OR LOCAL INTOLERANCE,
BY RISK GROUP
ALL NORTH AMERICAN CEFEPIME COURSES
Cefepime Safety Summary**

Risk Group	Number (%) of Cefepime Patients Cefepime (N = 396)				
	N	ACE	Abn. Labs	Intol.	Total
High-dose (>2000 mg/d)	64	4 (6.3)	4 (6.3)	0	8
Max. Dose (>4000 mg/d)	234	10 (4.3)	1 (0.4)	0	11
Neutropenic	98	8 (8.2)	0	0	8
TOTAL (North America)	396	22 (5.5)	5 (1.2)	0	27

NOTE: Abn. = Abnormal; Intol. = Intolerance

The following table presents a listing of all clinical adverse events that led to discontinuation of study therapy by relationship to therapy and body system for North American courses. Rash followed by fever were the most frequent adverse clinical events associated with discontinuation.

**ADVERSE CLINICAL EVENTS WHICH LED TO DISCONTINUATION
OF THERAPY BY RELATIONSHIP TO CEFEPIME AND BODY SYSTEM
ALL PATIENTS
Cefepime Safety Summary**

Body System	Prob. Rel.	Number of Patients		
		Unknown	Not Rel.	Total
----- Cefepime (N=396) -----				
Body as a Whole				
Chills	1	0	0	1
Fever	3	1	0	4
Headache	1	0	1	2
Malaise	0	0	1	1
Pain	1	0	0	1
Cardiovascular System				
Endocarditis	0	0	1	1
Hypotension	1	0	0	1
Syncope	0	0	1	1
Chest Pain	0	1	0	1
Tachycardia	1	0	0	1
Digestive System				
Diarrhea	1	0	0	1
Eructation	0	1	0	1
Hemorrhage	0	0	1	1
Nausea	0	1	0	1
Lesion	0	0	1	1
Vomiting	1	1	0	2
Nervous System				
Anxiety	0	1	0	1
Confusion	0	1	2	3
Dizziness	0	0	1	1
Drowsiness	1	0	1	2
Meningitis	0	0	1	1
Speech Disorder	0	1	0	1
Respiratory System				
Apnea	0	0	2	2
Dyspnea	1	1	0	2
Skin & Appendages				
Pruritus	1	0	0	1
Rash	10	0	0	10
Sweating	1	0	0	1

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

The following tables demonstrate comparative data with regard to additional discontinuations for the North American patients submitted since the NDA. The reasons for discontinuation were similar for both comparative groups.

**NUMBER OF PATIENTS WHO DISCONTINUED DUE TO ACE,
LABORATORY ABNORMALITIES, OR LOCAL INTOLERANCE
BY RISK GROUP
ALL NORTH AMERICAN PATIENTS
Cefepime vs. Ceftazidime
Cefepime 4 Month Safety Summary**

Risk Group	Number (%) of Patients							
	Cefepime (N = 202)				Ceftazidime (N = 195)			
	N	ACE	Abn. Labs	Intol.	N	ACE	Abn. Labs	Intol.
Maximum dose (> 4000 mg/d cefepime) (> 3000 mg/d ceftaz)	146	9(6.2)	1 (0.7)	0	141	5(3.5)	1(0.7)	0
Neutropenic	56	4(7.1)	0	0	54	3(5.6)	0	0
TOTAL	202	13(6.4)	1 (0.5)	0	195	8(4.1)	1(0.5)	0

NOTE: Abn. = Abnormal; Intol. = Intolerance.

Below is a table listing all ACE that led to discontinuation of study therapy, by relationship to study drug and body system in all North American comparative studies where ceftazidime was the comparative agent.

**ADVERSE CLINICAL EVENTS WHICH LED TO DISCONTINUATION OF STUDY THERAPY
BY RELATIONSHIP TO CEFEPIME AND CEFTAZIDIME AND BODY SYSTEM
ALL PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Body System Primary Term	Number of Patients							
	Cefepime (N=202)				Ceftazidime (N=195)			
	Prob. Rel.	Unknown	Not Rel.	Total	Prob. Rel.	Unknown	Not Rel.	Total
Body as a Whole								
Fever	2	1	0	3	0	0	0	0
Headache	1	0	1	2	0	0	0	0
Malaise	0	0	1	1	0	0	0	0
Pain	1	0	0	1	0	0	0	0
Cardiovascular System								
Cerebral infarct	0	0	0	0	0	0	1	1
DVT	0	0	0	0	0	0	1	1
Endocarditis	0	0	1	1	0	0	0	0
Hypotension	1	0	0	1	0	0	1	1
Pain, chest	0	1	0	1	0	0	0	0
Tachycardia	1	0	0	1	0	1	0	1
Digestive System								
Erectation	0	1	0	1	0	0	0	0
Gastritis	0	0	0	0	0	0	1	1
Nausea	0	1	0	1	0	0	0	0
Pain Abdomen	0	0	0	0	0	0	1	1
Vomiting	0	1	0	1	0	0	0	0
Hemorrhage	0	0	1	1	0	0	0	0
Lesion	0	0	1	1	0	0	0	0
Nervous System								
Anxiety	0	1	0	1	0	0	0	0
Confusion	0	1	2	3	0	0	0	0
Dementia	0	0	0	0	0	0	1	1
Drowsiness	1	0	1	2	0	0	0	0
Meningitis	0	0	1	1	0	0	0	0
Speech Disorder	0	1	0	1	0	0	0	0
Subdural	0	0	0	0	0	0	1	1
Respiratory System								
Apnea	0	0	1	1	0	0	1	1
Dyspnea	1	1	0	2	0	0	0	0
Hyperventilate	0	0	0	0	0	0	1	1
Skin & Appendages								
Erythema	0	0	0	0	0	1	0	1
Rash	4	0	0	4	2	0	0	2
Angioedema	0	0	0	0	1	0	0	1

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related

North American Discontinuations Due to Laboratory Abnormalities

Five courses of cefepime were discontinued because of abnormal laboratory values during cefepime treatment. Two of these discontinuations were because of neutropenia. The investigator judged that cefepime had probably caused the leukopenia/neutropenia. Three patients ended therapy with cefepime due to elevated serum creatinine levels. In these cases, the rise in creatinine was considered probably related in one case, not related in another case and of unknown relationship in the third case.

Europe

There were 112 cefepime patients enrolled in European studies between the NDA cut-off date and June 30, 1992. There were also 16 patients who received control drug. There were five cefepime (5/112 = 4.5%) patients who discontinued therapy because of an adverse clinical event. Three of the five patients discontinued therapy due to a mild to moderate rash. All investigators believed the rash to be probably related to study drug. One patient discontinued treatment due diarrhea; the relationship was undetermined. The fifth patient discontinued cefepime therapy due to drug fever deemed unrelated to study drug. There was one ceftazidime (1/16 = 6.2%) patient who discontinued treatment prematurely; he developed edema and erythema.

Pharmacokinetic Studies

There were no discontinuations in this period.

Compassionate Use Study

Of the twenty-three patients enrolled in this period, there were two patients who discontinued cefepime therapy due to an adverse clinical event. One patient experienced rectal bleeding and melena after fourteen days of treatment. This was considered unrelated to study drug and the patient recovered. A second patient discontinued treatment due to a rash after 54 days of therapy. No patients discontinued therapy due to laboratory abnormalities or local intolerance.

Blinded Studies

There were 27 patients enrolled in blinded studies at the time of the first safety update. The blind had not been broken. There was one patient who discontinued due to the development of eosinophilia. The eosinophilia resolved after the drug was withdrawn.

Japanese Studies

There was no further information with regard to Japanese patients.

SECOND SAFETY UPDATE

This safety update was to summarize the safety experience for all patients who were enrolled after the NDA data cut-off but on or before December 31, 1992. Generally, the post-NDA studies targeted patients with more severe infections. Therefore, adult dosing in the post NDA studies was generally 6 g of cefepime per day. Post NDA studies also increased the enrollment of children.

A total of 742 patients received 750 courses (508 in North America and 192 in Europe) of cefepime in these post-NDA studies. In the comparative studies, 401 patients received a total of 412 courses (362 in North America and 40 in Europe) of comparator drugs. There were 42 patients enrolled in blinded studies; 15 cefepime patients enrolled in pharmacokinetic studies; and 24 patients in Individual treatment protocols.

North America

A total of 500 patients received 508 courses of cefepime in the post-NDA North American clinical efficacy studies.

**NUMBER OF COURSES DISCONTINUED DUE TO ACE,
LABORATORY ABNORMALITIES, OR LOCAL INTOLERANCE,
BY RISK GROUP
POST NDA NORTH AMERICAN CEFEPIME COURSES
Cefepime Second Safety Summary**

Risk Group	Number (%) of Cefepime Patients				
	N	ACE	Abn. Labs	Intol.	Total
High-dose	51	3 (5.9)	4 (7.8)	0	7 (13.7)
Max. Dose	344	13 (3.8)	2 (0.6)	0	15 (4.4)
Neutropenic	113	8 (7.1)	0	0	8 (7.1)
TOTAL (North America)	508	24 (4.7)	6 (1.2)	0	30 (5.9)

NOTE: Abn. = Abnormal; Intol. = Intolerance

The following chart catalogues the clinical reasons post-NDA cefepime treated patients discontinued therapy prematurely. Rash was the most common adverse clinical event that led to cefepime discontinuation.

**ADVERSE CLINICAL EVENTS WHICH LED TO DISCONTINUATION
OF THERAPY BY RELATIONSHIP TO CEFEPIME AND BODY SYSTEM
ALL PATIENTS
Cefepime Safety Summary**

Body System	Prob. Rel.	Number of Patients		Total
		Unknown	Not Rel.	
----- Cefepime (N=508) -----				
Body as a Whole				
Chills	1	0	0	1
Fever	3	1	0	4
Headache	1	0	1	2
Malaise	0	0	1	1
Pain	1	0	0	1
Cardiovascular System				
Endocarditis	0	0	1	1
Hypotension	1	0	0	1
Syncope	0	0	1	1
Chest Pain	0	1	0	1
Tachycardia	1	0	0	1
Digestive System				
Diarrhea	1	0	0	1
Eructation	0	1	0	1
Hemorrhage	0	0	1	1
Nausea	0	1	0	1
Lesion	0	0	1	1
Vomiting	1	1	0	2
Metabolism & Nutrition				
Edema	1	0	0	1
Nervous System				
Anxiety	0	1	0	1
Confusion	0	1	2	3
Dizziness	0	0	1	1
Drowsiness	1	0	1	2
Meningitis	0	0	1	1
Speech Disorder	0	1	0	1
Respiratory System				
Apnea	0	0	2	2
Asthma	1	0	0	1
Dyspnea	1	1	0	2
Skin & Appendages				
Pruritus	1	0	0	1
Rash	11	0	0	11
Sweating	1	0	0	1

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

The following tables demonstrate comparative data with regard to additional discontinuations for the North American patients submitted since the NDA. The reasons for discontinuation were similar for both comparative groups.

**NUMBER OF PATIENTS WHO DISCONTINUED DUE TO ACE,
LABORATORY ABNORMALITIES, OR LOCAL INTOLERANCE
BY RISK GROUP
ALL NORTH AMERICAN PATIENTS
Cefepime vs. Ceftazidime
Cefepime Second Safety Summary**

Risk Group	----- Number (%) of Patients -----							
	Cefepime (N = 273)				Ceftazidime (N = 276)			
	N	ACE	Abn. Labs	Intol.	N	ACE	Abn. Labs	Intol.
Maximum dose	209	10(4.8)	1(0.5)	0	214	7(3.3)	1(0.5)	0
Neutropenic	64	4(6.3)	0	0	62	3(4.8)	0	0
TOTAL	273	14(5.1)	1 (0.4)	0	276	10(3.6)	1(0.4)	0

NOTE: Abn. = Abnormal; Intol. = Intolerance.

**ADVERSE CLINICAL EVENTS WHICH LED TO DISCONTINUATION OF STUDY THERAPY
BY RELATIONSHIP TO CEFEPIME AND CEFTAZIDIME AND BODY SYSTEM
POST-NDA NORTH AMERICAN PATIENTS
Cefepime vs. Ceftazidime
Cefepime Second Safety Summary**

Body System Primary Term	Number of Patients							
	Cefepime (N=273)				Ceftazidime (N=276)			
	Prob. Rel.	Unknown	Not Rel.	Total	Prob. Rel.	Unknown	Not Rel.	Total
Body as a Whole								
Fever	2	1	0	3	0	1	0	1
Headache	1	0	1	2	0	0	0	0
Malaise	0	0	1	1	0	0	0	0
Pain	1	0	0	1	0	0	0	0
Cardiovascular System								
Cerebral infarct	0	0	0	0	0	0	1	1
DVT	0	0	0	0	0	0	1	1
Endocarditis	0	0	1	1	0	0	0	0
Hypotension	1	0	0	1	0	0	1	1
Pain, chest	0	1	0	1	0	0	0	0
Tachycardia	1	0	0	1	0	1	0	1
Metabolism and Nutrition								
Edema	1	0	0	1	0	0	0	0
Digestive System								
Eructation	0	1	0	1	0	0	0	0
Nausea	0	1	0	1	0	0	0	0
Pain Abdomen	0	0	0	0	0	0	1	1
Vomiting	0	1	0	1	0	0	0	0
Hemorrhage	0	0	1	1	0	0	1	1
Lesion	0	0	1	1	0	0	0	0
Nervous System								
Anxiety	0	1	0	1	0	0	0	0
Confusion	0	1	2	3	0	0	0	0
Dementia	0	0	0	0	0	0	1	1
Drowsiness	1	0	1	2	0	0	0	0
Meningitis	0	0	1	1	0	0	0	0
Speech Disorder	0	1	0	1	0	0	0	0
Subdural	0	0	0	0	0	0	1	1
Respiratory System								
Apnea	0	0	1	1	0	0	1	1
Dyspnea	1	1	0	2	0	0	0	0
Hyperventilate	0	0	0	0	0	0	1	1
Skin & Appendages								
Erythema	0	0	0	0	0	1	0	1
Rash	4	0	0	4	3	0	0	3
Angioedema	0	0	0	0	1	0	0	1

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

In the period between the first and second safety update, there were 10 patients who discontinued therapy due to an adverse event. All except the single European Patient are incorporated in the aforementioned tables; they are catalogued below.

Discontinuations Due to Adverse Events and Relationship to Drug

<u>Patient Number</u>	<u>Drug</u>	<u>Dose</u>	<u>US/Europe</u>	<u>Abnormality</u>	<u>Related?</u>
1.	Cefepime	Peds	US	Rash, Bronchospasm Wheezing	Probably
2.	Mez/Gentamicin	N/A	US	Rash, Nausea, Diarrhea	Probably
3.	Mez/Gentamicin	N/A	US	Rash, Diarrhea	Probably
4.	Mez/Gentamicin	N/A	US	Rash, Diarrhea	Probably
5.	Cefepime	2g	Europe	Nausea, Diarrhea, Dyspepsia	Probably
6.	Ceftazidime	2g	US	fever	Probably
7.	Cefepime	2g	US	Rash, Decr. Consciousness	Probably
8.	Cefepime	2g	US	Swelling face and Neck	Probably
9.	Ceftazidime	2g	US	Rash	Probably
10.	Cefepime	2g	US	ARDS, Sepsis	Not

Laboratory Abnormalities of North American Patients

Since the NDA cut-off period, six courses of cefepime were discontinued because of abnormal laboratory values during cefepime treatment. Two of these discontinuations were because of neutropenia and four were because of elevated serum creatinine levels. Five of these discontinuations occurred prior to the four Month Safety Update. One additional patient was noted by the applicant. This patient was a pediatric patient who was noted to have an elevated pre-treatment serum creatinine value. This was not related to cefepime treatment. The reviewer noted that two patients listed as discontinued patients due to an adverse clinical event also were discontinued due to an abnormal laboratory value. Patient who was treated with cefepime discontinued due to probably drug-related eosinophilia. Patient who was treated with ceftazidime also discontinued treatment due to thrombocytopenia.

European Studies

Six (6/192 = 3.1%) patients discontinued treatment prematurely because of an adverse clinical event. Four of the six were attributed to the study drug. Mild to moderate skin rashes were reported in three patients and a combination of mild gastrointestinal symptoms (diarrhea, nausea, and dyspepsia) were reported in one patient (listed above). One case of moderate diarrhea was judged to be of unknown relationship and one case of drug fever was thought to be unrelated to cefepime therapy.

Pharmacokinetic Studies

There were no new patients enrolled in pharmacokinetic studies since the first safety update.

Compassionate Use Study

There were no discontinuations in this groups since the previous update.

Blinded Studies

There were no patients that discontinued due to an adverse clinical event. The single patient of the 42 enrolled who discontinued therapy due to probable drug related eosinophilia was described in the first safety update. No new discontinuations occurred.

Japanese Studies

There was no additional information.

FINAL SAFETY UPDATE

This safety update was meant to summarize the safety experience of all patients who were enrolled in clinical trials between January 1, 1993 and October 31, 1993 as well as post-marketing experience from countries in which cefepime is approved. Twenty-three clinical trials were conducted in North America and Europe during 1993; 967 courses of cefepime therapy were administered.

The applicant did not specify which patients, if any, were discontinued due to an adverse event related to cefepime therapy. There were 190 serious adverse events; however, "only four events in four patients were judged by the investigator to be possibly related to cefepime. They consisted of thrombophlebitis, hepatic insufficiency, renal insufficiency and hypoglycemia."

LOCAL TOLERANCE

NDA

Below is a table taken from the applicant's safety summary which presents local tolerance to administration of cefepime by risk group and route of administration for all cefepime courses.

LOCAL TOLERANCE BY RISK GROUP AND DOSE ADMINISTRATION
ALL CEFEPIME COURSES
Cefepime Safety Summary

Administration Tolerance	Number (%) of Cefepime Courses			
	Low-dose (< 2000 mg/day) N = 2047	High-dose (> 2000 mg/day) N = 2125	Renally Impaired N = 88	Neutropenic N = 209
IV Administration	N = 1843	N = 2096	N = 87	N = 198
Tolerated Drug Well	1739 (94.4)	1927 (91.9)	81 (93.1)	191 (96.5)
Local Intolerance	103 (5.6)	167 (8.0)	6 (6.9)	7 (3.5)
Infiltration ^a	35 (1.9)	86 (4.1)	1 (1.1)	4 (2.0)
Phlebitis ^b	63 (3.4)	52 (2.5)	4 (4.6)	2 (1.0)
Redness/Inflammation ^c	3 (0.2)	10 (0.9)	1 (1.1)	0
Pain/Discomfort ^d	7 (0.4)	7 (0.9)	1 (1.1)	1 (0.5)
Swelling ^e	2 (0.1)	7 (0.3)	0	2 (1.0)
Other ^f	1 (<0.1)	7 (0.3)	0	0
Not Recorded	1	2	0	0
IM Administration	187	8	0	0
Tolerated Drug Well	186 (99.5)	5 (62.5)		
Local Intolerance	1 (0.5)	3 (37.5)		
Infiltration ^a	0	1 (12.5)		
Redness/Inflammation ^c	0	1 (12.5)		
Pain/Discomfort ^d	0	1 (12.5)		
Swelling ^e	1 (0.5)	0		
IV & IM Administration	17	20	1	0
Tolerated Drug Well	15 (88.2)	14 (70.0)	1 (100.0)	
Local Intolerance	2 (11.8)	6 (30.0)		
Infiltration ^a	1 (5.9)	5 (25.0)		
Phlebitis ^b	1 (5.9)	0		
Pain/Discomfort ^d	0	1 (5.0)		

^a Includes terms: infiltration, extravasation.

^b Includes terms: phlebitis, superficial phlebitis, infiltration-hematoma-phlebitis, infiltration and phlebitis, superficial thrombophlebitis.

^c Includes terms: papular erythema IV site, rash at IV site, redness, inflammation, erythematous, rash, reddened site.

^d Includes terms: burning, pain at infusion site, soreness at site, tingling at IV site, area became red and tender, pain, IV site soreness, pustules and itching, soreness at IV site, tenderness, tenderness and swelling, discomfort at site of IV/slight edema, pain at site of injection, swelling and tender.

^e Includes terms: edema, swollen, induration, swelling.

^f Includes terms: lymphangitis, hematoma, collapsing veins, IV dislodged, knot on forearm due to heparin lock, routine change due.

The following table presents local tolerance to administration of cefepime by risk group and route of administration, for all North American cefepime courses.

LOCAL TOLERANCE BY RISK GROUP AND DOSE ADMINISTRATION
ALL NORTH AMERICAN CEFEPIME COURSES
 Cefepime Safety Summary

Administration	----- Number (%) of Cefepime Courses -----			
	Low-dose (≤ 2000 mg/day)	High-dose (> 2000 mg/day)	Renally Impaired	Neutropenic
Tolerance	N = 1467	N = 1705	N = 73	N = 90
IV Administration	N = 1403	N = 1688	N = 72	N = 90
Tolerated Drug Well	1351 (96.3)	1548 (91.7)	68 (94.4)	84 (93.3)
Local Intolerance	51 (3.6)	140 (8.3)	4 (5.6)	6 (6.7)
Infiltration	30 (2.1)	83 (4.9)	1 (1.4)	4 (4.4)
Phlebitis	17 (1.2)	28 (1.7)	2 (2.8)	1 (1.1)
Redness/Inflammation ^a	3 (0.2)	16 (0.9)	1 (1.4)	0
Pain/Discomfort ^b	6 (0.4)	18 (1.1)	1 (1.4)	1 (1.1)
Swelling ^c	2 (0.1)	8 (0.5)	0	2 (2.2)
Other ^d	0	4 (0.4)	0	0
Not Recorded	1	0	0	0
IM Administration	59	6	0	0
Tolerated Drug Well	59 (100.0)	4 (66.7)	0	0
Local Intolerance	0	2 (33.3)	0	0
Infiltration	0	0	0	0
Phlebitis	0	0	0	0
Redness/Inflammation ^a	0	1 (16.7)	0	0
Pain/Discomfort ^b	0	1 (16.7)	0	0
Swelling ^c	0	0	0	0
Other ^d	0	0	0	0
Not Recorded	0	0	0	0
IV & IM Administration	5	10	1	0
Tolerated Drug Well	5 (100.0)	8 (80.0)	1 (100.0)	0
Local Intolerance	0	2 (20.0)	0	0
Infiltration	0	1 (10.0)	0	0
Phlebitis	0	0	0	0
Redness/Inflammation ^a	0	0	0	0
Pain/Discomfort ^b	0	1 (10.0)	0	0
Swelling ^c	0	0	0	0
Other ^d	0	0	0	0
Not Recorded	0	0	0	0

^a Included terms: redness; papular erythema IV site; rash at IV site; inflammation; erythematous; rash; reddened site.

^b Includes terms: pain; burning; pain at infusion site; soreness at site; tingling at IV site; area became red and tender; IV site soreness; pain at IV site; pustules and itching; soreness at IV site; tenderness; tenderness and swelling; discomfort at site of IV/slight edema; pain at site of injection; swelling and tenderness.

^c Includes terms: swelling; edema; swollen; induration.

^d Includes terms: hematoma; collapsing veins; IV dislodged; knot on forearm due to heparin lock; routine change due.

The following table presents local tolerance to administration of cefepime by risk group and route of administration, for all European cefepime courses.

LOCAL TOLERANCE BY RISK GROUP AND DOSE ADMINISTRATION^a
ALL EUROPEAN CEFEPIME COURSES
 Cefepime Safety Summary

Administration Tolerance	----- Number (%) of Cefepime Courses -----			
	Low-dose (≤ 2000 mg/day) N = 580	High-dose (> 2000 mg/day) N = 420	Renally Impaired N = 15	Neutropenic N = 119
IV Administration	N = 440	N = 408	N = 15	N = 108
Tolerated Drug Well	388 (88.2)	379 (92.9)	13 (86.7)	107 (99.1)
Local Intolerance	52 (11.8)	27 (6.6)	2 (13.3)	1 (0.9)
Infiltration ^a	5 (1.1)	3 (0.7)	0	0
Phlebitis ^b	46 (10.5)	24 (5.9)	2 (13.3)	1 (0.9)
Redness/Inflammation ^c	0	1 (0.2)	0	0
Pain/Discomfort ^d	1 (0.2)	0	0	0
Other ^e	1 (0.2)	1 (0.2)	0	0
Not Recorded	0	2	0	0
IM Administration	128	2	0	0
Tolerated Drug Well	127 (99.2)	1 (50.0)		
Local Intolerance	1 (0.8)	1 (50.0)		
Infiltration ^a	0	1 (50.0)		
Swelling ^f	1 (0.8)	0		
IV & IM Administration	12	10	0	0
Tolerated Drug Well	10 (83.3)	6 (60.0)		
Local Intolerance	2 (16.7)	4 (40.0)		
Infiltration ^a	1 (8.3)	4 (40.0)		
Phlebitis ^b	1 (8.3)	0		

^a Includes terms: infiltration; extravasation.

^b Includes terms: phlebitis; superficial phlebitis; infiltration; hematoma; phlebitis; infiltration and phlebitis; superficial thrombophlebitis.

^c Includes term: inflammation.

^d Includes term: burning.

^e Includes terms: lymphangitis; hematoma.

^f Includes term: induration.

The following table presents local tolerance data for comparative groups.

LOCAL TOLERANCE BY RISK GROUP AND DOSE ADMINISTRATION
ALL PATIENTS
 Cefepime vs. Ceftazidime
 Cefepime Safety Summary

Administration Tolerance ^a	----- Number(%) of Patients -----			
	Low-dose		High-dose	
	Cefepime (≤ 2000 mg/day) N = 1210	Ceftazidime (≤ 3000 mg/day) N = 634	Cefepime (> 2000 mg/day) N = 741	Ceftazidime (> 3000 mg/day) N = 705
IV Administration	N = 1021	N = 533	N = 738	N = 701
Tolerated Drug Well	965 (94.5)	504 (94.6)	678 (91.9)	659 (94.0)
Local Intolerance	56 (5.5)	29 (5.4)	59 (8.0)	42 (6.0)
Infiltration	34 (3.3)	17 (3.2)	19 (2.6)	12 (1.7)
Phlebitis	13 (1.3)	6 (1.1)	26 (3.5)	16 (2.3)
Pain/Discomfort ^b	6 (0.6)	3 (0.6)	7 (0.7)	12 (1.7)
Redness/Inflammation ^c	3 (0.2)	1 (0.2)	12 (1.6)	7 (1.0)
Swelling ^d	2 (0.2)	0	6 (0.8)	3 (0.4)
Other ^e	4 (0.4)	2 (0.4)	2 (0.3)	2 (0.3)
Not Recorded	0	0	1	0
IM Administration	180	94	2	1
Tolerated Drug Well	179 (99.4)	94 (100.0)	1 (50.0)	1 (100.0)
Local Intolerance	1 (0.6)	0	1 (50.0)	0
Swelling ^d	1 (0.6)	0	0	0
Inflammation	0	0	1 (50.0)	0
IV and IM Administration	9	6	1	3
Tolerated Drug Well	8 (88.9)	6 (100.0)	1 (100.0)	3 (100.0)
Local Intolerance	1 (11.1)	0	0	0
Infiltration	1	0	0	0

^a Patients may have experienced more than one type of intolerance.

^b Includes terms: burning; pain at infusion site; soreness at site; tingling at IV site; irritation; pain; discomfort; irritation and swelling; pain at IV site; pain, swelling at site; discomfort; area became red, tender.

^c Includes terms: papular erythema at IV site; rash at IV site; cellulitis, swelling, erythema; redness; inflammation.

^d Includes terms: edema; swollen; swelling; induration.

^e Includes terms: collapsing veins; knot on forearm due to heparin lock; lymphangitis; bleeding from line site; ecchymosis; hematoma; IV dislodged; blood clots in IV tubing.

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**LOCAL TOLERANCE BY RISK GROUP AND DOSE ADMINISTRATION
ALL PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Administration Tolerance ^a	Number (%) of Patients			
	Renally Impaired		Neutropenic	
	Cefepime N = 59	Ceftazidime N = 92	Cefepime N = 22	Ceftazidime N = 25
IV Administration	N = 53	N = 91	N = 22	N = 26
Tolerated Drug Well	53 (91.4)	87 (95.6)	17 (77.3)	21 (87.5)
Local Intolerance	5 (8.6)	4 (4.4)	5 (22.7)	3 (12.5)
Infiltration	1 (1.7)	2 (2.2)	4 (18.2)	3 (12.5)
Phlebitis	4 (6.9)	2 (2.2)	0	0
Pain/Discomfort	0	0	1 (4.5)	0
Redness/Inflammation	1 (1.7)	0	0	0
Swelling ^b	1 (1.7)	0	2 (9.1)	1 (4.2)
IM Administration	1	1	0	1
Tolerated Drug Well	1 (100.0)	1 (100.0)		1 (100.0)

^a Patients may have experienced more than one type of intolerance.

^b Includes terms: swelling and tender; edema.

The following tables examine tolerance of the infusion in North American comparative studies:

LOCAL TOLERANCE BY RISK GROUP AND DOSE ADMINISTRATION
ALL NORTH AMERICAN PATIENTS
 Cefepime vs. Ceftazidime
 Cefepime Safety Summary

Administration Tolerance ^a	----- Number (%) of Patients -----							
	Low-dose				High-dose			
	Cefepime (≤ 2000 mg/day) N = 910		Ceftazidime (≤ 3000 mg/day) N = 477		Cefepime (> 2000 mg/day) N = 581		Ceftazidime (> 3000 mg/day) N = 540	
IV Administration	N = 847		N = 439		N = 578		N = 536	
Tolerated Drug Well	800	(94.5)	411	(93.6)	539	(93.3)	505	(94.2)
Local Intolerance	47	(5.5)	28	(6.4)	39	(6.7)	31	(5.8)
Infiltration	31	(3.7)	17	(3.9)	19	(3.3)	12	(2.2)
Phlebitis	7	(0.8)	5	(1.1)	7	(1.2)	5	(0.9)
Pain/Discomfort ^b	5	(0.6)	4	(0.9)	7	(1.2)	12	(2.2)
Redness/Inflammation ^c	3	(0.4)	1	(0.2)	12	(2.1)	7	(1.3)
Swelling ^d	2	(0.2)	0		6	(1.0)	3	(0.6)
Other ^e	3	(0.4)	2	(0.5)	1	(0.2)	2	(0.4)
IM Administration	59		33		2		1	
Tolerated Drug Well	59	(100.0)	33	(100.0)	1	(50.0)	1	(100.0)
Local Intolerance	0		0		1	(50.0)	0	
Inflammation					1	(50.0)		
IV and IM Administration	4		4		1		3	
Tolerated Drug Well	4	(100.0)	4	(100.0)	1	(100.0)	3	(100.0)

^a Patients may have experienced more than one type of intolerance.

^b Includes terms: burning; pain at infusion site; soreness at site; tingling at IV site; irritation; pain; discomfort; irritation and swelling; pain at IV site; pain/swelling at site; area became red, tender.

^c Includes terms: papular erythema IV site; rash at IV site; cellulitis, swelling, erythema; redness; inflammation; inflammation and swelling.

^d Includes terms: edema; swollen; swelling; induration.

^e Includes terms: collapsing veins; knot on forearm due to heparin lock; bleeding from line site; ecchymosis; IV dislodged; blood clots in IV tubing; hematoma.

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LOCAL TOLERANCE BY RISK GROUP AND DOSE ADMINISTRATION
ALL NORTH AMERICAN PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary

Administration Tolerance ^a	----- Number (%) of Patients -----			
	Renally Impaired		Neutropenic	
	Cefepime N = 46	Ceftazidime N = 82	Cefepime N = 22	Ceftazidime N = 25
IV Administration	N = 45	N = 81	N = 22	N = 24
Tolerated Drug Well	42 (93.3)	77 (95.1)	17 (77.3)	21 (87.5)
Local Intolerance	3 (6.7)	4 (4.9)	5 (22.7)	3 (12.5)
Infiltration	1 (2.2)	2 (2.5)	4 (18.2)	3 (12.5)
Phlebitis	2 (4.4)	2 (2.5)	0	0
Pain/Discomfort ^b	1 (2.2)	0	1 (4.5)	0
Redness/Inflammation	1 (2.2)	0	0	0
Swelling ^c	0	0	2 (9.0)	1 (4.2)
IM Administration	0	0	0	1
Tolerated Drug Well				1 (100.0)
IV and IM Administration	1	1	0	0
Tolerated Drug Well	1 (100.0)	1 (100.0)		

^a Patients may have experienced more than one type of intolerance.

^b Includes terms: swelling and tender; pain.

^c Includes terms: edema; swelling.

When comparative European studies are examined separately:

**LOCAL TOLERANCE BY RISK GROUP AND DOSE ADMINISTRATION
ALL EUROPEAN PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Administration Tolerance ^a	----- Number (%) of Patients -----			
	Low-dose		High-dose	
	Cefepime (≤ 2000 mg/day) N = 300	Ceftazidime (≤ 3000 mg/day) N = 157	Cefepime (> 2000 mg/day) N = 160	Ceftazidime (> 3000 mg/day) N = 165
IV Administration	N = 174	N = 94	N = 160	N = 165
Tolerated Drug Well	165 (94.8)	93 (98.9)	139 (86.9)	154 (93.3)
Local Intolerance	9 (5.2)	1 (1.1)	20 (12.5)	11 (6.7)
Infiltration	3 (1.7)	0	0	0
Phlebitis	6 (3.4)	1 (1.1)	19 (11.9)	11 (6.7)
Other ^b	1 (0.6)	0	1 (0.6)	0
Not Recorded	0	0	1	0
IM Administration	121	61	0	0
Tolerated Drug Well	120 (99.2)	61 (100.0)		
Local Intolerance	1 (0.8)	0		
Swelling ^c	1 (0.8)			
IV and IM Administration	5	2	0	0
Tolerated Drug Well	4 (80.0)	2 (100.0)		
Local Intolerance	1 (20.0)	0		
Infiltration	1 (20.0)			

^a Patients may have experienced more than one type of intolerance.

^b Includes terms: hematoma, lymphangitis.

^c Includes terms: induration.

(continued)

**LOCAL TOLERANCE BY RISK GROUP AND DOSE ADMINISTRATION
ALL EUROPEAN PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Administration Tolerance ^a	----- Number (%) of Patients -----	
	Renally Impaired	
	Cefepime N = 13	Ceftazidime N = 10
IV Administration	N = 13	N = 10
Tolerated Drug Well	11 (84.6)	10 (100.0)
Local Intolerance	2 (15.4)	0
Phlebitis	2 (15.4)	

^a Patients may have experienced more than one type of intolerance.

Pharmacokinetic Studies

The following table summarizes the local tolerance data for single dose and multi-dose pharmacokinetic studies.

LOCAL TOLERANCE TO STUDY DRUGS
Clinical Pharmacokinetic Studies
Cefepime Safety Summary

Administration/ Tolerance	----- Number (%) of Subjects ^a -----			
	Single Dose ^b		Multiple Doses ^c	
	Cefepime	Comparative	Cefepime	Placebo
INTRAVENOUS	N = 82	N = 45^d	N = 63	N = 25
Tolerated Drug Well	82 (100)	45 (100)	43 (68)	15 (60)
Local Intolerance	0	0	20 (32)	10 (40)
Infiltration			3	2
Phlebitis			2	2
Redness				1
Redness, irritation			1	
Infection, redness				1
Throbbing			1	
Burning			3	1
Swelling			7	2
Pain			6	3
Tenderness			4	1
Dislodged catheter			2	
Catheter discomfort			1	
Unknown			3	1
INTRAMUSCULAR	N = 44^e	N = 20^f	N = 6^g	N = 3
Tolerated Drug Well	43 (98)	19 (95)	6 (100)	3 (100)
Local Intolerance	1 (2)	1 (5)	0	0
Pain	1	1		

^a A subject may have experienced more than one type of intolerance.

^b One hundred ninety-eight cefepime subjects and 16 subjects who received comparative drugs did not have tolerance recorded on the CRF.

^c Thirty-three cefepime subjects and seven placebo subjects did not have tolerance recorded on the CRF.

^d All 45 subjects received ceftazidime. Six subjects also received cefoperazone.

^e Includes 20 subjects from Study 411-079 and 24 subjects from Study 411-096.

^f All received ceftriaxone.

^g Study 411-096.

There was a special double-blind pharmacokinetic study (411-079) conducted to compare the tolerance of intramuscular injection of cefepime with ceftriaxone. The products were either reconstituted in water or 1% lidocaine. The applicant stated that the outcome of the study showed that the administration of cefepime dihydrochloride/arginine in water was substantially less painful than ceftriaxone in water. It also showed that the administration of cefepime dihydrochloride/arginine in 1% lidocaine was less painful than ceftriaxone in 1% lidocaine.

Compassionate Use Studies

There were no reported problems among these patients (N = 4).

Japanese Studies

Of the 1646 courses of cefepime that were administered to Japanese nationals, there was only a single report of local intolerance. The patient reported discomfort during the infusion.

FIRST SAFETY UPDATE - Local Tolerance

Below is a table which presents local tolerance to the administration of cefepime by risk group and route of administration, for North American cefepime courses. For the most part, cefepime was well tolerated. However, in the maximum dose group, the incidence of infiltration is higher than seen previously. This is probably partially a reflection of thrice daily dosing. Infiltration, *per se*, is a mechanical problem and not a toxic local reaction to the drug.

**LOCAL TOLERANCE BY RISK GROUP AND DOSE ADMINISTRATION
ALL NORTH AMERICAN CEFEPIME COURSES
Cefepime Safety Summary**

Administration Tolerance ^a	----- Number (%) of Cefepime Courses -----		
	High-dose (2 to 4g/day) N = 64	Max-dose (4 to 6g/day) N = 234	Neutropenic N = 98
IV Administration	N = 64	N = 233	N = 98
Tolerated Drug Well	60 (93.8)	185 (79.4)	93 (94.9)
Local Intolerance	4 (6.3)	48 (20.6)	5 (5.1)
Infiltration	3 (4.7)	27 (12.4)	
Phlebitis		14 (6.0)	
Redness/Inflammation ^b		11 (4.7)	1 (1.0)
Pain/Discomfort ^c		11 (4.7)	2 (2.0)
Swelling ^d		6 (2.6)	1 (1.0)
Other ^e	1 (1.6)	2 (0.9)	1 (1.0)
IV & IM Administration		N = 1	
Tolerated Drug Well		1 (100)	

^a Patients may have had more than one reason for intolerance.

^b Includes redness, cellulitis; IV site red, swollen and tender.

^c Includes pain, discomfort, burning, swelling and tenderness, stiffness in arm, pain at site, needle removed - cause of tender porta cath site.

^d Includes redness and swelling, edema, and induration.

^e Includes thrombosed in vein from IV site, ecchymoses, and hematomas.

^f Includes tenderness, lymphangitis, hematomas, collapsing veins, IV dislodged, knot on forearm due to heparin lock, routine change due.

Below is a table of the local tolerance of cefepime and ceftazidime by risk groups and dose administration. In the maximum risk group, the tolerance to cefepime (109/146 = 75%) administration is similar to that of ceftazidime (108/138 = 78%).

**LOCAL TOLERANCE BY RISK GROUP AND DOSE ADMINISTRATION
ALL NORTH AMERICAN PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Administration Tolerance ^a	Number (%) of Patients			
	Max-dose		Neutropenic	
	Cefepime N = 146	Ceftazidime N = 141	Cefepime N = 56	Ceftazidime N = 54
IV Administration	N = 146	N = 138	N = 56	N = 54
Tolerated Drug Well	109 (74.7)	108 (78.3)	51 (91.1)	47 (87.0)
Local Intolerance	37 (25.3)	30 (21.7)	5 (8.9)	7 (13.0)
Infiltration	21 (14.4)	18 (13.0)		2 (3.7)
Phlebitis	13 (8.9)	4 (2.9)		
Pain/Discomfort ^b	10 (6.8)	8 (5.8)	2 (3.6)	1 (1.9)
Redness/Inflammation ^c	10 (6.8)	9 (6.5)	1 (1.8)	2 (3.7)
Swelling ^d	6 (4.1)	3 (2.2)	1 (1.8)	
Other ^e	2 (1.4)	4 (2.9)	1 (1.8)	2 (3.7)
IV and IM Administration	0	3	0	0
Tolerated Drug Well		3 (100.0)		

^a Patients may have experienced more than one type of intolerance.

^b Includes terms: discomfort, burning, pain, swelling and tenderness, and needle removed because of tender porta cath site.

^c Includes terms: cellulitis; IV site red, swollen, tender; inflammation at central 2nd site; redness; and warm.

^d Includes edema; swollen; swelling; induration and bruise and swelling.

^e Includes ecchymosis; hematoma, leaking, multiple ecchymotic areas - arm, 1 cm cord in vein from IV site, line fell out, and IV restarted for reasons not specified.

European Studies

There were 112 European patients who were treated with cefepime and there were 16 patients treated with comparator drug. One cefepime IV patient (1/112 = 1%) had infiltration and one ceftazidime IM patient had erythema.

Pharmacokinetic studies

Cefepime was administered as an intravenous infusion to 15 patients. One patient developed phlebitis which resolved without treatment within 48 hours.

Compassionate Use Studies

Of the 22 patients who received treatment in the individual treatment protocol, 18 tolerated cefepime well. Tolerance of administration was not recorded for one patient; there was no information with regard to tolerance of administration given for the four remaining patients.

Blinded Studies

Of the 27 patients enrolled in blinded study A1411-160 who received study drug, 23 (85%) tolerated the infusion well. Four patients experienced local intolerance at the infusion site - either pain, redness, infiltration or phlebitis.

SECOND SAFETY UPDATE - Local Tolerance

The following table presents local tolerance to the administration of cefepime by treatment group and route of administration for North American cefepime courses. Intravenous administration of cefepime was well tolerated in 84.2 (425/505) of all courses across all treatment groups.

**LOCAL TOLERANCE BY RISK GROUP AND DOSE ADMINISTRATION
POST NDA NORTH AMERICAN CEFEPIME COURSES
Cefepime Second Safety Summary**

Administration Tolerance	----- Number (%) of Cefepime Courses -----		
	High-dose	Max-dose	Neutropenic
IV Administration	N = 51	N = 341	N = 113
Tolerated Drug Well	47 (92.2)	271 (79.5)	107 (94.7)
Local Intolerance ^a	4 (7.8)	70 (20.5)	6 (5.3)
Infiltration	3 (5.9)	38 (11.1)	1 (0.9)
Phlebitis		19 (5.6)	
Redness/Inflammation ^b		20 (5.9)	1 (0.9)
Pain/Discomfort ^c	1 (2.0)	15 (4.4)	2 (1.8)
Swelling ^d		10 (2.9)	1 (0.9)
Other ^e		2 (0.6)	1 (0.9)
IV & IM Administration		N = 3	
Tolerated Drug Well		2 (67)	
Local Intolerance/Phlebitis		1 (33)	

- a Patients may have had more than one reason for intolerance.
- b Includes redness, cellulitis; IV site red, swollen and tender.
- c Includes pain, discomfort, burning, swelling and tenderness, stiffness in arm, pain at site, needle removed because of tender porta cath site.
- d Includes bruise and swelling, edema, and induration.
- e Includes 1 cm cord in vein from IV site, ecchymoses, and hematoma.

The following catalogues the comparative trials summarized in the second safety update. Intravenous administration was well tolerated by the majority of patients who received either study drug (cefepime 77.7 %; ceftazidime 81.0%). The distribution of reasons for local intolerance were similar for both groups with the exception of local phlebitis which was reported more often in the cefepime group.

**LOCAL TOLERANCE BY ROUTE OF ADMINISTRATION
IN CLINICAL STUDIES WHERE CEFEPIME WHERE CEFTAZIDIME WAS COMPARED TO CEFTAZIDIME
POST-NDA NORTH AMERICAN PATIENTS
Cefepime Second Safety Update**

Route of Administration	Number (%) of Patients	
	Cefepime N = 273	Ceftazidime N = 276
Tolerance		
<u>Intravenous Administration</u>		
Tolerated Study Drug Well	212 (77.7)	221 (81.0)
Local Intolerance ^a	61 (22.3)	52 (19.1)
Infiltration	28 (10.3)	27 (9.9)
Phlebitis	17 (6.2)	4 (1.5)
Redness/Inflammation ^b	20 (7.3)	13 (4.8)
Pain/Discomfort ^c	16 (5.9)	15 (5.5)
Swelling ^d	10 (3.7)	5 (1.8)
Other ^e	4 (1.5)	8 (2.9)
<u>Intravenous and Intramuscular Injection</u>		N = 3
Tolerated Study Drug Well		3 (100)

- ^a Patients may have had more than one reason for intolerance.
^b Includes cellulitis; IV site red, swollen and tender; inflammation at second IV site.; redness and warm.
^c Includes pain, discomfort, burning, swelling and tenderness, tenderness, needle removed because of tender porta cath site and irritation.
^d Includes edema, induration, swelling, swollen and bruise and swelling.
^e Includes ecchymoses, hematoma, leaking, bruising, unable to flush central line, multiple ecchymotic areas - arm, 1 cm corci in vein from IV site, line fell out, and IV restarted for reasons not specified.

European Studies

Of the 192 patients treated with cefepime in European studies conducted post-NDA, there were only three patients who did not tolerate the cefepime infusion well. Two patients had local pain and one patient had infiltration. All patients continued their study regimen.

Compassionate Use Studies

There was no summary information provided with regard to infusion tolerance for these patients.

Blinded Studies

Four of forty-two patients reported local intolerance. Two indicated problems with infiltration and two with phlebitis.

FINAL SAFETY UPDATE

There was no additional information with regard to tolerance provided.

TOLERANCE**MEDICAL OFFICER'S COMMENTS:**

In general, cefepime was well tolerated by both the intravenous and the intramuscular routes. There was little discomfort with the low dose ($\leq 2\text{g/day}$) intramuscular injections; there were too few high dose ($> 2\text{g/day}$) patients treated with the intramuscular formulation to make a comment. The most frequent problems with the intravenous route were infiltration, inflammation and phlebitis. Infiltration is a mechanical problem and does not require further clarification. Phlebitis is a more significant event. The incidence rates of phlebitis in cefepime patients varied from 2.1% to over 10%. In the post-NDA safety data, the incidence of phlebitis is considerably higher. The explanation is possibly related a) to thrice daily dosing (three infusions per day) and/or b) to longer duration of therapy. In the second safety update, there were 341 patients who received cefepime at the maximum dosage. Nineteen (5.6%) patients experienced phlebitis. In the preceding charts, the reviewer noted that the percentage of phlebitis was consistently higher in the cefepime patients than in the ceftazidime group. Inflammation also occurred at variable rates from 0.2% to 7.3%. For the intravenous route, the reviewer suggests that the label reflect that phlebitis and inflammation occur at the sites of infusion. For patients dosed at the 2g BID or lower, an incidence rate of 3 percent for phlebitis is reasonable. For the intramuscular injection, tolerance for the 1g BID dose has been demonstrated. Pain was an infrequent side effect.

ADVERSE CLINICAL EVENTS

NDA

The following table is a modification of the adverse clinical events table presented by the applicant in their NDA summary. The table below presents adverse clinical events by relationship to cefepime by body system and lists adverse clinical events which occurred at the (grand total) frequency of 0.7% or greater, for all cefepime courses. (The applicant chose to present those clinical events of $\geq 1\%$.)

**ADVERSE CLINICAL EVENTS
BY RELATIONSHIP TO CEFEPIME AND BODY SYSTEM
ALL CEFEPIME COURSES
Cefepime Safety Summary**

Body System Primary Term ^a	Number (%) of Cefepime Courses (N = 4469)				
	Prob. Rel.	Unknown	Total	Not Rel.	Grand Total
Any Body System	214 (4.8)	407 (9.1)	621 (13.9)	324 (7.2)	946 (21.2) ^b
Body as a Whole	38 (0.9)	149 (3.3)	187 (4.2)	97 (2.2)	284 (6.4)
Fever*	12 (0.3)	8 (0.2)	20 (0.4)	13 (0.3)	33 (0.7)
Headache	15 (0.3)	88 (2.0)	103 (2.3)	39 (0.9)	142 (3.2)
Pain*	1 (<0.1)	17 (0.4)	18 (0.4)	18 (0.4)	36 (0.8)
Cardiovascular System	5 (0.1)	39 (0.9)	44 (1.0)	80 (1.8)	124 (2.8)
Chest Pain*	-	12 (0.3)	12 (0.3)	21 (0.5)	33 (0.7)
Digestive System	86 (1.9)	214 (4.8)	300 (6.7)	161 (3.6)	462 (10.3) ^b
Constipation	3 (<0.1)	37 (0.8)	40 (0.9)	27 (0.6)	67 (1.5)
Diarrhea	44 (1.0)	64 (1.4)	108 (2.4)	39 (0.9)	147 (3.3)
Nausea	22 (0.5)	67 (1.5)	89 (1.9)	46 (1.0)	136 (3.0) ^b
Pain Abdomen	4 (<0.1)	26 (0.6)	30 (0.7)	28 (0.6)	59 (1.3) ^b
Vomiting	13 (0.3)	53 (1.2)	66 (1.5)	32 (0.7)	98 (2.2)
Hemic & Lymphatic System	1 (<0.1)	4 (<0.1)	5 (0.1)	6 (0.1)	11 (0.2)
Metabolism & Nutrition Disorder	1 (<0.1)	13 (0.3)	14 (0.3)	12 (0.3)	26 (0.6)
Musculoskeletal System	1 (<0.1)	3 (<0.1)	4 (0.1)	6 (0.1)	10 (0.2)
Nervous System	12 (0.3)	82 (1.8)	94 (2.1)	99 (2.2)	193 (4.3)
Confusion*	1 (<0.1)	5 (0.1)	6 (0.1)	29 (0.6)	35 (0.8)
Dizziness	4 (<0.1)	22 (0.5)	26 (0.6)	21 (0.5)	47 (1.1)
Insomnia*	-	26 (0.6)	26 (0.6)	14 (0.3)	40 (0.9)
Respiratory System	1 (<0.1)	43 (1.0)	44 (1.0)	60 (1.3)	104 (2.3)
Skin & Appendages	84 (1.9)	60 (1.3)	144 (3.2)	69 (1.5)	211 (4.7)
Pruritus	19 (0.4)	23 (0.5)	42 (0.9)	14 (0.3)	56 (1.3)
Rash	64 (1.4)	30 (0.7)	94 (2.1)	25 (0.6)	119 (2.7)
Special Senses	3 (<0.1)	5 (<0.1)	8 (0.2)	11 (0.2)	19 (0.4)
Urogenital System	12 (0.3)	21 (0.5)	33 (0.7)	37 (0.8)	70 (1.6)

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

^a The primary ACE terms listed highlight incidence rates of 1% or greater.

^b Includes one ACE for which relationship to cefepime was not recorded.

* After a review of the complete list of adverse events, the reviewer identified a more natural breakpoint (at 0.7%) in the incidence of listed events. Those events that occurred at a frequency of $\geq 0.7\%$ and $< 1.0\%$ were marked with an asterisk (*).

There were five additional terms (fever, pain, chest pain, confusion and insomnia) which were added by lowering the frequency threshold from the applicant's 1% to the reviewer's 0.7%. Of interest, these five events were thought to be largely unrelated to cefepime administration by the assessing physicians.

The comprehensive list of terms, that the applicant has tabulated in the appendix of NDA volume 287, uses the COSTART adverse experience classification to summarize investigator primary terms. However, there are terms that the reviewer feels should be combined. By not combining terms, the incidence of a phenomenon is diluted. For examples, allergic reaction, facial edema and anaphylactoid reaction; edema and peripheral edema; vasodilation and hypotension; colitis, pseudomembranous colitis and enterocolitis pseudomembranous; anuria, kidney failure and abnormal kidney function; anxiety and nervousness; cerebral ischemia and cerebrovascular accident. The danger in combining terms is that two events i.e. facial edema listed under the skin system and allergic reaction listed under body as a whole could be the same patient/same event.

The following events deserve comment:

Hypotension: There were 18 reports of hypotension and 4 reports of vasodilation. The incidence of these events together is 22/4469 (0.5%). However, only 8 (0.2%) events were related or of unknown relationship.

Colitis: Using the terms colitis, pseudomembranous colitis, and enterocolitis pseudomembranous, there were 7/4469 (0.2%) cases of colitis of probable or unknown relationship to cefepime. Of interest, there were 147 (3.3%) cases of diarrhea reported. It was unclear to the reviewer the percentage of patients who were tested for the presence of *C. difficile* toxin. The applicant noted that *C. difficile* was identified in the stool of patients receiving 30 (0.7%) of the 4,469 courses of cefepime therapy. Seventeen patients of these 30 (57%) cefepime courses had diarrhea.

Moniliasis: Combining the terms moniliasis, oral moniliasis, vaginal moniliasis and vaginitis, there were 20 (0.4%) events that were probably or of unknown relatedness to the study drug. There were three additional reports which were thought not to be related.

Anxiety: There were 11 events termed anxiety that were probably or of unknown relationship to cefepime administration. There were an additional 5 events termed nervousness that were of unknown relationship to cefepime. (Ten reports of anxiety and 8 reports of nervousness were considered unrelated.) If these were indeed different names for the same events, the incidence of these events was 16 (0.4%) of probable or unknown relationship and 34/4469 (0.8%) for all reported events.

Renal Failure: The construct of the applicant's table was such that a single patient was listed only once within a body system. Therefore, the following four terms refer to separate individuals and can be combined: acute kidney failure (1), anuria (1), kidney failure (5) and kidney function abnormal (3). All but one of these patients had kidney dysfunction that was deemed unrelated to study drug.

Convulsion: There were 11 (0.2%) patients that were reported to have had a convulsion by the applicant. Three of these events were of probable or of unknown relationship to the study drug. The reviewer noted one additional patient with seizure that was not recorded by the applicant. This would bring the total to 12 patients or an incidence of 0.3%.

The following adverse clinical events of either probable or unknown relationship occurred in greater than or equal to 0.3%: asthenia, fever, headache, pain, chest pain, constipation, diarrhea, dyspepsia, nausea, abdomen pain, vomiting, anxiety, dizziness, insomnia, paresthesia, pruritus, rash, and sweating.

Adverse clinical events of any relationship to cefepime were reported in 946 (21.2%) of the total 4,469 cefepime courses. The greatest proportion of adverse clinical events was considered to be of unknown relationship to cefepime. The most frequent events which were considered to be of probable or unknown relationship to cefepime were headache (2.3%), diarrhea (2.4%), nausea (1.9%), and rash (2.1%). Adverse clinical events considered to be of probable or unknown relationship to cefepime occurred most frequently in the digestive system (6.7%).

The previous chart categorized all adverse clinical events for all 4,469 courses. On the following pages, these clinical events are divided into several sub-classifications for further detailed inspection. These tables have been prepared by the applicant and have not been modified by the reviewer. The tables are presented as follows: by location, by severity (and by life threatening events), by formulation, by risk group (low dose, high dose, renally impaired, neutropenic), by age group, by gender, by infection type and by comparison with ceftazidime.

The following table lists adverse clinical events reported in cefepime patients in North America. Adverse events of any relationship were reported in 857 (25.7%) of the 3,335 North American cefepime courses.

**ADVERSE CLINICAL EVENTS
BY RELATIONSHIP TO CEFEPIME AND BODY SYSTEM
ALL NORTH AMERICAN CEFEPIME COURSES**
Cefepime Safety Summary

Body System Primary Term ^a	Number (%) of Cefepime Courses				
	Prob. Rel.	Unknown	Total	Not Rel.	Grand Total
Any Body System	164 (4.9)	390 (11.7)	554 (16.6)	303 (9.1)	857 (25.7) ^b
Body as a Whole	34 (1.0)	148 (4.4)	182 (5.4)	97 (2.9)	279 (8.4)
Headache	13 (0.4)	87 (2.6)	100 (3.0)	39 (1.2)	139 (4.2)
Pain	1 (<0.1)	17 (0.5)	18 (0.5)	18 (0.5)	36 (1.1)
Cardiovascular System	2 (<0.1)	39 (1.2)	41 (1.2)	78 (2.3)	119 (3.6)
Digestive System	64 (1.9)	201 (6.0)	265 (7.9)	154 (4.6)	420 (12.6) ^b
Constipation	3 (<0.1)	37 (1.1)	40 (1.2)	27 (0.8)	67 (2.0)
Diarrhea	30 (0.9)	58 (1.7)	88 (2.6)	35 (1.1)	123 (3.7)
Nausea	18 (0.5)	63 (1.9)	81 (2.4)	45 (1.4)	127 (3.8) ^b
Pain Abdomen	3 (<0.1)	24 (0.7)	27 (0.8)	27 (0.8)	55 (1.7) ^b
Vomiting	12 (0.4)	51 (1.5)	63 (1.9)	31 (0.9)	94 (2.8)
Hemic & Lymphatic System	1 (<0.1)	6 (0.1)	5 (0.1)	6 (0.2)	11 (0.3)
Metabolism & Nutrition Disorder	1 (<0.1)	13 (0.4)	14 (0.4)	12 (0.4)	26 (0.8)
Musculoskeletal System	1 (<0.1)	3 (<0.1)	4 (0.1)	5 (0.2)	9 (0.3)
Nervous System	11 (0.3)	82 (2.5)	93 (2.8)	97 (2.9)	190 (5.7)
Dizziness	3 (<0.1)	22 (0.7)	25 (0.8)	21 (0.6)	46 (1.4)
Insomnia	0	26 (0.8)	26 (0.8)	14 (0.4)	40 (1.2)
Respiratory System	1 (<0.1)	43 (1.3)	44 (1.3)	60 (1.8)	104 (3.1)
Skin & Appendages	63 (1.9)	54 (1.6)	117 (3.5)	56 (1.7)	173 (5.2)
Pruritus	17 (0.5)	22 (0.7)	39 (1.2)	14 (0.4)	53 (1.6)
Rash	47 (1.4)	27 (0.8)	74 (2.2)	19 (0.6)	93 (2.8)
Special Senses	1 (<0.1)	5 (0.1)	6 (0.2)	11 (0.3)	17 (0.5)
Urogenital System	12 (0.4)	20 (0.6)	32 (1.0)	36 (1.1)	68 (2.0)

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

^a The primary ACE terms listed highlight incidence rates of 1% or greater.

^b Includes one ACE for which relationship to cefepime was not recorded.

The following table catalogues adverse events reported for cefepime in the European trials. Adverse clinical events of any relationship were reported in 88 (7.8%) of the 1,134 European cefepime courses, which was lower than in the North American studies (25.7%).

**ADVERSE CLINICAL EVENTS
BY RELATIONSHIP TO CEFEPIME AND BODY SYSTEM
ALL EUROPEAN CEFEPIME COURSES
Cefepime Safety Summary**

Body System Primary Term ^a	Number (X) of Cefepime Courses				
	Prob. Rel.	Unknown	Total	Not Rel.	Grand Total
Any Body System	50 (4.4)	17 (1.5)	67 (5.9)	21 (1.9)	88 (7.8)
Body as a Whole	4 (0.4)	1 (<0.1)	5 (0.4)	0	5 (0.4)
Cardiovascular System	3 (0.3)	0	3 (0.3)	2 (0.2)	5 (0.4)
Digestive System	22 (1.9)	13 (1.1)	35 (3.0)	7 (0.6)	42 (3.7)
Diarrhea	14 (1.2)	6 (0.5)	20 (1.7)	4 (0.4)	24 (2.1)
Nervous System	1 (<0.1)	0	1 (<0.1)	2 (0.2)	3 (0.3)
Skin & Appendages	21 (1.9)	6 (0.5)	27 (2.4)	11 (1.0)	38 (3.4)
Rash	17 (1.5)	3 (0.3)	20 (1.8)	6 (0.5)	26 (2.3)
Special Senses	2 (0.2)	0	2 (0.2)	0	2 (0.2)
Urogenital System	0	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (0.2)

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

^a The primary ACE terms listed highlight incidence rates of 1% or greater.

The following table catalogues adverse events of probable or unknown relationship by severity. The greatest proportion of events were considered to be of mild severity. In the table below, the applicant chose to use the denominator of all cefepime courses given which is 4469. However, an alternative analysis which may have been useful would have been to calculate the percentage severity of an event as related to the total incidence of the clinical event. For example, there were a total of 621 events in any body system that were of probable or unknown relationship to cefepime. Three hundred thirty-four (334/621 = 54%) were mild and five (5/621 = 0.8%) were life-threatening.

**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN RELATIONSHIP
TO CEFEPIME BY SEVERITY AND BODY SYSTEM
ALL CEFEPIME COURSES
Cefepime Safety Summary**

Body System Primary Term ^a	Number (%) of Cefepime Courses					Total
	Mild	Mod.	Sev.	L-Th. ^b	NR	
Any Body System	334 (7.5)	221 (4.9)	42 (0.9)	5 (0.1)	19 (0.4)	621 (13.9)
Body as a Whole	114 (2.6)	51 (1.1)	15 (0.3)	0	7 (0.2)	187 (4.2)
Headache	72 (1.6)	23 (0.5)	5 (0.1)	0	3 (<0.1)	103 (2.3)
Cardiovascular System	25 (0.6)	11 (0.2)	5 (0.1)	3 (<0.1)	0	44 (1.0)
Digestive System	170 (3.8)	110 (2.5)	11 (0.2)	0	9 (0.2)	300 (6.7)
Diarrhea	46 (1.0)	53 (1.2)	6 (0.1)	0	3 (<0.1)	108 (2.4)
Nausea	56 (1.3)	31 (0.7)	0	0	2 (<0.1)	89 (2.0)
Vomiting	42 (0.9)	22 (0.5)	0	0	2 (<0.1)	66 (1.5)
Hemic & Lymphatic System	3 (<0.1)	1 (<0.1)	1 (<0.1)	0	0	5 (0.1)
Metabolism & Nutritional Disorders	10 (0.2)	2 (<0.1)	1 (<0.1)	0	1 (<0.1)	14 (0.3)
Musculoskeletal System	2 (<0.1)	2 (<0.1)	0	0	0	4 (<0.1)
Nervous System	58 (1.3)	24 (0.5)	4 (<0.1)	0	8 (0.2)	94 (2.1)
Respiratory System	22 (0.5)	12 (0.3)	2 (<0.1)	3 (<0.1)	5 (0.1)	44 (1.0)
Skin & Appendages	80 (1.8)	52 (1.2)	7 (0.2)	0	5 (0.1)	144 (3.2)
Rash	45 (1.0)	42 (0.9)	4 (<0.1)	0	3 (<0.1)	94 (2.1)
Special Senses	7 (0.2)	1 (<0.1)	0	0	0	8 (0.2)
Urogenital System	20 (0.4)	9 (0.2)	0	0	4 (<0.1)	33 (0.7)

NOTE: Mod. = Moderate; Sev. = Severe; L-Th. = Life Threatening; NR = Not Recorded.

^a The primary ACE terms listed highlight incidence rates of 1% or greater.

^b This category was not on the case report form in low-dose studies; Life-Threatening ACE in these studies would have been included in the Severe category.

The following table lists all life-threatening and severe adverse clinical events of probable or unknown relationship to cefepime by risk group, for North American cefepime courses (Note: Early cefepime studies provided only mild, moderate, and severe, but not life-threatening, as categories of severity). Only six events in five patients were considered life-threatening. In the High-dose Risk Group, two patients experienced three life-threatening events: one patient had a cardiac arrest, and one had hypotension and respiratory distress (Adult Respiratory Distress Syndrome). In the Renally Impaired group one patient had a life-threatening event (embolism). In the Neutropenic group, there were two life-threatening events: two patients had diffuse alveolar hemorrhage syndrome.

**ALL LIFE-THREATENING AND SEVERE ACE OF PROBABLE OR UNKNOWN RELATIONSHIP TO CEFEPIME BY RISK GROUP
ALL NORTH AMERICAN CEFEPIME COURSES**
Cefepime Safety Summary

----- Number (%) of Cefepime Courses -----				
	Low-dose ^a (≤ 2000 mg/day) N = 1467	High-dose ^b (> 2000 mg/day) N = 1705	Renally Impaired N = 73	Neutropenic N = 90
Headache	3(0.2)	Anaphylactoid Reaction	1(<0.1)	Embolism ^c 1(1.4)
Heart Arrest	1(<0.1)	Chills	2(<0.1)	Diarrhea 1(1.4)
Thrombosis	1(<0.1)	Fever	3 (0.2)	Delirium 1(1.4)
Diarrhea	1(<0.1)	Headache	1(<0.1)	
Enterocolitis,		Moniliasis	1(<0.1)	
Pseudomembranous	1(<0.1)	Pain	2(<0.1)	
Edema	1(<0.1)	Pain Hip(s)	1(<0.1)	
Asthma	1(<0.1)	Pain Wound	1(<0.1)	
		Heart Arrest ^c	1(<0.1)	
		Hypertension	1(<0.1)	
		Hypotension ^c	1(<0.1)	
		Pulmonary Embolus	1(<0.1)	
		Syncope	1(<0.1)	
		Constipation	1(<0.1)	
		Diarrhea	2(<0.1)	
		Duodenal Ulcer with Hemorrhage	1(<0.1)	
		Ulceration, Mouth	1(<0.1)	
		Cyanosis	1(<0.1)	
		Agitation	1(<0.1)	
		Convulsion	1(<0.1)	
		Paresthesia	1(<0.1)	
		Asthma	1(<0.1)	
		Respiratory Disorder ^c	1(<0.1)	
		Herpes Simplex	1(<0.1)	

^a The category of Life-Threatening was not on the case report form in Low-dose studies. Any Life-threatening ACE in these studies would have been included in the Severe category.

^b Some patients in this group experienced more than one Life-Threatening or severe ACE.

^c Life-threatening ACE.

The next table lists all severe adverse clinical events of probable or unknown relationship to cefepime by risk group, for European cefepime courses. There were no adverse clinical events of life-threatening severity in the European studies. The most frequent severe adverse events were rash and diarrhea.

**ALL LIFE-THREATENING AND SEVERE ACE OF PROBABLE OR
UNKNOWN RELATIONSHIP TO CEFEPIME BY RISK GROUP
ALL EUROPEAN CEFEPIME COURSES**
Cefepime Safety Summary

		Number (%) of Cefepime Courses				
	Low-dose ($\leq$ 2000 mg/day) N = 580	High-dose ^a ($>$ 2000 mg/day) N = 420	Renally Impaired N = 15	Neutropenic N = 119		
Headache	1(0.2)	Diarrhea	2(0.5)	(None)	Urticaria	1(0.8)
Rash	1(0.2)	Moniliasis, Oral	1(0.2)			
		Erythema	1(0.2)			

NOTE: No Life-Threatening ACE occurred in European studies.

^a Some patients in this group may have experienced more than one severe ACE.

Two formulations of cefepime were used in the NDA studies: lyophilized cefepime and sodium chloride (NaCl), and cefepime dihydrochloride buffered with L-arginine. The following table presents events of probable or unknown relationship to cefepime by formulation. With the exceptions of the nervous system and the body as a whole, the two low dose formulations appeared comparable.

**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN RELATIONSHIP TO CEFEPIME
BY FORMULATION, RISK GROUP, AND BODY SYSTEM
ALL CEFEPIME COURSES**
Cefepime Safety Summary

Body System Primary Term ^a	Number (%) of Cefepime Courses								
	Low-dose (≤2000 mg/day) Sodium Chloride Formulation (N = 717)			Low-dose (≤2000 mg/day) Arginine Formulation (N = 1291)			High-dose (>2000 mg/day) Arginine Formulation (N = 2093)		
	Prob. Rel.	Unk.	Total	Prob. Rel.	Unk.	Total	Prob. Rel.	Unk.	Total
Any Body System	29(4.0)	34(4.7)	63(8.8)	45(3.5)	70(5.4)	124(9.6)	105(5.0)	253(12.1)	358(17.1)
Body as a Whole	1(0.1)	11(1.5)	12(1.7)	10(0.8)	32(2.6)	43(3.3)	24(1.2)	93(4.4)	117(5.6)
Headache	1(0.1)	6(0.8)	7(1.0)	4(0.3)	22(1.7)	26(2.0)	10(0.5)	53(2.5)	63(3.0)
Cardiovascular System	2(0.3)	3(0.4)	5(0.7)	1(<0.1)	7(0.5)	8(0.6)	2(<0.1)	24(1.1)	26(1.2)
Digestive System	14(2.0)	20(2.8)	34(4.7)	15(1.2)	39(3.0)	54(4.2)	41(2.0)	129(6.2)	170(8.1)
Constipation	0	2(0.3)	2(0.3)	1(<0.1)	6(0.5)	7(0.5)	2(<0.1)	27(1.3)	29(1.4)
Diarrhea	8(1.1)	4(0.6)	12(1.7)	6(0.5)	10(0.8)	16(1.2)	19(0.9)	40(1.9)	59(2.8)
Nausea	2(0.3)	8(1.1)	10(1.4)	4(0.3)	10(0.8)	14(1.1)	10(0.5)	40(1.9)	50(2.4)
Vomiting	0	2(0.3)	2(0.3)	3(0.2)	11(0.9)	14(1.1)	6(0.3)	33(1.6)	39(1.9)
Hemic & Lymphatic System	0	0	0	0	1(<0.1)	1(<0.1)	1(<0.1)	3(0.1)	4(0.2)
Metabolism & Nutrition Disorder	1(0.1)	0	1(0.1)	0	2(0.2)	2(0.2)	0	11(0.5)	11(0.5)
Musculoskeletal System	1(0.1)	0	1(0.1)	0	1(<0.1)	1(<0.1)	0	2(<0.1)	2(<0.1)
Nervous System	0	5(0.7)	5(0.7)	4(0.3)	14(1.1)	18(1.4)	6(0.3)	54(2.6)	60(2.9)
Respiratory System	0	0	0	0	7(0.5)	7(0.5)	1(<0.1)	33(1.6)	34(1.6)
Skin & Appendages	9(1.3)	2(0.3)	11(1.5)	14(1.1)	7(0.5)	21(1.6)	45(2.2)	46(2.2)	91(4.3)
Pruritus	2(0.3)	1(0.1)	3(0.4)	3(0.2)	4(0.3)	7(0.5)	13(0.6)	16(0.8)	29(1.4)
Rash	7(1.0)	2(0.3)	9(1.3)	12(0.9)	2(0.2)	14(1.1)	32(1.5)	22(1.1)	54(2.6)
Special Senses	0	0	0	1(<0.1)	2(0.2)	3(0.2)	1(<0.1)	3(0.1)	4(0.2)
Urogenital System	3(0.4)	2(0.3)	5(0.7)	2(0.2)	4(0.3)	6(0.5)	6(0.3)	13(0.6)	19(0.9)

NOTE: Prob. Related = Probably Related; Unk. = Unknown.

^a The primary ACE terms listed highlight incidence rates of 1% or greater.

The following four tables present adverse clinical event data for cefepime by relationship to risk group. The applicant defined four risk groups: low dose, high dose, renally impaired and neutropenic patients. The clinical events which occurred more frequently than 1% are listed in the table. The frequency of events were dose related. The highest incidence of adverse clinical events occurred in the neutropenic risk group, which is not unexpected.

**ADVERSE CLINICAL EVENTS BY RELATIONSHIP TO CEFEPIME,
RISK GROUP AND BODY SYSTEM
ALL CEFEPIME COURSES
Cefepime Safety Summary**

Body System Primary Term ^a	----- Number (%) of Cefepime Courses ----- Low-dose (≤ 2000 mg/day) (N=2047)				
	Prob.	Unk.	Not Rel.	Not Rec.	Total
Any Body System	77 (3.8)	118 (5.8)	91 (4.45)	1 (<0.1)	287 (14.0)
Body as a Whole	12 (0.6)	45 (2.2)	19 (0.9)	0	76 (3.7)
Headache	5 (0.2)	30 (1.5)	9 (0.4)	0	44 (2.1)
Cardiovascular System	3 (0.1)	11 (0.5)	21 (1.0)	0	35 (1.7)
Digestive System	30 (1.5)	54 (3.1)	39 (1.9)	1 (<0.1)	134 (6.5)
Diarrhea	14 (0.7)	15 (0.7)	11 (0.5)	0	40 (2.0)
Nausea	6 (0.3)	19 (0.9)	9 (0.4)	1 (<0.1)	35 (1.7)
Vomiting	3 (0.1)	15 (0.7)	4 (0.2)	0	22 (1.1)
Hemic & Lymphatic System	0	1 (<0.1)	1 (<0.1)	0	2 (<0.1)
Metabolism & Nutritional Disorders	1 (<0.1)	2 (<0.1)	1 (<0.1)	0	4 (0.2)
Musculoskeletal System	1 (<0.1)	1 (<0.1)	1 (<0.1)	0	3 (0.1)
Nervous System	5 (0.2)	20 (1.0)	23 (1.1)	0	48 (2.3)
Respiratory System	0	7 (0.3)	17 (0.8)	0	24 (1.2)
Skin & Appendages	23 (1.1)	9 (0.4)	13 (0.6)	0	45 (2.2)
Rash	19 (0.9)	4 (0.2)	5 (0.2)	0	28 (1.4)
Special Senses	1 (<0.1)	2 (<0.1)	2 (<0.1)	0	5 (0.2)
Urogenital System	6 (0.3)	6 (0.3)	4 (0.2)	0	16 (0.8)

NOTE: Prob. = Probably Related; Unk. = Unknown; Not Rel. = Not Related; Not Rec. = Not Recorded.

^a The primary ACE terms listed highlight incidence rates of 1% or greater.

(continued)

**ADVERSE CLINICAL EVENTS BY RELATIONSHIP TO CEFEPIME,
RISK GROUP AND BODY SYSTEM
ALL CEFEPIME COURSES
Cefepime Safety Summary**

Body System Primary Term ^a	----- Number (%) of Cefepime Courses ----- High-dose (> 2000 mg/day) (N=2125)				
	Prob.	Unk.	Not Rel.	Not Rec.	Total
Any Body System	107 (5.0)	257 (12.1)	187 (8.8)	0	551 (25.9)
Body as a Whole	24 (1.1)	95 (4.5)	65 (3.1)	0	184 (8.7)
Fever	7 (0.3)	6 (0.2)	12 (0.6)	0	25 (1.2)
Headache	10 (0.5)	54 (2.5)	26 (1.2)	0	90 (4.2)
Pain	1 (<0.1)	13 (0.6)	11 (0.5)	0	25 (1.2)
Cardiovascular System	2 (<0.1)	24 (1.1)	50 (2.4)	0	76 (3.6)
Pain Chest	0	8 (0.4)	13 (0.6)	0	21 (1.0)
Digestive System	42 (2.0)	132 (6.2)	94 (4.4)	0	268 (12.6)
Constipation	2 (<0.1)	27 (1.3)	22 (1.0)	0	51 (2.4)
Diarrhea	20 (0.9)	41 (1.9)	14 (0.7)	0	75 (3.5)
Nausea	10 (0.5)	40 (1.9)	28 (1.3)	0	78 (3.7)
Pain Abdomen	2 (<0.1)	15 (0.7)	20 (0.9)	0	37 (1.7)
Vomiting	6 (0.3)	34 (1.6)	21 (1.0)	0	61 (2.9)
Hemic & Lymphatic System	1 (<0.1)	3 (0.1)	5 (0.2)	0	9 (0.4)
Metabolism & Nutritional Disorders	0	11 (0.5)	6 (0.3)	0	17 (0.8)
Musculoskeletal System	0	2 (<0.1)	4 (0.2)	0	6 (0.3)
Nervous System	6 (0.3)	54 (2.5)	64 (3.0)	0	124 (5.8)
Confusion	0	3 (0.1)	18 (0.8)	0	21 (1.0)
Dizziness	3 (0.1)	10 (0.5)	15 (0.7)	0	28 (1.3)
Insomnia	0	18 (0.8)	11 (0.5)	0	29 (1.4)
Respiratory System	1 (<0.1)	33 (1.6)	33 (1.6)	0	67 (3.2)
Skin & Appendages	46 (2.2)	46 (2.2)	34 (1.6)	0	126 (5.9)
Pruritus	14 (0.7)	16 (0.8)	10 (0.5)	0	40 (1.9)
Rash	32 (1.5)	22 (1.0)	11 (0.5)	0	65 (3.1)
Special Senses	1 (<0.1)	3 (0.1)	6 (0.3)	0	10 (0.5)
Urogenital System	6 (0.3)	13 (0.6)	27 (1.3)	0	46 (2.2)

NOTE: Prob. = Probably Related; Unk. = Unknown; Not Rel. = Not Related; Not Rec. = Not Recorded.

^a The primary ACE terms listed highlight incidence rates of 1% or greater.

(continued)

**ADVERSE CLINICAL EVENTS BY RELATIONSHIP TO CEFEPIME,
RISK GROUP AND BODY SYSTEM
ALL CEFEPIME COURSES
Cefepime Safety Summary**

Body System Primary Term ^a	----- Number (%) of Cefepime Courses ----- Really Impaired (N=88)					Total
	Prob.	Unk.	Not Rel.	Not Rec.		
Any Body System	4 (4.5)	11 (12.5)	5 (5.7)	0	20 (22.7)	
Body as a Whole	1 (1.1)	2 (2.3)	1 (1.1)	0	4 (4.5)	
Cardiovascular System	0	2 (2.3)	1 (1.1)	0	3 (3.4)	
Digestive System	3 (3.4)	2 (2.3)	1 (1.1)	0	6 (6.8)	
Metabolism & Nutritional Disorders	0	0	1 (1.1)	0	1 (1.1)	
Nervous System	0	3 (3.4)	2 (2.3)	0	5 (5.7)	
Respiratory System	0	0	1 (1.1)	0	1 (1.1)	
Skin & Appendages	0	0	1 (1.1)	0	1 (1.1)	
Special Senses	0	0	1 (1.1)	0	1 (1.1)	
Urogenital System	0	1 (1.1)	1 (1.1)	0	2 (2.3)	

NOTE: Prob. = Probably Related; Unk. = Unknown; Not Rel. = Not Related; Not Rec. = Not Recorded.

^a The primary ACE terms are not listed; due to the small number of patients in this group, all ACE occurred at incidence rates of 1% or greater.

(continued)
**ADVERSE CLINICAL EVENTS BY RELATIONSHIP TO CEFEPIME,
 RISK GROUP AND BODY SYSTEM
 ALL CEFEPIME COURSES**
 Cefepime Safety Summary

Body System Primary Term ^a	Number (%) of Cefepime Courses Neutropenic (N=209)				
	Prob.	Unk.	Not Rel.	Not Rec.	Total
Any Body System	26 (12.4)	21 (10.0)	41 (19.6)	0	88 (42.1)
Body as a Whole	1 (0.5)	7 (3.3)	12 (5.7)	0	20 (9.6)
Chills	0	2 (1.0)	4 (1.9)	0	6 (2.9)
Headache	0	4 (1.9)	4 (1.9)	0	8 (3.8)
Pain	0	0	3 (1.4)	0	3 (1.4)
Cardiovascular System	0	2 (1.0)	8 (3.8)	0	10 (4.8)
Hypotension	0	0	3 (1.4)	0	3 (1.4)
Digestive System	11 (5.3)	16 (7.7)	27 (12.9)	0	54 (25.8)
Constipation	0	2 (1.0)	1 (0.5)	0	3 (1.4)
Diarrhea	8 (3.8)	6 (2.9)	13 (6.2)	0	27 (12.9)
Nausea	5 (2.4)	8 (3.8)	9 (4.3)	0	22 (10.5)
Pain Abdomen	1 (0.5)	1 (0.5)	5 (2.4)	0	7 (3.3)
Vomiting	4 (1.9)	4 (1.9)	7 (3.3)	0	15 (7.2)
Metabolism & Nutritional Disorders	0	0	4 (1.9)	0	4 (1.9)
Musculoskeletal System	0	0	1 (0.5)	0	1 (0.5)
Nervous System	1 (0.5)	5 (2.4)	10 (4.8)	0	16 (7.7)
Anxiety	0	2 (1.0)	3 (1.4)	0	5 (2.4)
Confusion	0	0	5 (2.4)	0	5 (2.4)
Dizziness	0	3 (1.4)	4 (1.9)	0	7 (3.3)
Insomnia	0	3 (1.4)	0	0	3 (1.4)
Respiratory System	0	3 (1.4)	9 (4.3)	0	12 (5.7)
Dyspnea	0	0	3 (1.4)	0	3 (1.4)
Epistaxis	0	1 (0.5)	5 (2.4)	0	6 (2.9)
Pleural Effusion	0	0	4 (1.9)	0	4 (1.9)
Skin & Appendages	15 (7.2)	4 (1.9)	20 (9.6)	0	39 (18.7)
Erythema	1 (0.5)	0	6 (2.9)	0	7 (3.3)
Pruritus	0	2 (1.0)	2 (1.0)	0	4 (1.9)
Rash	13 (6.2)	3 (1.4)	9 (4.3)	0	25 (12.0)
Urticaria	1 (0.5)	0	3 (1.4)	0	4 (1.9)
Special Senses	1 (0.5)	0	2 (1.0)	0	3 (1.4)
Urogenital System	0	1 (0.5)	5 (2.4)	0	6 (2.9)
Urinary Retention	0	0	3 (1.4)	0	3 (1.4)

NOTE: Prob. = Probably Related; Unk. = Unknown; Not Rel. = Not Related; Not Rec. = Not Recorded.

^a The primary ACE terms listed highlight incidence rates of 1% or greater.

The following tables present adverse clinical events of probable or unknown relationship to cefepime by risk group, age group, and body system. The three age groups examined are pediatric courses (2 to 12 years of age), adult courses (13 to 64 years of age), and geriatric courses (≥ 65 years of age). Pediatric patients were dosed at 50 mg/kg BID to a maximum dose of 2 g BID and are included in the High-dose Risk Group. There were no European pediatric studies, and no renally impaired or neutropenic pediatric patients in North American studies. Pediatric courses are found only in the North American High-dose Risk Group. In the general population, age did not appear to affect the incidence of adverse clinical events. Dosage did appear to correlate with numbers of adverse clinical events.

**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN RELATIONSHIP
TO CEFEPIME BY RISK GROUP, AGE GROUP AND BODY SYSTEM
ALL NORTH AMERICAN CEFEPIME COURSES
Cefepime Safety Summary**

Body System	Number (%) of Cefepime Courses							
	Low-dose (≤ 2000 mg/day)				High-dose (>2000 mg/day)			
	≤ 12 years N = 0	13-64 years N = 898	≥ 65 years N = 568	Total 1466	≤ 12 years N = 71	13-64 years N = 1241	≥ 65 years N = 393	Total 1705
Any Body System	0	108 (12)	59 (10)	167	6 (9)	263 (21)	72 (18)	341
Body as a Whole	0	40 (5)	14 (3)	54	2 (3)	100 (8)	15 (4)	117
Cardiovascular System	0	8 (<1)	3 (<1)	11	0	18 (2)	8 (2)	26
Digestive System	0	39 (4)	40 (7)	79	2 (3)	122 (10)	40 (10)	164
Hemic & Lymphatic System	0	1 (<1)	0	1	0	2 (<1)	2 (<1)	4
Metabolic & Nutritional Disorders	0	3 (<1)	0	3	0	7 (<1)	4 (1.0)	11
Musculoskeletal System	0	1 (<1)	1 (<1)	2	0	2 (<1)	0	2
Nervous System	0	15 (2)	9 (2)	24	0	40 (3)	20 (5)	60
Respiratory System	0	4 (<1)	3 (<1)	7	0	27 (2)	7 (2)	34
Skin & Appendages	0	18 (2)	6 (1)	24	1 (1)	61 (5)	18 (5)	80
Special Senses	0	2 (<1)	0	2	0	3 (<1)	0	3
Urogenital System	0	6 (<1)	6 (1)	12	0	15 (1)	3 (<1)	18

**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN RELATIONSHIP
TO CEFEPIME BY RISK GROUP, AGE GROUP AND BODY SYSTEM
ALL NORTH AMERICAN CEFEPIME COURSES**
Cefepime Safety Summary

Body System	Number (%) of Cefepime Courses							
	Renally Impaired				Neutropenic			
	≤12 years N = 0	13-64 years N = 27	≥65 years N = 46	Total 73	≤12 years N = 0	13-64 years N = 77	≥65 years N = 13	Total 90
Any Body System	0	4 (15)	10 (22)	14	0	29 (38)	3 (23)	32
Body as a Whole	0	0	3 (7)	3	0	8 (10)	0	8
Cardiovascular System	0	0	2 (4)	2	0	2 (3)	0	2
Digestive System	0	3 (11)	2 (4)	5	0	15 (20)	2 (15)	17
Nervous System	0	0	3 (7)	3	0	6 (8)	0	6
Respiratory System	0	0	0	0	0	3 (4)	0	3
Skin & Appendages	0	0	0	0	0	13 (17)	0	13
Special Senses	0	0	0	0	0	0	1 (8)	1
Urogenital System	0	0	1 (2.2)	1	0	1 (1)	0	1

The following table presents adverse clinical events of probable or unknown relationship to cefepime by risk group, age group, and body system for European cefepime courses. The total number of events reported are small. Overall, geriatric patients did not experience an increased number of adverse events.

**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN RELATIONSHIP
TO CEFEPIME BY RISK GROUP, AGE GROUP AND BODY SYSTEM
ALL EUROPEAN CEFEPIME COURSES
Cefepime Safety Summary**

Body System	----- Number (%) of Cefepime Courses -----					
	Low-dose (≤ 2000 mg/day)			High-dose (> 2000 mg/day)		
	13-64 years N = 269	≥ 65 years N = 311	Total 580	13-64 years N = 203	≥ 65 years N = 217	Total 420
Any Body System	16 (6)	12 (4)	28	15 (7)	8 (4)	23
Body as a Whole	3 (1)	0	3	2 (1)	0	2
Cardiovascular System	3 (1)	0	3	0	0	0
Digestive System	7 (3)	8 (3)	15	6 (3)	4 (2)	10
Nervous System	0	1 (<1)	1	0	0	0
Skin & Appendages	4 (2)	4 (1)	8	6 (3)	6 (3)	12
Special Senses	0	1 (<1)	1	1 (<1)	0	1
Urogenital System	0	0	0	1 (<1)	0	1
	Renally Impaired			Neutropenic		
Body System	13-64 years N = 2	≥ 65 years N = 13	Total 15	13-64 years N = 105	≥ 65 years N = 14	Total 119
Any Body System	0	1 (8)	1	11 (11)	4 (29)	15
Digestive System	0	0	0	8 (8)	2 (14)	10
Skin & Appendages	0	1 (8)	1	3 (3)	3 (21)	6

The following table presents adverse clinical events of probable or unknown relationship to cefepime by risk group, sex, and body system for North America. In the high dose group, of the 341 adverse clinical events that occurred in any body system, almost two-thirds (211/341 = 62%) were reported in women.

**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN
RELATIONSHIP TO CEFEPIME BY RISK GROUP, SEX AND BODY SYSTEM
ALL NORTH AMERICAN CEFEPIME COURSES**
Cefepime Safety Summary

Body System	Number (%) of Cefepime Courses					
	Low-dose (≤2000 mg/day)			High-dose (>2000 mg/day)		
	Female N=515	Male N=952	Total	Female N=857	Male N=848	Total
Any Body System	70 (14)	97 (10)	167	211 (25)	130 (15)	341
Body as a Whole	21 (4)	33 (4)	54	80 (9)	37 (4)	117
Cardiovascular System	3 (<1)	8 (<1)	11	15 (2)	11 (1)	26
Digestive System	35 (7)	44 (5)	79	105 (12)	59 (7)	164
Hemic & Lymphatic System	0	1 (<1)	1	3 (<1)	1 (<1)	4
Metabolism & Nutrition Disorder	0	3 (<1)	3	9 (1)	2 (<1)	11
Musculoskeletal System	1 (<1)	1 (<1)	2	1 (<1)	1 (<1)	2
Nervous System	8 (2)	16 (2)	24	32 (4)	28 (3)	60
Respiratory System	1 (<1)	6 (<1)	7	18 (2)	16 (2)	34
Skin & Appendages	13 (3)	11 (1)	24	37 (4)	43 (5)	80
Special Senses	0	2 (<1)	2	2 (<1)	1 (<1)	3
Urogenital System	6 (1)	6 (<1)	12	16 (2)	2 (<1)	18

**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN
RELATIONSHIP TO CEFEPIME BY RISK GROUP, SEX AND BODY SYSTEM
ALL NORTH AMERICAN CEFEPIME COURSES**
Cefepime Safety Summary

Body System	----- Number (%) of Cefepime Courses -----					
	Renally Impaired			Neutropenic		
	Female N=34	Male N=39	Total	Female N=44	Male N=46	Total
Any Body System	8 (24)	6 (15)	14	15 (34)	17 (38)	32
Body as a Whole	2 (6)	1 (3)	3	4 (9)	4 (9)	8
Cardiovascular System	2 (6)	0	2	1 (2)	1 (2)	2
Digestive System	1 (3)	4 (10)	5	11 (25)	6 (13)	17
Nervous System	3 (9)	0	3	5 (11)	1 (2)	6
Respiratory System	0	0	0	3 (7)	0	3
Skin & Appendages	0	0	0	5 (11)	8 (17)	13
Special Senses	0	0	0	1 (2)	0	1
Urogenital System	0	1 (3)	1	1 (2)	0	1

The following table presents adverse clinical events of probable or unknown relationship to cefepime by risk group, sex, and body system for Europe.

**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN
RELATIONSHIP TO CEFEPIME BY RISK GROUP, SEX AND BODY SYSTEM
ALL EUROPEAN CEFEPIME COURSES
Cefepime Safety Summary**

Body System	Number (%) of Cefepime Courses					
	Low-dose (≤ 2000 mg/day)			High-dose (> 2000 mg/day)		
	Female N=221	Male N=359	Total	Female N=165	Male N=255	Total
Any Body System	18 (8)	10 (3)	28	7 (4)	16 (6)	23
Body as a Whole	3 (1)	0	3	0	2 (<1)	2
Cardiovascular System	3 (1)	0	3	0	0	
Digestive System	7 (3)	8 (2)	15	4 (2)	6 (2)	10
Nervous System	0	1 (<1)	1	0	0	
Skin & Appendages	6 (3)	2 (<1)	8	2 (1)	10 (4)	12
Special Senses	0	1 (<1)	1	1 (<1)	0	1
Urogenital System	0	0		0	1 (<1)	1

Body System	Renally Impaired			Neutropenic		
	Female N=5	Male N=10	Total	Female N=56	Male N=63	Total
Any Body System	0	1 (10)	1	9 (16)	6 (10)	15
Digestive System	0	0		7 (13)	3 (5)	10
Skin & Appendages	0	1 (10)	1	3 (5)	3 (5)	6

The following table presents adverse clinical events of probable or unknown relationship to cefepime by risk group, infection type, and body system for all North American cefepime low dose and high dose courses. The highest incidence of adverse clinical events occurred in patients with urinary tract infections.

**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN RELATIONSHIP
TO CEFEPIME BY RISK GROUP, INFECTION TYPE, AND BODY SYSTEM
ALL NORTH AMERICAN CEFEPIME COURSES
Cefepime Safety Summary**

Body System	--- Number (%) of Cefepime Courses Low-dose: ($\leq$ 2000 mg/day) ---				Total N = 1467
	UTI N = 438	SSTI N = 514	N = 522	N = 86	
Any Body System	43 (10)	58 (11)	65 (13)	11 (13)	163
Body as a Whole	13 (3)	21 (4)	18 (3)	5 (6)	52
Cardiovascular System	4 (<1)	2 (<1)	4 (<1)	2 (2)	10
Digestive System	26 (6)	22 (4)	31 (6)	4 (5)	78
Hemic & Lymphatic System	0	0	1 (<1)	0	1
Metabolic & Nutritional Disorder	1 (<1)	1 (<1)	1 (<1)	1 (1)	3
Musculoskeletal System	1 (<1)	0	1 (<1)	1 (1)	2
Nervous System	6 (1)	7 (1)	11 (2)	1 (1)	24
Respiratory System	1 (<1)	0	4 (<1)	1 (1)	5
Skin & Appendages	4 (<1)	13 (3)	9 (2)	1 (1)	24
Special Senses	0	1 (<1)	1 (<1)	0	2
Urogenital System	4 (<1)	2 (<1)	6 (1)	0	12

NOTE: UTI = Urinary tract infection; SSTI = skin and skin-structure infection;

NOTE: n = total number of cefepime courses with a specific indication within a particular dose group in all studies.

NOTE: Some cefepime courses are included in more than one infection type, therefore the totals of each row may not equal the totals of the columns in this table.

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**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN RELATIONSHIP
TO CEFEPIME BY RISK GROUP, INFECTION TYPE, AND BODY SYSTEM
ALL NORTH AMERICAN CEFEPIME COURSES**
Cefepime Safety Summary

Body System	----- Number (%) of Cefepime Courses High-dose: (> 2000 mg/day) -----							Total
	UTI N = 334	SSTI N = 364	N = 410	N = 350	N = 159	N = 202	N = 116	
Any Body System	113 (34)	49 (14)	85 (21)	58 (17)	57 (36)	52 (26)	33 (29)	341
Body as a Whole	41 (12)	14 (4)	30 (7)	21 (6)	21 (13)	19 (9)	11 (10)	117
Cardio-vascular System	9 (3)	0	8 (2)	6 (2)	2 (1)	6 (3)	2 (2)	26
Digestive System	59 (18)	20 (6)	41 (10)	26 (7)	32 (20)	25 (12)	17 (15)	164
Hemic & Lymphatic System	2 (<1)	0	1 (<1)	0	1 (<1)	1 (<1)	1 (<1)	4
Metabolism & Nutrition Disorder	8 (2)	2 (<1)	1 (<1)	0	7 (4)	1 (<1)	1 (<1)	11
Musculo-skeletal System	0	0	0	0	0	1 (<1)	1 (<1)	2
Nervous System	13 (4)	12 (3)	23 (6)	7 (2)	7 (4)	6 (3)	3 (3)	60
Respiratory System	16 (5)	4 (1)	6 (2)	6 (2)	8 (5)	4 (2)	2 (2)	34
Skin & Appendages	15 (5)	24 (7)	19 (5)	6 (2)	5 (3)	11 (5)	16 (14)	80
Special Senses	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	0	0	3
Urogenital System	10 (3)	4 (1)	2 (<1)	3 (1)	4 (3)	3 (2)	0	18

NOTE: UTI = urinary tract infection; SSTI = skin and skin-structure infection:

NOTE: N = total number of cefepime courses with a specific indication within a particular dose group in all studies.

NOTE: Some patients are included in more than one infection type, therefore the totals of each row may not equal the totals of the columns in this table.

* Includes 6 patients with diagnosis of endocarditis.

The following table presents adverse clinical events of probable or unknown relationship to cefepime by risk group, infection type, and body system for European cefepime courses. The highest incidence of events was seen in patients with skin and skin structure infections.

**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN RELATIONSHIP
TO CEFEPIME BY RISK GROUP, INFECTION TYPE, AND BODY SYSTEM
ALL EUROPEAN CEFEPIME COURSES**
Cefepime Safety Summary

B	----- Number (%) of Cefepime Courses Low-dose: ($\leq$ 2000 mg/day) -----				
	UTI N = 179	SSTI N = 48	N = 356	N = 55	Total N = 580
Any Body System	11 (6)	2 (4)	15 (4)	3 (6)	28
Body as a Whole	1 (<1)	0	2 (<1)	0	3
Cardiovascular System	2 (1)	0	1 (<1)	0	3
Digestive System	5 (3)	1 (2)	9 (3)	1 (2)	15
Nervous System	0	0	1 (<1)	0	1
Skin & Appendages	3 (2)	1 (2)	4 (1)	2 (4)	8
Special Senses	0	0	1 (<1)	0	1

Body System	--- Number (%) of Cefepime Courses High-dose: (> 2000 mg/day) ---					
	UTI N = 91	SSTI N = 36	N = 279	N = 8	N = 95	Total N = 420
Any Body System	2 (2)	6 (17)	13 (5)	0	3 (3)	21
Digestive System	1 (1)	4 (11)	5 (2)	0	2 (2)	10
Skin & Appendages	1 (1)	3 (8)	8 (3)	0	1 (1)	12
Special Senses	0	0	1 (<1)	0	0	1
Urogenital System	0	0	1 (<1)	0	0	1

NOTE: UTI = urinary tract infection; SSTI = skin and skin structure infection;

NOTE: N = total number of cefepime courses with a specific indication within a particular dose group in all studies.

NOTE: Some patients are included in more than one infection type, therefore the totals of each row may not equal the totals of the columns in this table.

To this point, the critical look of adverse clinical events has been for all cefepime courses of treatment. The following chart catalogues ALL adverse clinical events reported during comparative (ceftazidime only) clinical trials.

**ADVERSE CLINICAL EVENTS AT $\geq$ 1% FREQUENCY
IN NORTH AMERICAN AND EUROPEAN PATIENTS BY BODY SYSTEM**
Cefepime vs. Cefazidime
Cefepime Safety Summary

Body System Primary Term	----- Number (%) of Patients -----			
	North American		European	
	Cefepime N = 1559	Ceftazidime N = 1124	Cefepime N = 473	Ceftazidime N = 332
Any Body System	389 (25.0)	321 (28.6)	23 (4.9)	16 (4.8)
Body as a Whole	134 (8.6)	98 (8.7)	4 (0.8)	4 (1.2)
Headache	67 (4.3)	51 (4.5)	2 (0.4)	0
Cardiovascular System	56 (3.6)	47 (4.2)	0	0
Pain Chest	13 (0.8)	16 (1.4)		
Digestive System	191 (12.3)	163 (14.5)	6 (1.3)	6 (1.8)
Constipation	34 (2.2)	29 (2.6)	0	0
Diarrhea	48 (3.1)	56 (5.0)	2 (0.4)	3 (0.9)
Nausea	51 (3.3)	42 (3.7)	1 (0.2)	0
Pain Abdomen	27 (1.7)	19 (1.7)	0	0
Vomiting	38 (2.4)	27 (2.4)	1 (0.2)	1 (0.3)
Metabolism & Nutrition Disorder	12 (0.8)	24 (2.1)	0	0
Edema	10 (0.6)	19 (1.7)	0	0
Nervous System	99 (6.4)	77 (6.9)	1 (0.2)	1 (0.3)
Anxiety	18 (1.2)	15 (1.3)	0	0
Confusion	16 (1.0)	11 (1.0)	1 (0.2)	0
Dizziness	24 (1.5)	14 (1.2)	0	0
Insomnia	17 (1.1)	15 (1.3)	0	0
Respiratory System	45 (2.9)	60 (5.3)	0	0
Dyspnea	12 (0.8)	14 (1.2)		
Skin & Appendages	78 (5.0)	71 (6.3)	12 (2.5)	2 (0.6)
Pruritus	24 (1.5)	17 (1.5)	0	0
Rash	35 (2.2)	38 (3.4)	11 (2.3)	2 (0.6)

On the following five pages, adverse clinical events of probable or unknown relationship to cefepime or ceftazidime are presented with respect to risk groups, body system and study location. Adverse clinical events are presented by body system and by events which occurred at a frequency of 1% or greater. In the low dose and high dose risk groups, there is a similar patient incidence of probably or unknown clinical adverse events when cefepime treated patients are compared to ceftazidime treated patients. There were significantly fewer events reported from the European patients.

**ADVERSE CLINICAL EVENTS
BY RELATIONSHIP TO CEFEPIME AND CEFTAZIDIME, RISK GROUP AND BODY SYSTEM
ALL NORTH AMERICAN PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Body System Primary Term ^a	Number (%) of Patients					
	Cefepime Low-dose (≤ 2000 mg/day) (N=910)			Ceftazidime Low-dose (≤ 3000 mg/day) (N=477)		
	Prob. Rel.	Unknown	Not Rel.	Prob. Rel.	Unknown	Not Rel.
Any Body System	36 (4.0)	102 (11.2)	59 (6.5)	16 (3.4)	48 (10.1)	48 (10.1)
Body as a Whole	7 (0.8)	42 (4.6)	16 (1.8)	2 (0.4)	13 (2.7)	11 (2.3)
Asthenia	0	9 (1.0)	0	0	1 (0.2)	1 (0.2)
Headache	2 (0.2)	25 (2.7)	8 (0.9)	1 (0.2)	9 (1.9)	6 (1.3)
Cardiovascular System	0	12 (1.3)	19 (2.1)	0	2 (0.4)	11 (2.3)
Pain chest	0	4 (0.4)	6 (0.7)	0	0	4 (0.8)
Digestive System	13 (1.4)	55 (6.0)	29 (3.2)	7 (1.5)	31 (6.5)	19 (4.0)
Constipation	1 (<0.1)	11 (1.2)	4 (0.4)	0	7 (1.5)	4 (0.8)
Diarrhea	5 (<0.5)	10 (1.1)	6 (0.7)	3 (0.6)	8 (1.7)	2 (0.4)
Dyspepsia	0	5 (0.4)	3 (0.2)	0	5 (1.0)	1 (0.2)
Nausea	3 (<0.3)	16 (1.8)	5 (0.5)	2 (0.4)	8 (1.7)	4 (0.8)
Pain Abdomen	0	9 (1.0)	3 (0.3)	0	4 (0.8)	5 (1.0)
Vomiting	2 (<0.2)	14 (1.5)	2 (0.2)	0	6 (1.3)	6 (1.3)
Hemic & Lymphatic System	0	1 (0.1)	1 (0.1)	1 (0.2)	0	1 (0.2)
Metabolism & Nutritional Disorders	1 (0.1)	3 (0.3)	0	0	2 (0.4)	2 (0.4)
Musculoskeletal System	0	1 (0.1)	2 (0.2)	0	0	1 (0.2)
Nervous System	5 (0.5)	25 (2.7)	13 (1.4)	0	11 (2.3)	10 (2.1)
Anxiety	1 (0.1)	7 (0.8)	3 (0.3)	0	1 (0.2)	2 (0.4)
Confusion	1 (0.1)	2 (0.2)	0	1	3 (0.6)	3 (0.6)
Dizziness	0	9 (1.0)	2 (0.2)	0	3 (0.6)	2 (0.4)
Respiratory System	0	6 (0.7)	16 (1.8)	0	4 (0.8)	8 (1.7)
Skin & Appendages	8 (0.9)	7 (0.8)	6 (0.7)	6 (1.3)	5 (1.0)	7 (1.5)
Pruritus	2 (0.2)	2 (0.2)	2 (0.2)	3 (0.6)	1 (0.2)	1 (0.2)
Rash	6 (0.7)	4 (0.4)	1 (0.1)	3 (0.6)	1 (0.2)	3 (0.6)
Special Senses	0	2 (0.2)	1 (0.1)	0	0	1 (0.2)
Urogenital System	3 (0.3)	4 (0.4)	3 (0.3)	1 (0.2)	2 (0.4)	3 (0.6)

^a The primary adverse events terms listed highlight incidence rates of 1% or greater.

**ADVERSE CLINICAL EVENTS
BY RELATIONSHIP TO CEFEPIME AND CEFTAZIDIME, RISK GROUP AND BODY SYSTEM
ALL NORTH AMERICAN PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Body System Primary Term ^a	Number (%) of Patients					
	Cefepime High-dose (≥2000mg/day) (N=581)			Ceftazidime High-dose (≥3000mg/day) (N=540)		
	Prob. Rel.	Unknown	Not Rel.	Prob. Rel.	Unknown	Not Rel.
Any Body System	28 (4.8)	82 (14.1)	55 (9.5)	33 (6.1)	84 (15.6)	44 (8.1)
Body as a Whole	6 (1.0)	29 (5.0)	22 (3.8)	11 (2.0)	26 (4.8)	18 (3.3)
Headache	5 (0.9)	13 (2.2)	10 (1.7)	6 (1.1)	16 (3.0)	6 (1.1)
Pain	0	3 (0.5)	3 (0.5)	0	0	3 (0.6)
Cardiovascular System	0	7 (1.2)	15 (2.6)	1 (0.2)	6 (1.1)	11 (2.1)
Pain chest	0	1 (0.2)	3 (0.3)	1 (0.2)	4 (0.7)	5 (0.9)
Digestive System	12 (2.1)	39 (6.7)	27 (4.6)	15 (2.8)	43 (8.0)	18 (3.3)
Constipation	2 (0.3)	11 (1.9)	5 (0.9)	1 (0.2)	11 (2.1)	0
Diarrhea	4 (0.7)	11 (1.9)	4 (0.7)	5 (0.9)	18 (3.3)	6 (1.1)
Nausea	3 (0.5)	11 (1.9)	6 (1.0)	7 (1.3)	7 (1.3)	5 (0.9)
Pain Abdomen	0	3 (0.5)	9 (1.5)	3 (0.6)	3 (0.6)	1 (0.2)
Vomiting	2 (0.3)	10 (1.7)	4 (0.7)	2 (0.4)	6 (1.1)	2 (0.4)
Hemic & Lymphatic System	0	1 (0.2)	1 (0.2)	1 (0.2)	0	2 (0.4)
Metabolism & Nutritional Disorders	0	3 (0.5)	4 (0.7)	0	7 (1.3)	2 (0.4)
Edema	0	3 (0.5)	2 (0.3)	0	6 (1.1)	2 (0.4)
Musculoskeletal System	0	1 (0.2)	1 (0.2)	0	0	0
Nervous System	0	27 (4.6)	19 (3.3)	5 (0.9)	17 (3.1)	15 (2.8)
Confusion		2 (0.3)	7 (1.2)	0	1 (0.2)	0
Dizziness		4 (0.7)	4 (0.7)	2 (0.4)	3 (0.6)	0
Insomnia		7 (1.2)	3 (0.5)	0	8 (1.5)	3 (0.6)
Nervousness		4 (0.7)	2 (0.3)	1 (0.2)	2 (0.4)	0
Paresthesia		4 (0.7)	2 (0.3)	0	1 (0.2)	1 (0.2)
Respiratory System	0	11 (1.9)	9 (1.5)	0	10 (1.9)	14 (2.6)
Skin & Appendages	14 (2.4)	19 (3.3)	16 (2.8)	14 (2.6)	17 (3.1)	7 (1.3)
Erythema	0	1 (0.2)	2 (0.3)	3 (0.6)	3 (0.6)	0
Pruritus	6 (1.0)	10 (1.7)	4 (0.6)	6 (1.1)	2 (0.4)	3 (0.6)
Rash	8 (1.4)	7 (1.2)	3 (0.5)	8 (1.5)	7 (1.3)	5 (0.9)
Sweating	0	5 (0.9)	2 (0.3)	0	0	0
Special Senses	0	1 (0.2)	0	0	3 (0.6)	3 (0.6)
Urogenital System	1 (0.2)	8 (1.4)	7 (1.2)	2 (0.4)	6 (1.1)	6 (1.1)

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

^a The primary ACE terms listed highlight incidence rates of 1% or greater.

**ADVERSE CLINICAL EVENTS
BY RELATIONSHIP TO CEFEPIME AND CEFTAZIDIME, RISK GROUP AND BODY SYSTEM
ALL NORTH AMERICAN PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Body System Primary Term ^a	----- Number (%) of Patients -----					
	Renally Impaired Cefepime Patients (N=46)			Renally Impaired Ceftazidime Patients (N=82)		
	Prob. Rel.	Unknown	Not Rel.	Prob. Rel.	Unknown	Not Rel.
Any Body System	1 (2.2)	4 (8.7)	3 (6.5)	6 (7.3)	7 (8.5)	12 (14.6)
Body as a Whole	0	1 (2.2)	1 (2.2)	0	4 (4.9)	2 (2.4)
Cardiovascular System	0	1 (2.2)	0	0	1 (1.2)	5 (6.1)
Digestive System	1 (2.2)	0	1 (2.2)	5 (6.1)	2 (2.4)	3 (3.7)
Metabolism & Nutritional Disorders	0	0	0	0	1 (1.2)	3 (3.7)
Nervous System	0	1 (2.2)	1 (2.2)	0	1 (1.2)	3 (3.7)
Respiratory System	0	0	1 (2.2)	2 (2.4)	2 (2.4)	5 (6.1)
Skin & Appendages	0	0	0	1 (1.2)	2 (2.4)	2 (2.4)
Special Senses	0	0	0	0	1 (1.2)	1 (1.2)
Urogenital System	0	1 (2.2)	1 (2.2)	1 (1.2)	0	1 (1.2)

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

^a Primary ACE terms are not listed; due to the small number of patients in each group, all ACE occurred at incidence rates of 1% or greater.

**ADVERSE CLINICAL EVENTS
BY RELATIONSHIP TO CEFEPIME AND CEFTAZIDIME, RISK GROUP AND BODY SYSTEM
ALL NORTH AMERICAN PATIENTS
Cefepime vs. Cefazidime
Cefepime Safety Summary**

Body System Primary Term ^a	Number (%) of Patients					
	Neutropenic Cefepime Patients (N=22)			Neutropenic Cefazidime Patients (N=25)		
	Prob. Rel.	Unknown	Not Rel.	Prob. Rel.	Unknown	Not Rel.
Any Body System	4 (18.2)	6 (27.3)	8 (36.4)	4 (16.0)	14 (56.0)	5 (20.0)
Body as a Whole	0	4 (18.2)	6 (27.3)	1 (4.0)	5 (20.0)	5 (20.0)
Cardiovascular System	0	1 (4.5)	1 (4.5)	0	4 (24.0)	4 (16.0)
Digestive System	0	4 (18.2)	9 (40.9)	1 (4.0)	10 (40.0)	9 (36.0)
Metabolism & Nutritional Disorders	0	0	1 (4.5)	0	2 (8.0)	5 (20.0)
Musculoskeletal System	0	0	0	0	0	1 (4.0)
Nervous System	1 (4.5)	2 (9.1)	5 (22.7)	0	4 (16.0)	11 (44.0)
Respiratory System	0	0	2 (9.1)	0	4 (16.0)	10 (40.0)
Skin & Appendages	3 (13.6)	1 (4.5)	4 (18.2)	1 (4.0)	4 (16.0)	5 (20.0)
Special Senses	0	0	2 (9.1)	0	2 (8.0)	0
Urogenital System	0	1 (4.5)	0	1 (4.0)	3 (12.0)	2 (8.0)

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

^a Primary ACE terms are not listed; due to the small number of patients in each group, all ACE occurred at incidence rates of 1% or greater.

**ADVERSE CLINICAL EVENTS
BY RELATIONSHIP TO CEFEPIME AND CEFTAZIDIME, RISK GROUP AND BODY SYSTEM
ALL EUROPEAN PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Body System Primary Term ^a	Number (%) of Patients					
	Cefepime Low-dose (≤2000mg/day) (N=300)			Ceftazidime Low-dose (≤3000mg/day) (N=157)		
	Prob. Rel.	Unknown	Not Rel.	Prob. Rel.	Unknown	Not Rel.
Any Body System	7 (2.3)	0	2 (0.7)	3 (1.9)	0	1 (0.6)
Body as a Whole	2 (0.7)	0	0	0	0	0
Digestive System	1 (0.3)	0	1 (0.3)	2 (1.3)	0	0
Hemic & Lymphatic System	0	0	0	0	0	1 (0.6)
Skin & Appendages	4 (1.3)	0	1 (0.3)	1 (0.6)	0	0
Rash	4 (1.3)	0	1 (0.3)	1 (0.6)	0	0
	Cefepime High-dose (≥2000mg/day) (N=160)			Ceftazidime High-dose (≥3000mg/day) (N=165)		
Body System Primary Term ^a	Prob. Rel.	Unknown	Not Rel.	Prob. Rel.	Unknown	Not Rel.
Any Body System	7 (4.4)	2 (1.2)	4 (2.5)	9 (5.5)	2 (1.2)	0
Body as a Whole	1 (0.6)	1 (0.6)	0	4 (2.4)	0	0
Moniliasis	1 (0.6)	0	0	2 (1.2)	0	0
Mucositis	0	0	0	2 (1.2)	0	0
Digestive System	4 (2.5)	0	0	3 (1.8)	1 (0.6)	0
Diarrhea	2 (1.2)	0	0	2 (1.2)	0	0
Moniliasis oral	2 (1.2)	0	0	1 (0.6)	1 (0.6)	0
Hemic & Lymphatic System	0	0	0	1 (0.6)	0	0
Nervous System	0	0	1 (0.6)	0	1 (0.6)	0
Skin & Appendages	2 (1.2)	1 (0.6)	3 (1.9)	0	0	0
Rash	2 (1.2)	1 (0.6)	2 (1.2)	0	0	0
Vesiculobullous rash	0	0	1 (0.6)	0	0	0
Urogenital System	0	0	0	1 (0.6)	0	0
Vaginal moniliasis	0	0	0	1 (0.6)	0	0
	Renally Impaired Cefepime Patients (N=13)			Renally Impaired Ceftazidime Patients (N=10)		
Body System Primary Term ^a	Prob. Rel.	Unknown	Not Rel.	Prob. Rel.	Unknown	Not Rel.
Any Body System	0	1 (7.7)	0	0	1 (10.0)	0
Skin & Appendages	0	1 (7.7)	0	0	1 (10.0)	0
Rash	0	1 (7.7)	0	0	1 (10.0)	0

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

^a The primary ACE terms listed highlight incidence rates of 1% or greater.

The following chart catalogues the comparative data for the greater than and less than 65 year old patients in North America by risk group and body system. The data for Europe are not presented, because too few adverse clinical events were reported. Among high dose patients, the younger patients appeared to experience more adverse clinical events than his/her geriatric counterpart.

**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN RELATIONSHIP
TO CEFEPIME AND CEFTAZIDIME BY RISK GROUP, AGE GROUP AND BODY SYSTEM
ALL NORTH AMERICAN PATIENTS**
Cefepime vs. Ceftazidime
Cefepime Safety Summary

Body System	Number (%) of Patients							
	Low-dose (Cefepime, <2000mg/day; Ceftazidime, <3000mg/day)				High-dose (Cefepime, >2000mg/day; Ceftazidime >3000mg/day)			
	13<65 years		≥ 65 years		13<65 years		≥ 65 years	
	Cefepime N = 536	Ceftazidime N = 257	Cefepime N = 374	Ceftazidime N = 220	Cefepime N = 360	Ceftazidime N = 350	Cefepime N = 221	Ceftazidime N = 190
Any Body System	76 (14)	32 (13)	62 (17)	32 (15)	76 (21)	85 (24)	34 (15)	32 (17)
Body as a Whole	32 (6)	10 (4)	17 (5)	5 (2)	29 (8)	30 (9)	6 (3)	7 (4)
Cardiovascular System	6 (1)	1 (<1)	6 (2)	1 (<1)	3 (<1)	6 (2)	4 (2)	1 (<1)
Digestive System	29 (5)	20 (8)	39 (10)	18 (8)	32 (9)	41 (12)	19 (9)	17 (9)
Hemic & Lymphatic System	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Metabolism & Nutritional Disorders	3 (<1)	2 (<1)	1 (<1)	0	0	7 (2)	3 (1)	0
Musculo-skeletal System	1 (<1)	0	0	0	1 (<1)	0	0	0
Nervous System	15 (3)	3 (1)	15 (4)	8 (4)	17 (5)	20 (6)	10 (5)	2 (1)
Respiratory System	2 (<1)	1 (<1)	4 (1)	3 (1)	8 (2)	8 (2)	3 (1)	2 (1)
Skin & Appendages	10 (2)	4 (2)	5 (1)	7 (3)	24 (7)	20 (6)	9 (4)	11 (6)
Special Senses	2 (<1)	0	0	0	1 (<1)	3 (<1)	0	0
Urogenital System	2 (<1)	2 (<1)	5 (1)	1 (<1)	7 (2)	5 (1)	2 (<1)	3 (2)

**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN RELATIONSHIP
TO CEFEPIME AND CEFTAZIDIME BY RISK GROUP, AGE GROUP AND BODY SYSTEM
ALL NORTH AMERICAN PATIENTS**
Cefepime vs. Ceftazidime
Cefepime Safety Summary

Body System	Number (%) of Patients							
	Renally Impaired				Neutropenic			
	13<65 years		≥ 65 years		13<65 years		≥ 65 years	
	Cefepime N = 14	Ceftazidime N = 21	Cefepime N = 32	Ceftazidime N = 61	Cefepime N = 19	Ceftazidime N = 23	Cefepime N = 3	Ceftazidime N = 2
Any Body System	0	3 (14)	5 (16)	10 (16)	9 (47)	17 (74)	1 (33)	1 (50)
Body as a Whole	0	1 (5)	1 (3)	3 (5)	4 (21)	6 (26)	0	0
Cardiovascular System	0	0	1 (3)	1 (2)	1 (5)	6 (26)	0	0
Digestive System	0	2 (10)	1 (3)	5 (8)	3 (16)	11 (48)	1 (33)	0
Metabolism & Nutritional Disorders	0	0	0	1 (2)	0	2 (9)	0	0
Nervous System	0	0	1 (3)	1 (2)	3 (16)	4 (17)	0	0
Respiratory System	0	0	0	4 (7)	0	4 (17)	0	0
Skin & Appendages	0	0	0	3 (5)	4 (21)	4 (17)	0	1 (50)
Special Senses	0	0	0	1 (2)	0	2 (9)	0	0
Urogenital System	0	0	1 (3)	1 (2)	1 (5)	4 (17)	0	0

The following pages document the data of the comparative studies of North American patients by risk group, sex and body system. In the high dose groups for both drugs, women experience more adverse clinical events. The European data are not presented, because the numbers were too small.

**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN RELATIONSHIP
TO CEFEPIME AND CEFTAZIDIME BY RISK GROUP, SEX AND BODY SYSTEM
ALL NORTH AMERICAN PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Body System	Number (%) of Patients							
	Low-dose (Cefepime, <2000mg/day; Ceftazidime, <3000mg/day)				High-dose (Cefepime, >2000mg/day; Ceftazidime >3000mg/day)			
	Female		Male		Female		Male	
	Cefepime N = 348	Ceftazidime N = 180	Cefepime N = 562	Ceftazidime N = 297	Cefepime N = 219	Ceftazidime N = 213	Cefepime N = 362	Ceftazidime N = 327
Any Body System	61 (18)	28 (16)	77 (14)	36 (12)	56 (26)	60 (28)	54 (15)	57 (17)
Body as a Whole	25 (7)	11 (6)	24 (4)	4 (1)	21 (10)	22 (10)	14 (4)	15 (5)
Cardiovascular System	3 (<1)	1 (<1)	9 (2)	1 (<1)	5 (2)	4 (2)	2 (<1)	3 (<1)
Digestive System	30 (9)	14 (8)	38 (7)	24 (8)	27 (12)	33 (16)	24 (7)	25 (8)
Hemic & Lymphatic System	1 (<1)	0	0	1 (<1)	1 (<1)	0	0	1 (<1)
Metabolism & Nutritional Disorders	1 (<1)	1 (<1)	3 (<1)	1 (<1)	1 (<1)	4 (2)	2 (<1)	3 (<1)
Musculo-skeletal System	0	0	1 (<1)	0	1 (<1)	0	0	0
Nervous System	15 (4)	5 (3)	15 (3)	6 (2)	9 (4)	8 (4)	18 (5)	14 (4)
Respiratory System	1 (<1)	3 (2)	5 (<1)	1 (<1)	2 (<1)	7 (3)	9 (3)	3 (<1)
Skin & Appendages	9 (3)	6 (3)	6 (1)	5 (2)	12 (6)	13 (6)	21 (6)	18 (6)
Special Senses	0	0	2 (<1)	0	1 (<1)	3 (1)	0	0
Urogenital System	3 (<1)	2 (1)	4 (<1)	1 (<1)	7 (3)	6 (3)	2 (<1)	2 (<1)

(continued)
**ADVERSE CLINICAL EVENTS OF PROBABLE OR UNKNOWN RELATIONSHIP
 TO CEFEPIME AND CEFTAZIDIME BY RISK GROUP, SEX AND BODY SYSTEM
 ALL NORTH AMERICAN PATIENTS**
 Cefepime vs. Ceftazidime
 Cefepime Safety Summary

Body System	Number (X) of Patients							
	Renally Impaired				Neutropenic			
	Female		Male		Female		Male	
	Cefepime N = 22	Ceftazidime N = 38	Cefepime N = 24	Ceftazidime N = 44	Cefepime N = 11	Ceftazidime N = 12	Cefepime N = 11	Ceftazidime N = 13
Any Body System	3 (14)	8 (21)	2 (8)	5 (11)	5 (46)	8 (67)	5 (46)	10 (77)
Body as a Whole	0	3 (8)	1 (4)	1 (2)	2 (18)	2 (17)	2 (18)	4 (31)
Cardiovascular System	1 (5)	0	0	1 (2)	0	2 (17)	1 (9)	4 (31)
Digestive System	1 (5)	6 (16)	0	1 (2)	4 (36)	5 (42)	0	6 (46)
Metabolism & Nutritional Disorders	0	0	0	1 (2)	0	2 (17)	0	0
Nervous System	1 (5)	0	0	1 (2)	2 (18)	2 (17)	1 (9)	2 (15)
Respiratory System	0	2 (5)	0	2 (5)	0	1 (8)	0	3 (23)
Skin & Appendages	0	1 (3)	0	2 (5)	2 (18)	0	2 (18)	5 (39)
Special Senses	0	0	0	1 (2)	0	0	0	2 (15)
Urogenital System	0	1 (3)	1 (4)	0	1 (9)	2 (17)	0	2 (15)

Pharmacokinetic Studies

The following charts summarize the clinical adverse events that volunteer subjects experienced during single and multiple dose pharmacokinetic trials. The most common complaint in the single-dose studies was headache. The incidence of headache was 5% (eight subjects) among cefepime/arginine recipients and 3% (two subjects) among cefepime/NaCl recipients. All 10 headaches occurred with 1 g or 2 g single doses. The headaches were mild to moderate in intensity, and all subjects recovered without serious adverse sequelae.

**ACE OF PROBABLE OR UNKNOWN RELATIONSHIP TO CEFEPIME
ALL HEALTHY SUBJECTS, BY TOTAL SINGLE OR REPEATED SINGLE DOSES^a**
Clinical Pharmacokinetic Studies
Cefepime Safety Summary

Body System/ Primary Term	Number (%) of ACE				
	125 mg N = 5	250 mg N = 10	1 g N = 91	2 g N = 144	Total ^b N = 277
Body as a Whole		1 (10)	8 (9)	3 (2)	12 (4)
Allergic Reaction				1 (<1)	1 (<1)
Headache			8 (9)	2 (1)	10 (4)
Pain			1 (1)		1 (<1)
Sensation of Heat		1 (10)			1 (<1)
Cardiovascular					
System	1 (20)				1 (<1)
Murmur	1 (20)				1 (<1)
Digestive System			2 (2)	2 (1)	4 (1)
Diarrhea			1 (1)	2 (1)	3 (1)
Nausea			1 (1)		1 (<1)
Nervous System	1 (20)		2 (2)	1 (1)	4 (1)
Dizziness	1 (20)		2 (2)	1 (1)	4 (1)
Skin & Appendages				2 (1)	2 (1)
Maculopapular rash				1 (1)	1 (<1)
Urticaria				1 (1)	1 (<1)
Special Senses				2 (1)	2 (1)
Blurred Vision				1 (1)	1 (<1)
Taste Perversion				1 (1)	1 (<1)

^a Subjects given a single dose, or two doses one week apart.

^b Included in the total are 27 subjects who received 62.5 mg, 500 mg, or various doses (0.25 g, 0.5 g, 1 g, 2 g), but who did not report any ACE that were considered to be of probable or unknown relationship to cefepime. NOT included in this total are 59 renally impaired and 12 hepatically impaired subjects, and 20 subjects in drug-interaction studies.

The following table documents the adverse clinical events that occurred in multiple dose pharmacokinetic studies. The most frequent adverse clinical events of probable or unknown relationship in subjects who received multiple doses of cefepime in the pharmacokinetic trials were headache in 13 (15%) subjects, diarrhea in 11 (13%), back pain in seven (8%), abdominal pain in six (7%), asthenia in five (6%), and rash in five (6%). There appeared to be no increased incidence of events in subjects when they were evaluated by cefepime formulation received, by age, or by sex.

NOTE: There appear to be numerical errors (See N's) in the applicant table given below.

**ACE OF PROBABLE OR UNKNOWN RELATIONSHIP TO CEFEPIME
ALL HEALTHY SUBJECTS, BY MULTIPLE DOSES^a**
Clinical Pharmacokinetic Studies
Cefepime Safety Summary

Body System/ Primary Term	Number (%) of ACE						Total N = 86
	250 mg Q8h N = 11	500 mg Q8h N = 23	1 g Q12h N = 7	1 g Q8h N = 15	2 g Q8h N = 9	4 g Q8h N = 21	
Body as a Whole	2 (18)	11 (48)	7 (33)	1 (14)	3 (20)		24 (28)
Asthenia	1 (9)		4 (19)				5 (6)
Chills		4 (17)					4 (5)
Fever		4 (17)					4 (5)
Headache	1 (9)	4 (17)	5 (24)	1 (14)	2 (13)		13 (15)
Pain, Arm(s)		2 (9)			1 (7)		3 (4)
Pain, Back		6 (26)			1 (7)		7 (8)
Pain, Body		2 (9)					2 (2)
Pain, Leg(s)		4 (17)					4 (5)
Sensation of Heat		3 (13)					3 (4)
Cardiovascular System		3 (13)					3 (4)
Pain, Chest		1 (4)					1 (1)
Syncope		1 (4)					1 (1)
Vasodilation		1 (4)					1 (1)
Digestive System	1 (9)	3 (13)	4 (19)	2 (29)	4 (27)	2 (22)	16 (19)
Anorexia		1 (4)					1 (1)
Diarrhea	1 (9)	1 (4)	3 (14)	2 (29)	3 (20)	1 (11)	11 (13)
Dry Mouth	1 (9)					1 (11)	2 (2)
Dyspepsia			1 (5)				1 (1)
Nausea		1 (4)			1 (7)		2 (2)
Pain, Abdomen		3 (13)	1 (5)		2 (13)		6 (7)
Musculoskeletal System		3 (13)					3 (4)
Myalgia		3 (13)					3 (4)
Nervous System	2 (18)	2 (9)					4 (5)
Confusion		1 (4)					1 (1)
Dizziness	2 (18)						2 (2)
Drowsiness	1 (9)						1 (1)
Twitching		1 (4)					1 (1)
Respiratory System		1 (4)					1 (1)
Pain, Throat		1 (4)					1 (1)
Skin & Appendages		1 (4)		1 (14)	1 (7)	2 (22)	5 (6)
Rash		1 (4)		1 (14)	1 (7)	2 (22)	5 (6)
Special Senses	1 (9)	3 (13)	1 (5)				5 (6)
Eye Disorder ^b		2 (9)					2 (2)
Eye Pain	1 (9)	1 (4)					2 (2)
Visual Field Defect			1 (5)				1 (1)

^a Subjects given multiple doses Q12h or Q8h.

^b Not otherwise specified.

The following table illustrates that subjects who received cefepime did experience more adverse events than those individuals that received placebo. There was one center that reported a cluster (411-058) of subjects who reported "flu-like" symptoms. Adverse clinical events from placebo and drug study patients are presented below.

**ACE OF PROBABLE OR UNKNOWN RELATIONSHIP
IN SUBJECTS WHO RECEIVED PLACEBO OR CEFEPIME
IN MULTIPLE-DOSE, PLACEBO-CONTROLLED STUDIES**
Clinical Pharmacokinetic Studies
Cefepime Safety Summary

Body System/ Primary Term	Placebo Subjects N = 35	All Cefepime Subjects N = 86	All Cefepime Subjects Minus Study 411-058 ^a N = 78
Body as a Whole			
Asthenia	3 (9)	5 (6)	5 (6)
Chills		4 (5)	
Fever		4 (5)	2 (3)
Headache	2 (6)	13 (15)	9 (12)
Pain, Arms		3 (4)	1 (1)
Pain, Back		7 (8)	2 (3)
Pain, Body		2 (2)	1 (1)
Pain, Leg(s)		4 (5)	1 (1)
Sensation of Heat		3 (4)	1 (1)
Cardiovascular System			
Pain, Chest		1 (1)	
Phlebitis	1 (3)		
Syncope		1 (1)	
Vasodilation		1 (1)	1 (1)
Digestive System			
Anorexia		1 (1)	
Diarrhea	2 (6)	11 (13)	11 (14)
Dry Mouth		2 (2)	2 (3)
Dyspepsia		1 (1)	1 (1)
Nausea	1 (3)	2 (2)	1 (1)
Pain, Abdomen		6 (7)	5 (6)
Musculoskeletal System			
Myalgia		3 (4)	1 (1)
Nervous System			
Confusion		1 (1)	1 (1)
Dizziness		2 (2)	2 (3)
Drowsiness		1 (1)	1 (1)
Twitching		1 (1)	
Respiratory System			
Pain, Throat		1 (1)	
Skin & Appendages			
Rash		5 (6)	5 (6)
Special Senses			
Eye Disorder		2 (2)	1 (1)
Eye Pain		2 (2)	1 (1)
Photophobia	1 (3)		
Visual Field Defect		1 (1)	1 (1)

^a Numbers in this column include all subjects who received cefepime, excluding eight subjects in Study 411-058 who experienced flu-like symptoms.

Compassionate Use Studies

There were four adverse clinical events reported in two of four patients enrolled in these studies. The four events were as follows: convulsion (moderate severity), hypertension (moderate), abdominal pain (mild) and a respiratory disorder (mild). No event was thought to be related to study drug.

Japanese Studies

The following information was available from the Japanese studies. The Japanese studies enrolled 1,730 cefepime patients; the Japanese committee excluded 89 patients from their safety analysis. Patients were excluded for reasons other than safety considerations. The table that follows includes the incidence of adverse events by body system, dose group, and relationship to cefepime for the 1,646 cefepime courses evaluated for safety.

INCIDENCE OF ACE BY BODY SYSTEM, DOSE GROUP,
AND RELATIONSHIP TO CEFEPIME
Cefepime Studies in Japan
Additional Safety Patients

Body System/Primary Term	Number of Events					
	1-2 g/day (N=1629)		2-6 g (N=17)		Total (N=1646)	
	Rel.	Not Rel.	Rel.	Not Rel.	Rel.	Not Rel.
Body as a Whole						
Fever	9				9	
Headache	1				1	
Discomfort during infusion	1				1	
Lumbago		1				1
Chills			1			1
Cardiovascular System						
Loss of Consciousness ¹	1				1	
Hypotension ^{1,2}	2				2	
Facial Flushing	2				2	1
Digestive System						
Diarrhea	5	1			5	1
Nausea	4				4	
Abdominal Pain	3				3	
Soft Stools	3				3	
Anorexia	1		1		1	1
Paralytic Ileus	1				1	
Vomiting	1				1	
Hemic System						
Pancytopenia	1				1	
Tremors in Both Hands	1				1	
Insomnia		1				1
Skin and Appendages						
Rash	16				16	
Itching	2				2	
Facial Erythema	1				1	
Labial rash/Swelling	1				1	
Urticaria	1				1	
Urogenital System						
Theruria	1				1	
Vulvovaginal Candidiasis	1				1	
Total						
No. of Occurrences of Adverse Events	58	3	0	2	59	5
No. of Cases with Adverse Events (%)	46 (2.8)	2 (0.1)	0	1	46 (2.8)	3 (0.2)

NOTE: Rel. = Adverse event probably related, possibly related, or of unknown relationship to study drug; Not Rel. = Adverse event not related to study drug.
¹ Patient who had encephalitis.
² Patient who had anaphylaxis.

Summary

Adverse clinical events were analyzed by the applicant by various permutations in the preceding charts. The most common body systems apparently related to cefepime administration are the body system as a whole, the digestive system, the nervous system and the integument. The most frequent events which were considered to be of probable or unknown relationship to cefepime were headache, diarrhea, nausea and rash.

The following adverse clinical events of either probable or unknown relationship occurred in greater than or equal to 0.3% cefepime patients: asthenia, fever, headache, pain, chest pain, constipation, diarrhea, dyspepsia, nausea, abdomen pain, vomiting, anxiety, dizziness, insomnia, paresthesia, pruritus, rash, and sweating. At a minimum, these terms should be included in the adverse events section of the proposed label.

SAFETY UPDATES

First Safety Update

At the time of the first safety update, three hundred ninety-one patients (396 courses) had received cefepime therapy in North American clinical trials since the NDA cut-off date. It should be noted that the incidence of adverse clinical events regardless of relationship in these patients were higher in this submission than in the population analyzed in the NDA. Two factors accounted for this increased incidence in adverse clinical events: a) the trials that were conducted post-NDA enrolled patients with an increased severity of illness (e.g cancer patients with fever and neutropenia) and b) the patients received higher dosages (6g/day of cefepime) and/or increased duration of therapy.

There were 249 (249/396 = 63%) adverse clinical events reported for cefepime in these trials. The adverse clinical events of probable or unknown relationship to the study drug which were reported at a frequency of 1% or greater were as follows: asthenia (5 cases or 1.3%); fever (12 cases or 3.0%); headache (19 cases or 4.8%); chest pain (6 cases or 1.5%); constipation (5 cases or 1.3%); diarrhea (40 cases or 10.1%); nausea (28 cases or 7.1%); abdominal pain (17 cases or 4.3 %); vomiting (24 cases or 6.1%); confusion (5 cases or 1.3%); dizziness (6 cases or 1.5%); insomnia (7 cases or 1.8%); hyperventilation (5 cases or 1.3%); pruritus (8 cases or 2.0%); rash (29 cases or 7.3%); sweating (4 cases or 1.0%); taste perversion (4 cases or 1.0%); and urine abnormality (4 cases or 1.0%). The body systems most frequently affected by adverse clinical events of probable or unknown relationship to the drug regimen were the digestive system (78/396 = 19.7%), the body as a whole (49/396 = 12.4%) and the integument (44/396 = 11.1%).

In comparative North American studies, 76.2% (154/202) of cefepime patients reported an adverse clinical event as compared to 67.7% (132/195) of ceftazidime patients. The most common adverse clinical events with any relationship to study drugs were diarrhea (cefepime 18.3%, ceftazidime 11.3%); headache (cefepime 16.3%, ceftazidime 11.3%); nausea (cefepime 12.4%, ceftazidime 12.3%); vomiting (cefepime 12.9%, ceftazidime 11.3%); abdominal pain (cefepime 10.9%, ceftazidime 7.7%); rash (cefepime 11.4%, ceftazidime 6.2%); and tachycardia (cefepime 6.9%, ceftazidime 10.3%).

Of the 112 cefepime courses that were administered in Europe, there were seven adverse clinical events reported in seven patients. Three (rashes) of these adverse clinical events were considered to be probably related to the study drug.

There were seven adverse events reported for the 15 pharmacokinetic study patients during this period. Six of the seven were judged to be unrelated to the study drug. The only event of unknown relationship to study drug was an episode of mild nausea.

In the compassionate use treatment protocol, 19 of 23 patients reported at least adverse clinical event. A total of 56 events were reported. The only clinical events attributed directly to cefepime treatment were rash, pruritus and taste perversion. Rash occurred in three patients.

In the blinded studies, twenty (74.1%) of the twenty seven patients reported at least one adverse clinical event during the conduct of the study. Of the 58 events reported, 13 (22%) were considered to be of probable or unknown relationship to study drug. The most frequently reported event which was of probable or unknown relationship to study drug was diarrhea (three patients).

Second Safety Update

There were 500 patients who received 508 cefepime courses in the post-NDA North American clinical efficacy studies. Most patients were seriously ill and received maximum dosing regimens (such as 2g TID of cefepime). Twenty-two percent of patients were immunocompromised patients being treated for fever and neutropenia. More than a third of the enrolled (189/500 = 37.8%) patients were pediatric (2 months to 12 years); one hundred ten (21.7%) were over 65 years of age. The following data are the cumulative experience of the post-NDA studies; however, it should be noted that the composition of the study population was different. In the NDA population, there were a handful of pediatric patients; there were a significantly lower proportion of extremely ill patients; and there were few patients treated with thrice daily dosing.

Adverse clinical events regardless of relationship were reported in 63.6 (323/508) of the post-NDA North American patients. Adverse events of unknown or probable relationship occurred in 37.2% of cefepime courses.

In the post-NDA studies, the body system most frequently affected by adverse clinical events of probable or unknown relationship to cefepime was the digestive system (21.9%), followed by the body as a whole (12.0%) and the skin (10.8%). The most frequently reported adverse clinical events were diarrhea (10.8%), rash (7.1%), nausea (5.9%), vomiting (5.7%), and headache (4.7%).

The summary data for adverse clinical events of probable or unknown relationship that were reported in 1.0% or more of all 500 post-NDA North American cefepime patients are seen on the following page.

**ADVERSE CLINICAL EVENTS
BY RELATIONSHIP TO CEFEPIME AND BODY SYSTEM
POST NDA NORTH AMERICAN CEFEPIME COURSES
Cefepime Second Safety Update**

Body System Primary Term ^a	----- Number (%) of Cefepime Courses ----- (N = 508)				
	Prob. Rel.	Unknown	Total	Not Rel.	Grand Total
Any Body System	60(11.8)	129(25.4)	189(37.2)	134(26.4)	323(63.6)
Body as a Whole	9 (1.8)	52(10.2)	61(12.0)	89(17.5)	150(29.5)
Asthenia	-	6 (1.2)	6 (1.2)	5 (1.0)	11 (2.2)
Fever	7 (1.4)	6 (1.2)	13 (2.6)	15 (3.0)	28 (5.5)
Headache	2 (0.4)	22 (4.3)	24 (4.7)	28 (5.5)	52(10.2)
Cardiovascular System	1 (0.2)	21 (4.1)	22 (4.3)	57(11.2)	79(15.6)
Chest Pain	-	10 (2.0)	10 (2.0)	10 (2.0)	20 (3.9)
Tachycardia	1 (0.2)	7 (1.4)	8 (1.6)	10 (2.0)	18 (3.5)
Digestive System	31 (6.1)	80(15.7)	111(21.9)	81(15.9)	192(37.8)
Constipation	-	10 (2.0)	10 (2.0)	15 (3.0)	25 (4.9)
Diarrhea	22 (4.3)	33 (6.5)	55(10.8)	26 (5.1)	81(15.9)
Nausea	7 (1.4)	23 (4.5)	30 (5.9)	24 (4.7)	54(10.6)
Pain Abdomen	-	20 (3.9)	20 (3.9)	16 (3.1)	36 (7.1)
Vomiting	4 (0.8)	25 (4.9)	29 (5.7)	32 (6.3)	61(12.0)
Nervous System	1 (0.2)	25 (4.9)	26 (5.1)	62(12.2)	88(17.3)
Confusion	-	7 (1.4)	7 (1.4)	14 (2.8)	21 (4.1)
Dizziness	-	6 (1.2)	6 (1.2)	13 (2.6)	19 (3.7)
Insomnia	-	10 (2.0)	10 (2.0)	8 (1.6)	18 (3.5)
Respiratory System	3 (0.6)	19 (3.7)	22 (4.3)	87(17.1)	109(21.5)
Dyspnea	1 (0.2)	4 (0.8)	5 (1.0)	19 (3.7)	24 (4.7)
Hyperventilation	-	6 (1.2)	6 (1.2)	9 (1.8)	15 (3.0)
Skin & Appendages	25 (4.9)	30 (5.9)	55(10.8)	33 (6.5)	88(17.3)
Erythema	1 (0.2)	4 (0.8)	5 (1.0)	10 (2.0)	15 (3.0)
Pruritus	3 (0.6)	6 (1.2)	9 (1.8)	7 (1.4)	16 (3.1)
Rash	21 (4.1)	15 (3.0)	36 (7.1)	15 (3.0)	51(10.0)
Special Senses,	2 (0.4)	9 (1.8)	11 (2.2)	9 (1.8)	21 (4.1)
Taste Perversion	2 (0.4)	3 (0.6)	5 (1.0)	-	5 (1.0)
Urogenital System	7 (1.4)	13 (2.6)	20 (3.9)	23 (4.5)	43 (8.5)

NOTE: Prob. Rel. = Probably Related; Not Rel. = Not Related.

^a The primary ACE terms listed highlight incidence rates of 1% or greater.

^b Includes one ACE for which relationship to cefepime was not recorded.

The applicant divided the post-NDA patients into three risk groups - high dose (2g cefepime BID), maximum dose (2g cefepime TID) and the neutropenic group. In the high dose group (51 courses), adverse clinical events of probable or unknown relationship that occurred most frequently ($\geq 4\%$) were nausea (10 cases or 19.6%); vomiting (6 cases or 11.8%); chest pain (4 cases or 7.8%); pruritus (4 cases or 7.8%); and insomnia (3 cases or 5.9%). In the maximum dose group (344 courses), adverse clinical events of probable or unknown relationship that occurred most frequently ($\geq 4\%$) were diarrhea (28 cases or 8.1%); rash (19 cases or 5.5%); and headache (18 cases or 5.2%). Of note vaginal yeast infections were reported in 5/344 or 1.4% courses of treatment; at least three were judged as probably related. In the neutropenic group (113 courses), adverse clinical events of probable or unknown relationship that occurred most frequently ($\geq 4\%$) were nausea (12 cases or 10.6%); vomiting (11 cases or 9.7%); abdominal pain (9 cases or 8.0%); rash (15 cases or 13.3%); and diarrhea (25 cases or 22.1%). In the applicant's risk assessment, pediatric patients experienced more diarrhea and rash than adults. The elderly had a higher incidence of tachycardia, confusion and hyperventilation. When the risk analysis examined gender, the applicant determined that the outcome was less clear. Women in the maximum treatment group experienced more (41.7%) adverse clinical events than their male counterparts (31.8%). However, neutropenic men had more (43.3%) events than women patients (34.8%).

The majority of cefepime clinical studies were randomized, comparative trials in which ceftazidime was the comparative agent. Post NDA, two studies enrolled a total of 549 patients (273 cefepime and 276 ceftazidime). All adult cefepime dosing was thrice daily (maximum) and pediatric dosing was 150 mg/kg/day. It should be noted that ceftazidime was given at its usual recommended 2g TID dosing. In one of the fever and neutropenia trials, patients were allowed to be randomized for multiple episodes and therefore 126 patients received 161 courses of treatment. However, the data that was presented by the applicant contained only the first enrollment of each of these patients.

The frequency and pattern of adverse clinical events were generally comparable for cefepime and ceftazidime patients. Adverse events of probable or unknown relationship occurred in 42.1% and 3.1% of the cefepime and ceftazidime patients, respectively. The most frequent categories of clinical events seen with cefepime and ceftazidime were: diarrhea (10.6% and 9.4%, respectively) and headaches (7.0% and 6.2%), respectively. Further details are seen on the chart of the following page.

**ADVERSE CLINICAL EVENTS
POST NDA NORTH AMERICAN CEFEPIME COURSES
Cefepime Second Safety Update**

Body System Primary Term	Number (%) of Cefepime Courses (N = 508)				
	Prob. Rel.	Unknown	Total	Not Rel.	Grand Total
CEFEPIE (N = 273)					
Any Body System	25 (9.2)	90(33.0)	115(42.1)	92(33.7)	207(75.8)
Body as a Whole	5 (1.8)	39(14.3)	44(16.1)	62(22.7)	106(38.8)
Asthenia	-	5 (1.8)	5 (1.8)	5 (1.8)	10 (3.7)
Fever	4 (1.5)	2 (0.7)	6 (2.2)	10 (3.7)	16 (5.9)
Headache	2 (0.7)	17 (6.2)	19 (7.0)	19 (7.0)	38(13.9)
Cardiovascular System	1 (0.4)	16 (5.9)	17 (6.2)	43(15.8)	60(22.0)
Chest Pain	-	6 (2.2)	6 (2.2)	6 (2.2)	12 (4.4)
Tachycardia	1 (0.4)	7 (2.6)	8 (2.9)	10 (3.7)	18 (6.6)
Digestive System	7 (2.6)	57(20.9)	64(23.4)	56(20.5)	120(44.0)
Constipation	-	7 (2.6)	7 (2.6)	11 (4.0)	18 (6.6)
Diarrhea	6 (2.2)	23 (8.4)	29(10.6)	21 (7.7)	50(18.3)
Nausea	-	12 (4.4)	12 (4.4)	16 (5.9)	28(10.3)
Pain Abdomen	-	14 (5.1)	14 (5.1)	11 (4.0)	25 (9.2)
Vomiting	-	14 (5.1)	14 (5.1)	18 (6.6)	32(11.7)
Nervous System	1 (0.4)	19 (7.0)	20 (7.3)	46(16.8)	66(24.2)
Confusion	-	7 (2.6)	7 (2.6)	12 (4.4)	19 (7.0)
Dizziness	-	3 (1.1)	3 (1.1)	12 (4.4)	15 (5.5)
Insomnia	-	7 (2.6)	7 (2.6)	7 (2.6)	14 (5.1)
Respiratory System	2 (0.7)	17 (6.2)	19 (7.0)	52(19.0)	71(26.0)
Dyspnea	1 (0.4)	4 (1.5)	5 (1.8)	13 (4.8)	18 (6.6)
Hyperventilation	-	6 (2.2)	6 (2.2)	8 (2.9)	14 (5.1)
Skin & Appendages	10 (3.7)	16 (5.9)	26 (9.5)	25 (9.2)	51(18.7)
Erythema	1 (0.4)	3 (1.1)	4 (1.5)	6 (2.2)	10 (3.7)
Pruritus	1 (0.4)	3 (1.1)	4 (1.5)	6 (2.2)	10 (3.7)
Rash	8 (2.9)	6 (2.2)	14 (5.1)	12 (4.4)	26 (9.5)
Special Senses	1 (0.4)	7 (2.6)	8 (2.9)	7 (2.6)	16 (5.9)
Taste Perversion	1 (0.4)	3 (1.1)	4 (1.5)	-	4 (1.5)
Urogenital System	4 (1.5)	9 (3.3)	13 (4.8)	17 (6.2)	30(11.0)
CEFTAZIDIME (N = 276)					
Any Body System	28(10.1)	80(29.0)	108(39.1)	85(30.8)	193(69.9)
Body as a Whole	2 (0.7)	31(11.2)	33(12.0)	58(21.0)	91(33.0)
Asthenia	-	5 (1.8)	5 (1.8)	6 (2.2)	11 (4.0)
Fever	-	6 (2.2)	6 (2.2)	3 (1.1)	9 (3.3)
Headache	1 (0.4)	16 (5.8)	17 (6.2)	13 (4.7)	30(10.9)
Cardiovascular System	-	15 (5.4)	15 (5.4)	41(14.9)	56(20.3)
Chest Pain	-	2 (0.7)	2 (0.7)	10 (3.6)	12 (4.3)
Tachycardia	-	6 (2.2)	6 (2.2)	18 (6.5)	24 (8.7)
Digestive System	13 (4.7)	41(14.9)	54(19.6)	49(17.8)	103(37.3)
Constipation	-	2 (0.7)	2 (0.7)	6 (2.2)	8 (2.9)
Diarrhea	6 (2.2)	20 (7.2)	26 (9.4)	7 (2.5)	33(12.0)
Nausea	-	14 (5.1)	14 (5.1)	17 (6.2)	31(11.2)
Pain Abdomen	1 (0.4)	4 (1.4)	5 (1.8)	17 (6.2)	22 (8.0)
Vomiting	1 (0.4)	11 (4.0)	12 (4.3)	15 (5.4)	27 (9.8)
Nervous System	-	15 (5.4)	15 (5.4)	39(14.1)	54(19.6)
Confusion	-	3 (1.1)	3 (1.1)	8 (2.9)	11 (4.0)
Dizziness	-	3 (1.1)	3 (1.1)	6 (2.2)	9 (3.3)
Insomnia	-	1 (0.4)	1 (0.4)	7 (2.5)	8 (2.9)
Respiratory System	-	16 (5.8)	16 (5.8)	56(20.3)	72(26.1)
Dyspnea	-	1 (0.4)	1 (0.4)	12 (4.3)	13 (4.7)
Hyperventilation	-	4 (1.4)	4 (1.4)	17 (6.2)	21 (7.6)
Skin & Appendages	8 (2.9)	14 (5.1)	22 (8.0)	26 (9.4)	48(17.4)
Erythema	2 (0.7)	1 (0.4)	3 (1.1)	9 (3.3)	12 (4.4)
Pruritus	1 (0.4)	2 (0.7)	3 (1.1)	7 (2.5)	9 (3.6)
Rash	5 (1.8)	5 (1.8)	10 (3.6)	5 (1.8)	15 (5.4)
Special Senses	-	1 (0.4)	1 (0.4)	10 (3.6)	11 (4.0)
Taste Perversion	-	-	0	-	0
Urogenital System	6 (2.2)	12 (4.3)	18 (6.5)	13 (4.7)	31(11.2)

There were a total of 15 pharmacokinetic patients studied since the NDA was submitted; the adverse clinical events were previously discussed in the first safety update section.

In the European studies, 16 adverse clinical events occurred in 14 of the 192 (7.3%) patients. There were 10 events of probable or unknown relationship: rash (3 patients), diarrhea (three patients), nausea/pyrosis (one patient) and renal dysfunction (one patient). The latter patient also received amikacin.

In the compassionate use treatment protocol, there were 24 patients treated since the NDA. Nineteen of these patients were infants. The only reported adverse clinical events that were judged related to cefepime were rash, pruritus, and taste perversion.

Of the 40 patients enrolled in the blinded A1411-160 study, 29 (73%) patients experienced an adverse event. Of the adverse clinical events that were thought to be of probable or of unknown relationship to study, only diarrhea (5 patients), headache (2 patients) and pruritus (2 patients) were reported more than once.

FINAL SAFETY UPDATE

The final safety update was a brief summary of the clinical trials that were conducted in North America and Europe during the first 10 months of 1993. Nine hundred sixty-seven courses of cefepime were administered. In the clinical trials, 122 patients experiences 190 adverse clinical events. When tabulated by dosage group, the highest incidence of serious adverse events occurred in the high (2g BID) and maximum dosage groups (2g TID). Of the 190 adverse events, only four were considered possible related to cefepime administration. The four events were described as thrombophlebitis, renal insufficiency, hepatic insufficiency and hypoglycemia. A review of the applicant's narrative (the case report form was not submitted) suggests that the hepatic insufficiency and hypoglycemia were not related.

In support of a revision of the proposed label, the applicant presented a summary analysis of "selected" adverse events of probable or unknown origin for the 3587 courses of cefepime administered in North America prior to December 1992. The summary stated that the incidence of adverse clinical events was dose related. For example, one of the most frequently reported adverse event is headache. The incidence of headache in patients treated with cefepime 1g BID was 2.4%; it rose to 7.3% in patients treated with cefepime 2g TID.

**SELECTED ADVERSE EVENTS
OF PROBABLE OR UNKNOWN RELATIONSHIP TO CEFEPIME**

	LOW DOSE <2g/d N = 1502	HIGH DOSE 4g/d N = 1623	MAX DOSE (6g/d) N = 302	NEUTROPENIA 6g/d N = 160	ALL GROUPS N = 3587
Headache	36 (2.4%)	67 (3.5%)	22 (7.3%)	8 (5.0%)	123 (3.4%)
DIGESTIVE SYST					
Constipation	12 (0.8%)	27 (1.7%)	8 (2.6%)	3 (1.9%)	50 (1.4%)
Diarrhea	22 (1.5%)	69 (3.6%)	20 (6.6%)	29 (18.1%)	130 (3.6%)
Nausea	26 (1.7%)	60 (3.1%)	9 (3.0%)	23 (14.4%)	108 (3.0%)
Abdomen Pain	10 (0.7%)	16 (1.0%)	7 (2.3%)	9 (5.6%)	42 (1.2%)
Vomiting	18 (1.2%)	37 (2.3%)	11 (3.6%)	18 (11.2%)	84 (2.3%)
HYPERSENSITIVITY					
Pruritus	9 (0.6%)	30 (1.8%)	4 (1.3%)	4 (2.5%)	47 (1.3%)
Rash	18 (1.2%)	41 (2.5%)	14 (4.6%)	26 (16.2%)	99 (2.8%)
Urticaria	1 (<0.1%)	4 (0.2%)	1 (0.3%)	0	6 (0.2%)
Fever	6 (0.4%)	12 (0.7%)	4 (1.3%)	2 (1.2%)	24 (0.7%)
ANY ACE	188 12.5%	324 20.0%	114 37.7%	70 43.8%	696 19.4%

N = Number of Treatment courses (Note: A treatment course can be associated with ≥1 adverse event.)

In the supporting database of 3587 courses administered to adults in North America, the following adverse clinical events of either probable or unknown relationship were reported at a frequency of greater than or equal to 0.3%: asthenia (0.5%), fever (0.7%), headache (3.4%), pain (0.6%), back pain (0.3%), chest pain (0.6%), tachycardia (0.4%), constipation (1.4%), diarrhea (3.6%), dyspepsia (0.5%), nausea (3.0%), abdomen pain (1.2%), vomiting (2.3%), peripheral edema (0.3%), anxiety (0.4%), confusion (0.4%), dizziness (0.9%), insomnia (1.0%), paresthesia (0.4%), cough (0.3%), dyspnea (0.3%), throat pain (0.3%), pruritus (1.3%), rash (2.8%), sweating (0.4%) and infection (0.3%).

SPECIAL ISSUES - The applicant chose to examine three issues of safety which are described below:

Anaphylaxis

In the NDA, the applicant searched for terms in their database which specified symptoms of allergic phenomena. Three patients from the clinical efficacy studies, one patient from the pharmacokinetics studies and two patients from the Japanese studies experience anaphylaxis. Five of these patients received cefepime and one received ceftazidime. All recovered.

Clinical efficacy studies:	2/4442 (0.04%) - cefepime; 1/1456 (0.07%) - ceftazidime
Pharmacokinetic studies:	1/470 (0.2%)
Compassionate Use:	0/4 (0%)
Japanese studies:	2/1730 (0.1%)
Total for cefepime:	5/6646 (0.07%)

In the safety updates, there were two (2/716 = 0.3%) additional patients with anaphylactoid reactions.

Seizures

There were 17 patients identified by the applicant who had a seizure during treatment in the clinical efficacy studies. The reviewer identified two (1 cefepime and one ceftazidime) additional patients. There were no patients who experienced a seizure in Japan or in any pharmacokinetic study. One patient (of four) in the individual treatment protocol also had a seizure. Of these 20 patients, 13 had received treatment with cefepime and 7 had received treatment with ceftazidime. Therefore, the incidence of seizure in the clinical studies was 13/4446 = 0.3% for cefepime and 7/1456 = 0.5% for ceftazidime. At least 13/20 of the patients had a history of seizure or *prior* central nervous system injury. Although the investigators did assess the relationship of the incident to administration of the drug, it is difficult to interpret. For example, a drug could lower seizure thresholds and thus be related.

In the safety updates, there were three cefepime patients (3/716 = 0.4%) who experience seizure activity.

Bleeding Problems

Because some cephalosporins have been associated with bleeding diatheses, the applicant examined any adverse clinical events that indicated abnormal bleeding. In the comparative trials, 5 (5/2032 = 0.3%) cefepime patients had epistaxis; 12 (12/2032 = 0.6%) had a gastrointestinal hemorrhage; and 5 (5/2032 = 0.3%) cefepime patients had occult blood in the stool. Eight ceftazidime (8/1456 = 0.5%) had epistaxis; five (5/1456 = 0.3%) ceftazidime patients had a gastrointestinal hemorrhage; and five (5/1456 = 0.3%) had occult blood in the stool.

SUMMARY

The adverse event profile of cefepime appears to be similar to other cephalosporin. The incidence of adverse clinical events appears to be related to dose.

LABORATORY ABNORMALITIES

NDA

The following is a presentation of the applicant's summary data with regard to the "clinically relevant" laboratory changes seen during the administration of cefepime and comparator drugs. The tables that follow are derived from the applicant's integrated summary of safety and safety updates. Unlike the tables of adverse clinical events; the reviewer could not locate the supporting appendix (equivalent to appendices G22 and G23 found in each study report) for these tables in the integrated summary of safety. Therefore, these specific tables could not be validated by the reviewer. However, it should be noted that the information with regard to relative changes of laboratory values was presented for each study in the NDA and for each indication in NDA amendments.

Initially, the reviewer did not have any "raw" laboratory data to examine electronically; the ability to manipulate the actual data points would have facilitated the validation of the applicant's tables as well as would have provided the ability to review additional aspects of the data. At the reviewer's request, the applicant submitted actual laboratory values and other descriptive information in SAS files for all North American comparative clinical efficacy trials. The FDA statistician and the two FDA medical reviewers compiled independent tables to examine aspects of the laboratory data other than those already provided in the NDA. These tables follow the discussion of the applicant's summary tables.

At the outset of the trials, the applicant requested laboratory testing for all patients at three intervals: at entry, during the study and post-treatment. Any abnormal value was to have been followed to resolution. Laboratory data assessments were evaluated by comparing during- and post-treatment values with pre-treatment values. Patients with normal pre-treatment laboratory results were examined for evidence of change. A patient's most severe during- or post treatment value was recorded in the analysis. Patients with abnormal pre-treatment values were also evaluated for progression of their abnormal laboratory finding.

The applicant defined three classes of change in their analyses. A patient who was normal could have a mild change (Class II), a moderate change (Class III) or a severe (Clinically relevant) change. The summary data that follows present only the changes that the applicant defined as "clinically relevant." The definitions are as follows:

"For safety analyses, the laboratory tests listed below were selected as the most appropriate indicators of toxicity. To identify clinical abnormalities, "direction of toxicity" was defined for each of the selected tests as follows (clinically relevant levels are also provided for each unit):

<u>Below lower limit of normal for:</u>	<u>Clinically Relevant</u>	<u>Above upper limit of normal for:</u>	<u>Clinically Relevant</u>
Hematocrit:	≤ 23.9 vol %	Alkaline phosphatase:	≥ 3 x UNL
Neutrophil:	≤ 500/cmm	AST, ALT:	≥ 3 x UNL
WBC:	≤ 2000/cmm	Total bilirubin:	≥ 3.0 mg/dL
Platelet:	≤ 50,000/cmm	BUN:	≥ 50.0 mg/dL
		Creatinine:	≥ 3.0 mg/dL
		Prothrombin:	
		North America	> 15 sec
		Europe	> 25 sec
		PTT:	
		North America	> 45 sec
		Europe	> 90 sec
		Eosinophil:	≥ 1000/cmm
<u>Outside normal limits for:</u>	<u>Clinically Relevant</u>		
Sodium:	≤ 119 or ≥ 160 mEq/dL		
Potassium:	≤ 2.4 or ≥ 6.5 mEq/dL		
Calcium:	≤ 7.0 or ≥ 12.0 mg/dL		
Phosphorus:	≤ 1.7 or ≥ 6.1 mg/dL		

For direct Coombs' test, clinically relevant was defined as a positive test result.

Most laboratories reported neutrophil and eosinophil counts as percents of total white blood cells. The following algorithms were used to compare the patient results with the clinically relevant markers:

Absolute eosinophil count = % eosinophils x total WBC count.

Absolute neutrophil count = sum (% neutrophils and % of all immature neutrophilic forms) x total WBC count.

The following definitions apply to laboratory values:

Abnormal: Outside the normal range limit in the direction of toxicity.

Normal: All other laboratory values were defined to be normal."

NDA:

The following table catalogues the laboratory tests which became clinically relevant values in patients with normal baseline values, by risk group for all cefepime courses. Although obtained only in North American studies, the applicant noted that the most common laboratory abnormality was a positive Coombs' test. The next most frequently occurring abnormalities were elevations in the liver transaminases (SGOT and SGPT).

Partial prothrombin times are presented separately for Europe and North America, because they are calculated differently in each location. The applicant found that hematologic and coagulation abnormalities occurred in less than 2% of patients. Elevations in renal function tests were present in less than 0.5% of patients. Electrolyte changes were less than 0.5% for all but phosphorus. The meaning of the abnormal phosphorus levels was unclear to the applicant and the reviewer.

The applicant defined four treatment groups: low dose patients (1g BID), high dose patients (2g BID), renally impaired patients and neutropenic patients.

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING NORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT
DURING- OR POST-TREATMENT RESULT, BY RISK GROUP AND LABORATORY TEST
ALL CEFEPIME COURSES**
Cefepime Safety Summary

Laboratory Test	----- Number (%) of Cefepime Courses -----			
	Low-dose ($\leq$ 2000 mg/day)		High-dose ($>$ 2000 mg/day)	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	985	2 (0.2)	876	2 (0.2)
Platelet count	1540	3 (0.2)	1513	6 (0.4)
WBC	1769	0	1852	12 (0.6)
Neutrophil count	1561	3 (0.2)	1570	10 (0.6)
Eosinophil count	1419	18 (1.3)	1474	24 (1.6)
COAGULATION				
Prothrombin				
North America	901	13 (1.4)	750	11 (1.5)
PTT				
North America	958	14 (1.5)	805	15 (1.9)
Europe	300	1 (0.3)	197	4 (2.0)
LIVER FUNCTION				
Alkaline phosphatase	1226	3 (0.2)	1037	10 (1.0)
AST (SGOT)	1279	17 (1.3)	1174	36 (3.1)
ALT (SGPT)	1281	23 (1.8)	1081	40 (3.7)
Total bilirubin	1397	7 (0.5)	1339	13 (1.0)
RENAL FUNCTION				
BUN	1271	3 (0.2)	1271	5 (0.4)
Blood Urea	92	0	115	3 (2.6)
Creatinine	1507	1 (<0.1)	1576	7 (0.4)
ELECTROLYTES				
Sodium	1278		1335	
Increase		1 (0.1)		1 (0.1)
Decrease		1 (0.1)		1 (0.1)
Potassium	1441		1447	
Increase		5 (0.3)		3 (0.2)
Decrease		0		0
Calcium	650		937	
Increase				4 (0.4)
Decrease		3 (0.5)		3 (0.3)
Phosphorus	738		1076	
Increase		2 (0.3)		7 (0.7)
Decrease		15 (2.0)		36 (3.3)
IMMUNOLOGY				
Direct Coombs' (N. America)	12	2 (16.7)	796	121 (15.2)

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING NORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT
DURING- OR POST-TREATMENT RESULT, BY RISK GROUP AND LABORATORY TEST
ALL CEFEPIME COURSES
Cefepime Safety Summary**

Laboratory Test	Number (%) of Cefepime Courses			
	Renally Impaired		Neutropenic	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	18	1 (5.6)	7	0
Platelet count	65	1 (1.5)	28	3 (10.7)
WBC	80	0	5	5 (10.0)
Neutrophil count	76	1 (1.3)	23	10 (43.5)
Eosinophil count	65	2 (3.1)	87	0
COAGULATION				
PTT (N. America)	25	0	38	5 (13.2)
LIVER FUNCTION				
Alkaline phosphatase	28	0	122	3 (2.5)
AST (SGOT)	50	1 (2.0)	137	3 (2.2)
ALT (SGPT)	46	1 (2.2)	104	6 (5.8)
Total bilirubin	64	1 (1.6)	123	5 (4.1)
RENAL FUNCTION				
BUN	20	1 (5.0)	154	2 (1.3)
Creatinine	20	2 (10.0)	169	2 (1.2)
ELECTROLYTES				
Sodium	56		128	
Increase		0		0
Decrease		0		1 (0.8)
Potassium	68		149	
Increase		1 (1.5)		0
Decrease		0		1 (0.7)
Calcium	31		43	
Increase		1 (3.2)		0
Decrease		0		1 (2.3)
Phosphorus	64		54	
Increase		2 (4.5)		2 (3.7)
Decrease		1 (2.3)		2 (3.7)
IMMUNOLOGY				
Direct Coombs' (N. America)	43	5 (11.6)	40	8 (20.0)

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

Below is a table which presents the clinically relevant changes for North American patients, by risk group, who began the study with normal baseline values. The most common abnormalities are abnormal Coombs' tests and abnormal liver function studies.

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING NORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT
DURING- OR POST-TREATMENT RESULT, BY RISK GROUP AND LABORATORY TEST
ALL NORTH AMERICAN CEFEPIME COURSES**
Cefepime Safety Summary

Laboratory Test	Number (%) of Cefepime Courses			
	Low-dose (≤ 2000 mg/day)		High-dose (> 2000 mg/day)	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	644	2 (0.3)	703	2 (0.3)
Platelet count	1129	1 (<0.1)	1219	3 (0.2)
WBC	1276	0	1497	9 (0.6)
Neutrophil count	1135	3 (0.3)	1290	8 (0.6)
Eosinophil count	1009	15 (1.5)	1221	22 (1.8)
COAGULATION				
Prothrombin	901	13 (1.4)	750	11 (1.5)
PTT	958	14 (1.5)	805	15 (1.9)
LIVER FUNCTION				
Alkaline phosphatase	865	1 (0.1)	826	5 (0.6)
AST (SGOT)	886	14 (1.6)	957	30 (3.1)
ALT (SGPT)	876	14 (1.6)	849	32 (3.8)
Total bilirubin	1027	7 (0.7)	1138	11 (1.0)
RENAL FUNCTION				
BUN	1025	1 (<0.1)	1193	5 (0.4)
Creatinine	1114	0	1313	5 (0.4)
ELECTROLYTES				
Sodium	890		1094	
Increase		0		1 (<0.1)
Decrease		0		0
Potassium	1055		1180	
Increase		5 (0.5)		0
Decrease		0		0
Calcium	492		845	
Increase		3 (0.6)		2 (0.2)
Decrease		0		1 (0.1)
Phosphorus	579		964	
Increase		1 (0.2)		7 (0.7)
Decrease		14 (2.4)		29 (3.0)
IMMUNOLOGY				
Direct Coombs' (N. America)	17	2 (16.7)	796	121 (15.2)

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING NORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT
DURING- OR POST-TREATMENT RESULT, BY RISK GROUP AND LABORATORY TEST
ALL NORTH AMERICAN CEFEPIME COURSES
Cefepime Safety Summary**

Laboratory Test	Number (%) of Cefepime Courses			
	Renally Impaired		Neutropenic	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	13	1 (8.3)	5	0
Platelet count	56	1 (1.8)	13	1 (7.7)
WBC	68	0	2	2 (100.0)
Neutrophil count	65	0	16	6 (37.5)
Eosinophil count	55	1 (1.8)	52	0
COAGULATION				
PTT	25	0	38	5 (13.2)
LIVER FUNCTION				
AST (SGOT)	47	1 (2.1)	53	1 (1.9)
ALT (SGPT)	42	1 (2.4)	33	0
Total bilirubin	58	0	58	3 (5.2)
RENAL FUNCTION				
BUN	20	1 (5.0)	80	1 (1.3)
Creatinine	18	2 (11.1)	83	0
ELECTROLYTES				
Potassium	57		79	
Increase		1 (1.8)		0
Decrease		0		0
Calcium	27		38	
Increase		1 (3.7)		0
Decrease		0		0
Phosphorus	39		51	
Increase		2 (5.1)		2 (3.9)
Decrease		1 (2.6)		2 (3.9)
IMMUNOLOGY				
Direct Coombs' (N. America)	43	5 (11.6)	40	8 (20.0)

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

Similarly, the table below presents laboratory tests which worsened to clinically relevant values from normal baseline values, by risk group, for European courses. The most common abnormalities were liver function tests. Overall, the trends of abnormal laboratory tests were similar in North America and Europe.

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING NORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT
DURING- OR POST-TREATMENT RESULT, BY RISK GROUP AND LABORATORY TEST
ALL EUROPEAN CEFEPIME COURSES**
Cefepime Safety Summary

Laboratory Test	Number (%) of Cefepime Courses			
	Low-dose ($\leq$ 2000 mg/day)		High-dose ($>$ 2000 mg/day)	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Platelet count	411	2 (0.5)	294	3 (1.0)
WBC	493	0	355	3 (0.8)
Neutrophil count	426	0	280	2 (0.7)
Eosinophil count	410	3 (0.7)	253	2 (0.8)
COAGULATION				
PTT	300	1 (0.3)	197	4 (2.0)
LIVER FUNCTION				
Alkaline phosphatase	361	2 (0.6)	211	5 (2.4)
AST (SGOT)	393	3 (0.8)	217	6 (2.8)
ALT (SGPT)	405	9 (2.2)	232	8 (3.4)
Total bilirubin	370	0	201	2 (1.0)
RENAL FUNCTION				
BUN	246	2 (0.8)	78	0
Blood Urea	92	0	115	3 (2.6)
Creatinine	393	1 (0.3)	263	2 (0.8)
ELECTROLYTES				
Sodium	388		241	
Increase		1 (0.3)		0
Decrease		1 (0.3)		1 (0.4)
Potassium	386		267	
Increase		0		3 (1.1)
Decrease		0		0
Calcium	158		92	
Increase		0		2 (2.2)
Decrease		0		2 (2.2)
Phosphorus	159		112	
Increase		1 (0.6)		0
Decrease		1 (0.6)		7 (6.3)

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING NORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT
DURING- OR POST-TREATMENT RESULT, BY RISK GROUP AND LABORATORY TEST
ALL EUROPEAN CEFEPIME COURSES
Cefepime Safety Summary**

Laboratory Test	Number (%) of Cefepime Courses			
	Renally Impaired		Neutropenic	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Platelet count	9	0	15	2 (13.3)
WBC	12	0	3	3 (100.0)
Neutrophil count	11	1 (9.1)	7	4 (57.1)
Eosinophil count	10	1 (10.0)	35	0
LIVER FUNCTION				
Alkaline phosphatase	3	0	67	3 (4.5)
AST (SGOT)	3	0	84	2 (2.4)
ALT (SGPT)	4	0	71	6 (8.5)
Total bilirubin	6	1 (16.7)	65	2 (3.1)
RENAL FUNCTION				
BUN	1	0	74	1 (1.4)
Creatinine	2	0	86	2 (2.3)
ELECTROLYTES				
Sodium	7		75	
Increase		0		0
Decrease		0		1 (1.3)
Potassium	11		70	
Increase		0		0
Decrease		0		1 (1.4)
Calcium	4		5	
Increase		0		0
Decrease		0		1 (20.0)

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

MEDICAL OFFICER'S COMMENTS:

Overall, for the 4,000+ North American and European patients whose pretreatment values were normal, the incidence of developing a clinically relevant laboratory value during cefepime treatment was as follows:

Hematocrit	5/1886 = 0.2%	Alkaline Phosphatase	16/2413 = 0.7%
Platelets	13/3146 = 0.4%	AST/SGOT	57/2640 = 2.2%
WBC	17/3706 = 0.5%	ALT/SGPT	70/2512 = 2.8%
Neutrophils	24/3230 = 0.7%	Total Bilirubin	26/2923 = 0.9%
Eosinophils	44/3045 = 1.4%	BUN	11/2716 = 0.4%
PT	24/1651 = 1.5%	Creatinine	8/3272 = 0.2%
PTT	39/2323 = 1.6%	Sodium	5/2797 = 0.2%
Coombs' test	136/891 = 15.3%	Potassium	10/3105 = 0.3%
		Calcium	12/1661 = 0.7%
		Phosphorus	67/1912 = 3.5%

The values listed above are the percentage of NDA patients treated with cefepime who had a normal pretreatment value and developed a clinically relevant value either during or post treatment. If the incidence is equal to or exceeds 0.7%, the reviewer recommends that the information should appear in the adverse events section of the label. Of note, the applicant did not provide data to determine if these events were incidental, transient or sustained.

The following pages present laboratory tests which worsened (i.e. became clinically relevant) in patients whose baseline laboratory values were abnormal. They are presented by risk group for all cefepime courses. The incidence at which any test worsened to a clinically relevant value is greater in these patients than in patients who had normal baseline values. However, it should be stated that when antecedent pathology causes baseline tests to be abnormal; the interpretation of change becomes difficult. The most common clinically relevant abnormalities in this group are elevated hepatic transaminases.

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING ABNORMAL PRETREATMENT TEST RESULTS AND A DURING- OR POST-TREATMENT RESULT
WHICH WORSENER TO CLINICALLY RELEVANT, BY RISK GROUP AND LABORATORY TEST -
ALL CEFEPIME COURSES**
Cefepime Safety Summary

Laboratory Test	Number (%) of Cefepime Courses			
	Low-dose ($\leq$ 2000 mg/day)		High-dose ($>$ 2000 mg/day)	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	821	14 (1.7)	886	38 (4.3)
Platelet count	117	4 (3.4)	148	9 (6.1)
WBC	51	3 (5.9)	33	2 (6.1)
Neutrophil count	48	1 (2.1)	32	2 (6.3)
Eosinophil count	76	4 (5.3)	74	10 (13.5)
COAGULATION				
Prothrombin				
N. America	154	8 (5.2)	219	26 (11.9)
Europe	9	1 (11.1)	6	0
PTT				
N. America	75	3 (4.0)	73	10 (13.7)
Europe	53	0	60	3 (5.0)
LIVER FUNCTION				
Alkaline phosphatase	319	8 (2.5)	538	30 (5.6)
AST (SGOT)	292	22 (7.5)	370	44 (11.9)
ALT (SGPT)	180	23 (12.8)	293	44 (15.0)
Total bilirubin	148	7 (4.7)	247	16 (6.5)
RENAL FUNCTION				
BUN	320	15 (4.7)	243	25 (10.3)
Blood Urea	25	4 (16.0)	56	12 (21.4)
Creatinine	240	3 (1.3)	218	15 (6.9)
ELECTROLYTES				
Sodium	471		453	
Increase		2 (0.4)		0
Decrease		0		2 (0.4)
Potassium	310		342	
Increase		1 (0.3)		2 (0.6)
Decrease		1 (0.3)		2 (0.6)
Calcium	322		495	
Increase		1 (0.3)		0
Decrease		10 (3.1)		13 (2.6)
Phosphorus	168		265	
Increase		1 (0.6)		3 (1.1)
Decrease		6 (3.6)		12 (4.5)

NOTE: N = number of cefepime courses with abnormal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING ABNORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT
DURING- OR POST-TREATMENT RESULT, BY RISK GROUP AND LABORATORY TEST
ALL CEFEPIME COURSES
Cefepime Safety Summary**

Laboratory Test	----- Number (%) of Cefepime Courses -----			
	Renally Impaired		Neutropenic	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	49	3 (6.1)	129	33 (25.6)
Platelet count	11	1 (9.1)	48	24 (50.0)
WBC	3	2 (66.7)	8	5 (62.5)
Neutrophil count	1	0	3	2 (66.7)
Eosinophil count	8	2 (25.0)	13	0
COAGULATION				
Prothrombin (N. America)	30	4 (13.3)	10	2 (20.0)
PTT (N. America)	1	0	4	1 (25.0)
LIVER FUNCTION				
Alkaline phosphatase	36	2 (5.6)	38	7 (18.4)
AST (SGOT)	18	0	22	4 (18.2)
ALT (SGPT)	12	2 (16.7)	26	4 (15.4)
Total bilirubin	7	0	28	2 (7.1)
RENAL FUNCTION				
BUN	33	14 (42.4)	18	1 (5.6)
Blood Urea	4	2 (50.0)	0	0
Creatinine	47	6 (12.8)	18	1 (5.6)
ELECTROLYTES				
Sodium	24		60	
Increase		0		0
Decrease		0		1 (1.7)
Potassium	13		37	
Increase		0		1 (2.7)
Decrease		0		1 (2.7)
Calcium	30		39	
Increase		0		0
Decrease		2 (6.7)		2 (5.1)
Phosphorus	18		22	
Increase		1 (5.6)		1 (4.5)
Decrease		3 (16.7)		5 (22.7)

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

The following pages present laboratory tests which became clinically relevant values in patients with abnormal baseline values, by risk group, for North American cefepime courses.

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING ABNORMAL PRETREATMENT TEST RESULTS AND A DURING- OR POST-TREATMENT RESULT
WHICH WORSENE TO CLINICALLY RELEVANT, BY RISK GROUP AND LABORATORY TEST
ALL NORTH AMERICAN CEFEPIME COURSES**
Cefepime Safety Summary

Laboratory Test	Number (%) of Cefepime Courses			
	Low-dose ($\leq$ 2000 mg/day)		High-dose ($>$ 2000 mg/day)	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	657	10 (1.5)	703	28 (4.0)
Platelet count	56	3 (5.4)	88	4 (4.5)
WBC	39	3 (7.7)	22	1 (4.5)
Neutrophil count	28	0	25	2 (8.0)
Eosinophil count	61	3 (4.9)	61	10 (16.7)
COAGULATION				
Prothrombin	154	8 (5.2)	219	26 (11.9)
PTT	75	3 (4.0)	73	10 (13.7)
LIVER FUNCTION				
Alkaline phosphatase	249	6 (2.4)	459	18 (3.8)
AST (SGOT)	212	16 (7.5)	290	33 (11.0)
ALT (SGPT)	108	11 (10.2)	239	36 (14.8)
Total bilirubin	86	5 (5.8)	173	8 (4.6)
RENAL FUNCTION				
BUN	207	11 (5.3)	200	23 (11.5)
Creatinine	138	1 (0.7)	141	10 (7.1)
ELECTROLYTES				
Sodium	360		347	
Increase		2 (0.6)		0
Decrease		0		0
Potassium	199		263	
Increase		1 (0.5)		2 (0.8)
Decrease		1 (0.5)		1 (0.4)
Calcium	227		417	
Increase		0		0
Decrease		5 (2.2)		11 (2.6)
Phosphorus	109		224	
Increase		0		2 (0.9)
Decrease		5 (4.6)		10 (4.5)

NOTE: N = number of cefepime courses with abnormal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING ABNORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT
DURING- OR POST-TREATMENT RESULT, BY RISK GROUP AND LABORATORY TEST
ALL NORTH AMERICAN CEFEPIME COURSES
Cefepime Safety Summary**

Laboratory Test	----- Number (%) of Cefepime Courses -----			
	Renally Impaired		Neutropenic	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	43	2 (4.7)	67	11 (16.4)
Platelet count	8	1 (12.5)	29	14 (48.3)
WBC	3	2 (66.7)	3	2 (66.7)
Neutrophil count	1	0	2	1 (50.0)
Eosinophil count	7	2 (28.6)	10	0
COAGULATION				
Prothrombin	30	4 (13.3)	10	2 (20.0)
PTT	1	0	4	1 (25.0)
LIVER FUNCTION				
Alkaline phosphatase	30	1 (3.3)	17	3 (17.6)
AST (SGOT)	16	0	11	2 (18.2)
ALT (SGPT)	10	2 (20.0)	9	1 (11.1)
RENAL FUNCTION				
BUN	33	14 (42.4)	8	1 (12.5)
Creatinine	38	6 (15.8)	5	0
ELECTROLYTES				
Calcium	27		35	
Increase		0		0
Decrease		2 (7.4)		2 (5.7)
Phosphorus	16		17	
Increase		1 (6.3)		1 (5.9)
Decrease		3 (18.8)		5 (29.4)

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

The following pages present laboratory tests which became clinically relevant values in patients with abnormal baseline values, by risk group, for European cefepime courses.

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING ABNORMAL PRETREATMENT TEST RESULTS AND A DURING- OR POST-TREATMENT RESULT
WHICH WORSENEO TO CLINICALLY RELEVANT, BY RISK GROUP AND LABORATORY TEST
ALL EUROPEAN CEFEPIME COURSES**
Cefepime Safety Summary

Laboratory Test	----- Number (%) of Cefepime Courses -----			
	Low-dose ($\leq$ 2000 mg/day)		High-dose ($>$ 2000 mg/day)	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	164	4 (2.4)	183	10 (5.5)
Platelet count	61	1 (1.6)	60	5 (8.3)
WBC	12	0	11	1 (9.1)
Neutrophil count	20	1 (5.0)	7	0
Eosinophil count	15	1 (6.7)	13	0
COAGULATION				
Prothrombin	9	1 (11.1)	6	0
PTT	53	0	60	3 (5.0)
LIVER FUNCTION				
Alkaline phosphatase	70	2 (2.9)	69	12 (7.4)
AST (SGOT)	80	6 (7.5)	69	11 (15.9)
ALT (SGPT)	72	12 (16.7)	50	8 (16.0)
Total bilirubin	62	2 (3.2)	73	8 (11.0)
RENAL FUNCTION				
BUN	113	4 (3.5)	43	2 (4.7)
Blood Urea	25	4 (16.6)	56	12 (21.4)
Creatinine	102	2 (2.0)	77	5 (6.5)
ELECTROLYTES				
Sodium	111		106	
Increase		0		0
Decrease		0		2 (1.9)
Potassium	111		79	
Increase		0		0
Decrease		0		1 (1.3)
Calcium	95		78	
Increase		1 (1.1)		0
Decrease		5 (5.3)		2 (2.6)
Phosphorus	53		41	
Increase		1 (1.7)		1 (2.4)
Decrease		1 (1.7)		2 (4.9)

NOTE: N = number of cefepime courses with abnormal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING ABNORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT
DURING- OR POST-TREATMENT RESULT, BY RISK GROUP AND LABORATORY TEST
ALL EUROPEAN CEFEPIME COURSES
Cefepime Safety Summary**

Laboratory Test	Number (X) of Cefepime Courses			
	Renally Impaired		Neutropenic	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	6	1 (16.7)	62	22 (35.5)
Platelet count	3	0	19	10 (52.6)
WBC	0	0	5	3 (60.0)
Neutrophil count	0	0	1	1 (100)
LIVER FUNCTION				
Alkaline phosphatase	6	1 (16.7)	21	4 (19.0)
AST (SGOT)	2	0	11	2 (18.2)
ALT (SGPT)	2	0	17	3 (17.6)
Total bilirubin	3	0	20	2 (10.0)
RENAL FUNCTION				
Blood Urea	4	2 (50.0)	0	0
Creatinine	9	0	13	1 (7.7)
ELECTROLYTES				
Sodium	6		25	
Increase		0		0
Decrease		0		1 (4.0)
Potassium	2		29	
Increase		0		1 (3.4)
Decrease		0		1 (3.4)

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

Overall, when the number of courses allowed for comparisons, the incidence of clinically abnormal laboratory tests was similar in North American and European studies.

The following pages present laboratory summary test data for all patients in cefepime/ceftazidime comparative studies. This tabulation is presented by risk group (low dose, high dose, renally impaired and neutropenic patients) for all patients who began with normal baseline laboratory values. In the low and high dose risk groups, eosinophilia was higher in the ceftazidime group. Cefepime patients were more likely to have increased ALT and abnormal phosphorus values than ceftazidime patients. In the high dose group, there was a higher incidence of Coombs' test positivity in cefepime patients. Except for a higher percentage of eosinophilia in ceftazidime patients, the results for the renally impaired groups were comparable. There were too few neutropenic patients to comment.

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING NORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT
DURING- OR POST-TREATMENT RESULT, BY RISK GROUP AND LABORATORY TEST
ALL PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Laboratory Test	Number (%) of Patients			
	Cefepime		Ceftazidime	
	Low-dose (≤ 2000 mg/day)	Cl. Rel. ^a	Low-dose (≤ 3000 mg/day)	Cl. Rel. ^a
	N		N	
HEMATOLOGY				
Hematocrit	613	2 (0.3)	324	2 (0.6)
Platelet count	936	1 (0.1)	496	1 (0.2)
WBC	1049	0	545	1 (0.2)
Eosinophil count	837	7 (0.8)	452	5 (1.1)
COAGULATION				
Prothrombin (N. America)	580	7 (1.2)	298	4 (1.3)
PTT (N. America)	624	10 (1.6)	314	9 (2.9)
LIVER FUNCTION				
Alkaline phosphatase	753	0	394	2 (0.5)
AST (SGOT)	759	11 (1.4)	395	6 (1.5)
ALT (SGPT)	766	14 (1.8)	379	2 (0.5)
Total bilirubin	853	3 (0.4)	430	1 (0.2)
RENAL FUNCTION				
BUN	801	1 (0.1)	415	1 (0.2)
Creatinine	906	0	457	2 (0.4)
ELECTROLYTES				
Sodium	800		408	
Increase		0		2 (0.5)
Decrease		1 (0.1)		0
Potassium	872		457	
Increase		4 (0.5)		4 (0.9)
Decrease		0		1 (0.2)
Calcium	597		335	
Increase		0		0
Decrease		2 (0.3)		0
Phosphorus	675		346	
Increase		1 (0.1)		1 (0.3)
Decrease		12 (1.8)		4 (1.2)

NOTE: N = number of cefepime or ceftazidime patients with normal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING NORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT
DURING- OR POST-TREATMENT RESULT, BY RISK GROUP AND LABORATORY TEST
ALL PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Laboratory Test	Number (%) of Patients			
	Cefepime High-dose (> 2000 mg/day)		Ceftazidime High-dose (> 3000 mg/day)	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	265	0	233	3 (1.3)
Platelet count	558	4 (0.7)	531	0
WBC	633	6 (0.9)	600	6 (1.0)
Neutrophil count	584	3 (0.5)	561	2 (0.4)
Eosinophil count	529	5 (0.9)	516	9 (1.7)
COAGULATION				
Prothrombin (N. America)	268	3 (1.1)	260	3 (1.2)
PTT				
North America	305	9 (3.0)	290	6 (2.1)
Europe	58	1 (1.7)	50	2 (4.0)
LIVER FUNCTION				
Alkaline phosphatase	375	3 (0.8)	334	5 (2.3)
AST (SGOT)	408	6 (1.5)	349	4 (1.1)
ALT (SGPT)	372	9 (2.4)	337	4 (1.2)
Total bilirubin	458	4 (0.9)	414	2 (0.5)
RENAL FUNCTION				
BUN	403	1 (0.2)	402	2 (0.5)
Blood Urea	58	0	69	1 (1.4)
Creatinine	508	2 (0.4)	493	0
ELECTROLYTES				
Sodium	443		434	
Increase		1 (0.2)		0
Decrease		1 (0.2)		0
Potassium	507		464	
Increase		1 (0.2)		1 (0.2)
Decrease		0		3 (0.6)
Calcium	319		275	
Increase		2 (0.6)		0
Decrease		2 (0.6)		1 (0.4)
Phosphorus	398		363	
Increase		2 (0.5)		2 (0.5)
Decrease		14 (3.5)		8 (2.2)
IMMUNOLOGY				
Direct Coombs' - North America	283	41 (14.5)	251	22 (8.7)

NOTE: N = number of cefepime or ceftazidime patients with normal pretreatment values and at least one during- or post-treatment result; NA = North America.

^a Clinically relevant result.

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING NORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT
DURING- OR POST-TREATMENT RESULT, BY RISK GROUP AND LABORATORY TEST
ALL PATIENTS**

Cefepime vs. Ceftazidime
Cefepime Safety Summary

Laboratory Test	Number (%) of Patients			
	Cefepime Normally Impaired		Ceftazidime Normally Impaired	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	12	1 (8.3)	24	1 (4.2)
Platelet count	47	1 (2.1)	71	0
WBC	35	0	81	2 (2.5)
Neutrophil count	51	1 (2.0)	73	0
Eosinophil count	44	1 (2.3)	64	3 (4.7)
COAGULATION				
PTT (N. America)	15	0	39	1 (2.6)
LIVER FUNCTION				
AST (SGOT)	31	1 (3.2)	51	1 (2.0)
ALT (SGPT)	30	1 (3.3)	53	2 (3.8)
Total bilirubin	41	1 (2.4)	59	0
ELECTROLYTES				
Potassium	43		66	
Increase		1 (2.3)		0
Decrease		0		0
Calcium	20		30	
Increase		1 (5.0)		0
Decrease		0		0
Phosphorus	29		47	
Increase		1 (3.4)		0
Decrease		1 (3.4)		1 (2.1)
IMMUNOLOGY				
Direct Coombs' -North America	26	2 (7.7)	49	2 (4.1)

NOTE: N = number of cefepime or ceftazidime patients with normal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
HAVING NORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT
DURING- OR POST-TREATMENT RESULT, 2Y RISK GROUP AND LABORATORY TEST
ALL PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Laboratory Test	Number (%) of Patients			
	Cefepime Neutropenic		Ceftazidime Neutropenic	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Platelet count	6	1 (16.7)	1	0
WBC	0		1	1 (100.0)
Neutrophil count	2	1 (50.0)	5	5 (100.0)
COAGULATION				
Prothrombin (N. America)	11	0	11	1 (9.1)
PTT (N. America)	9	2 (22.2)	9	1 (11.1)
LIVER FUNCTION				
AST (SGOT)	13	1 (7.7)	11	0
Total bilirubin	14	2 (14.3)	15	1 (6.7)
RENAL FUNCTION				
BUN	21	0	19	1 (5.3)
ELECTROLYTES				
Phosphorus	13		17	
Increase		1 (7.7)		0
Decrease		0		1 (5.9)
IMMUNOLOGY				
Direct Coombs' - North America	10	2 (20.0)	5	1 (20.0)

NOTE: N = number of cefepime or ceftazidime patients with normal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

The following pages present tables of laboratory tests which worsened during therapy in patients who began with abnormal baseline values. It is presented by risk group for all comparative cefepime/ceftazidime comparative studies. The incidence at which any test worsened to a clinically relevant value is greater in these patients than in patients who had normal baseline values.

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
WITH ABNORMAL PRE-TREATMENT TEST RESULTS AND A DURING- OR
POST-TREATMENT TEST RESULT THAT WORSENE TO CLINICALLY RELEVANT,
BY DOSE GROUP AND LABORATORY TEST
ALL PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Laboratory Test	Number (%) of Patients			
	Cefepime Low-dose (≤ 2000 mg/day)		Ceftazidime Low-dose (≤ 3000 mg/day)	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	459	6 (1.3)	221	5 (2.2)
Platelet count	68	3 (4.4)	32	3 (9.4)
WBC	33	1 (3.0)	12	0
Eosinophil count	45	0	21	1 (4.8)
COAGULATION				
Prothrombin (N. America)	100	6 (6.0)	51	0
PTT (N. America)	55	2 (3.6)	33	0
LIVER FUNCTION				
Alkaline phosphatase	161	4 (2.5)	69	1 (1.4)
AST (SGOT)	170	14 (8.2)	81	8 (9.9)
ALT (SGPT)	105	11 (10.5)	53	8 (15.1)
Total bilirubin	73	2 (2.7)	39	1 (2.6)
RENAL FUNCTION				
BUN	197	9 (4.6)	102	5 (4.9)
ELECTROLYTES				
Sodium	239		128	
Increase		2 (0.8)		0
Decrease		0		2 (1.6)
Calcium	272		117	
Increase		0		0
Decrease		6 (2.2)		4 (3.4)
Phosphorus	138		75	
Increase		0		0
Decrease		6 (4.3)		0

NOTE: N = number of cefepime or ceftazidime patients with abnormal pretreatment values and at least one during or post-treatment result.

^a Clinically relevant result.

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
WITH ABNORMAL PRE-TREATMENT TEST RESULTS AND A DURING- OR
POST-TREATMENT TEST RESULT THAT WORSENE TO CLINICALLY RELEVANT,
BY DOSE GROUP AND LABORATORY TEST
ALL PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Laboratory Test	Number (%) of Patients			
	Cefepime High-dose (> 2000 mg/day)		Ceftazidime High-dose (> 3000 mg/day)	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	331	16 (4.8)	345	16 (4.6)
Platelet count	62	5 (8.1)	66	6 (9.1)
WBC	14	1 (7.1)	22	0
Neutrophil count	7	1 (14.3)	10	2 (20.0)
Eosinophil count	28	2 (7.1)	24	3 (12.5)
COAGULATION				
Prothrombin				
North America	110	12 (10.9)	106	11 (10.4)
Europe	6	0	9	1 (11.1)
PTT				
North America	24	7 (29.2)	18	3 (16.7)
Europe	21	0	32	1 (3.1)
LIVER FUNCTION				
Alkaline phosphatase	172	10 (5.8)	167	5 (3.0)
AST (SGOT)	124	10 (8.1)	147	11 (7.5)
ALT (SGPT)	105	13 (12.4)	106	13 (12.3)
Total bilirubin	93	7 (7.5)	87	7 (8.0)
RENAL FUNCTION				
BUN	117	16 (13.7)	84	2 (2.4)
Blood urea	30	6 (20.0)	21	0
Creatinine	106	3 (2.8)	84	0
ELECTROLYTES				
Sodium	179		150	
Increase		0		0
Decrease		1 (0.6)		0
Potassium	116		124	
Increase		0		0
Decrease		1 (0.9)		2 (1.6)
Calcium	206		211	
Increase		0		0
Decrease		6 (2.9)		8 (3.8)
Phosphorus	99		102	
Increase		1 (1.0)		0
Decrease		4 (4.0)		7 (6.7)

NOTE: N = number of cefepime or ceftazidime patients with abnormal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
WITH ABNORMAL PRE-TREATMENT TEST RESULTS AND A DURING- OR
POST-TREATMENT RESULT THAT WORSENE TO CLINICALLY RELEVANT,
BY DOSE GROUP AND LABORATORY TEST**

**ALL PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Laboratory Test	----- Number (%) of Patients -----			
	Cefepime Renally Impaired		Ceftazidime Renally Impaired	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	35	1 (2.9)	52	4 (7.7)
Platelet count	7	0	12	2 (16.7)
WBC	1	1(100.0)	4	1 (25.0)
Eosinophil count	5	1 (20.0)	10	3 (30.0)
COAGULATION				
Prothrombin (N. America)	20	3 (15.0)	21	3 (14.3)
LIVER FUNCTION				
Alkaline phosphatase	27	2 (7.4)	37	1 (2.7)
AST (SGOT)	13	0	20	2 (10.0)
ALT (SGPT)	8	2 (25.0)	12	1 (8.3)
RENAL FUNCTION				
BUN	22	9 (40.9)	37	3 (8.1)
Blood urea	4	2 (50.0)	4	2 (50.0)
Creatinine	32	3 (9.4)	45	4 (8.9)
ELECTROLYTES				
Calcium	20		33	
Increase		0		0
Decrease		1 (5.0)		1 (3.0)
Phosphorus	11		15	
Increase		1 (9.1)		0
Decrease		1 (9.1)		1 (6.7)

NOTE: N = number of cefepime or ceftazidime patients with abnormal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS
WITH ABNORMAL PRE-TREATMENT TEST RESULTS AND A DURING- OR
POST-TREATMENT RESULT THAT WORSENE TO CLINICALLY RELEVANT,
BY DOSE GROUP AND LABORATORY TEST
ALL PATIENTS
Cefepime vs. Ceftazidime
Cefepime Safety Summary**

Laboratory Test	----- Number (%) of Patients -----			
	Cefepime Neutropenic		Ceftazidime Neutropenic	
	N	Cl. Rel. ^a	N	Cl. Rel. ^a
HEMATOLOGY				
Hematocrit	16	5 (31.3)	14	5 (35.7)
Platelet count	6	4 (66.7)	7	3 (42.9)
WBC	1	1 (100.0)	1	1 (100.0)
Neutrophil count	1	1 (100.0)	1	1 (100.0)
COAGULATION				
PTT (N. America)	2	1 (50.0)	2	0
LIVER FUNCTION				
Alkaline phosphatase	6	1 (16.7)	5	2 (40.0)
AST (SGOT)	3	1 (33.3)	4	2 (50.0)
ALT (SGPT)	3	1 (33.3)	5	1 (20.0)
RENAL FUNCTION				
BUN	1	1 (100.0)	2	2 (50.0)
ELECTROLYTES				
Phosphorus	7		4	
Increase		0		0
Decrease		2 (28.6)		0

NOTE: N = number of cefepime or ceftazidime patients with abnormal pretreatment values and at least one during- or post-treatment result.

^a Clinically relevant result.

Overall, eosinophilia was more prominent in the ceftazidime groups. Liver functions tests were elevated in both high and low dose groups; the elevations were almost comparable for both drugs. Changes in phosphorus were usually more predominant in the cefepime groups.

Pharmacokinetic Studies

Laboratory data for subjects in the pharmacokinetic studies were analyzed with the same breakpoints as the laboratory data collected for the clinical studies. Data was difficult to pool, because of the exceptional drug exposures especially in cross-over studies. For example, at least 11 patients received both cefepime/NaCl and cefepime/arginine formulations. Subjects who did not have pre-treatment studies or appropriate follow-up studies were excluded for the analysis. Other subjects were excluded, because they received three study drugs.

Below is a table which shows the laboratory results that changed to clinically relevant during or post-treatment for all subjects, excluding renally and hepatically impaired subjects and pediatric patients. The number (N) is the number of subjects for whom appropriate pretreatment and post-treatment laboratory test results were available.

**HEALTHY CEFEPIME SUBJECTS WHO HAD CLASS III OR
CLINICALLY RELEVANT LABORATORY VALUES**
Clinical Pharmacokinetic Studies
Cefepime Safety Summary

Test	Number (%) of Subjects					
	Single-Dose Studies			Multiple-Dose Studies		
	N	Class III ^a	Clin. Rel. ^a	N	Class III ^a	Clin. Rel. ^a
HEMATOLOGY						
Hematocrit	191			94		
Platelet ct.	187			94		
WBC	191			94		
Neutrophil ct.	191			93		
Eosinophil ct.	178	3 (2)	1 (<1)	93	5 (5)	1 (1)
COAGULATION						
Prothrombin time	132		1 (<1)	86		1 (1)
PTT	131		1 (<1)	94		
LIVER FUNCTION						
Alkaline phosphatase	180			92		
AST (SGOT)	180	1 (<1)		92	1 (1)	2 (2)
ALT (SGPT)	153			92	7 (8)	5 (5)
Total bilirubin	180	2 (1)		91		
RENAL FUNCTION						
BUN	178			92		
Creatinine	184			92		
ELECTROLYTES						
Sodium	184			93		
Potassium	183		1 (<1)	93		
Calcium	159			85		
Phosphorus	123	1 (<1)		79	7 (9)	
IMMUNOLOGY						
Direct Coombs ^b				8		3 (38)

NOTE: N = the total number of subjects having either a normal or abnormal (in the direction of toxicity) pretreatment test result and at least one additional test during or after treatment.

^a Clin. rel. = Clinically relevant.

^b Moderate changes in laboratory values

An interesting observation was that there was a clustering of eosinophilia in study 411-058; this is the same study which reported the unusual "flu-like" adverse clinical events. These patients all received drug from the same lot number.

Overall, eosinophilia, changes in phosphorus, positive Coombs' tests and elevations of SGOT/SGPT were the most frequent laboratory abnormalities observed.

SPECIAL SAFETY ISSUES

1. Because bleeding diatheses has been a problem with some cephalosporins, the applicant examined decreases in hematocrit as an indicator of blood loss. In comparative trials, 55/2032 (2.9%) of cefepime patients compared to 39/1456 (2.7%) of ceftazidime patients had a 10% drop in baseline hematocrit. Approximately one fifth of these patients had undergone surgery.

2. The following chart examines five laboratory tests in cefepime and ceftazidime comparative trials.

**A COMPARISON OF FIVE ABNORMAL LABORATORY TEST RESULTS
FOR PATIENTS IN CEFTAZIDIME-CONTROLLED AND OTHER CLINICAL STUDIES^a**

Safety Issues Selected for Close Examination
Cefepime Safety Summary

Abnormal Laboratory Tests	Number (%) of Patients		
	Ceftazidime - Controlled		All Studies
	Cefepime	Ceftazidime	Cefepime (All Courses)
WBC count (≤ 2000 cells/ μ l)	<u>10</u> (0.6) 1786	<u>12</u> (0.9) 1266	<u>29</u> (0.8) 3801
Neutrophil count (Neutropenia - ≤ 500 cells/ μ l)	<u>7</u> (0.4) 1604	<u>10</u> (0.9) 1154	<u>29</u> (0.9) 3314
Probably or Possibly related ^b	<u>1</u> (0.06) 1604	<u>1</u> (0.09) 1154	<u>8</u> (0.2) 3314
Platelet count ($\leq 50,000$ cells/ μ l)	<u>19</u> (1.1) 1690	<u>15</u> (1.2) 1216	<u>51</u> (1.5) 3470
Prothrombin time ^c (> 15 sec)	<u>31</u> (2.5) ^d 1225	<u>23</u> (2.7) ^e 864	<u>65</u> (2.8) 2297
PTT (> 45 sec)	<u>32</u> (2.4) 1332	<u>23</u> (2.5) 907	<u>56</u> (2.1) 2659

NOTE: Denominators in this table indicate the number of patients who had the test performed, and whose values were at risk of becoming clinically relevant.

^a Includes febrile cancer patients enrolled in neutropenia studies.

^b The relationship to study drug was indicated by the investigator on the laboratory tests page of the case report form.

^c Most patients had an elevation in prothrombin time of at least three seconds from baseline.

^d Two patients had changes from baseline of one second or less, and three had changes from baseline of two to three seconds.

^e Includes one patient with less than one second change from baseline.

Abnormalities in clotting parameters (platelets, prothrombin time, partial prothrombin time) that were not attributable to risk factors such as hypersplenism or chemotherapy were not associated with bleeding episodes.

3. Nine (0.2%) episodes of neutropenia occurred for the 4,469 cefepime courses. Eight of the nine cases of neutropenia occurred in patients who were treated in excess of 25 days e.g. for osteomyelitis. There were 112 patients who received cefepime for three weeks or greater; this generates a rate of neutropenia of 7.1% (8/112). It appears that there is a risk of neutropenia with prolonged cefepime therapy.

FIRST AND SECOND SAFETY UPDATES

First Safety Update

In the first safety update, there were 508 courses of cefepime and 278 courses of comparator drug administered in North American and European clinical trials. The trends of laboratory abnormalities seen in the original NDA were seen again in the post-NDA study patients. The most frequent abnormality observed was a positive Direct Coombs' test. In comparative trials, Coombs' positivity was more frequent in cefepime patients than in ceftazidime patients. No apparent evidence of hemolysis nor cases of hemolytic anemia were reported. Abnormalities in eosinophil counts, liver transaminases, coagulation times, and serum phosphorus levels were observed in both cefepime and ceftazidime patients. These changes were similar to those noted in the NDA. As expected, a higher percentage of clinically relevant abnormalities occurred in patients with abnormal pretreatment laboratory values.

Of note, in this subset of post-NDA patients, two suspected cases of interstitial nephritis were reported. These cases were judged by the investigator to be of *probable or unknown relationship* to cefepime administration.

There was a pharmacokinetic study conducted in 12 patients undergoing transurethral prostatectomy. A low phosphorus and positive Coombs' test was reported in one patient. All subjects had (2+ to 3+) hematuria; eight patients had decreases in hemoglobin. The investigator thought these findings were not related to the administration of study drug.

There were two additional patients who developed clinically relevant neutropenia (2/391 patients = 0.5%). Both of these patients had received cefepime therapy in excess of 21 days; the neutropenia reversed after discontinuation of therapy. The investigator's judgment was that these episodes were probably related to cefepime administration. (A third patient, 0.8%, also developed neutropenia, but the absolute neutrophil count was 528 mcg/mL which is above the cut-off point of 500 mcg/mL. This patient also received cefepime for more than three weeks.)

Second Safety Update

In general, the patient composition of the post-NDA studies was different from the original clinical trials. More pediatric patients, more neutropenic patients and more seriously ill patients were studied. Therefore, dosing in the post-NDA studies was higher, generally 6g cefepime/day for adults and 150 mg/kg/day for children. Although the patient profile was different in these post-NDA studies, trends for abnormal laboratory values were similar.

The second safety update summarized the entire post NDA safety experience for all patients who were enrolled after the NDA cut-off date of May 31, 1991 and before December 31, 1992. This included 22 clinical studies in North America and Europe. A total of 742 patients received 750 courses of cefepime in these post-NDA studies; 401 patients received a total of 412 courses of comparator drug. There were 40 patients enrolled in blinded A1411-160 studies.

On the following pages, the overall changes in laboratory test values are given for all post-NDA, North American cefepime patients who either a) started with a normal pre-treatment value or b) started with an abnormal pre-treatment value. These charts are followed by comparative tables of laboratory abnormalities for cefepime and ceftazidime patients.

OVERALL CHANGES IN LABORATORY TEST VALUES IN COURSES GIVEN TO PATIENTS HAVING
 NORMAL PRE-TREATMENT TESTS RESULTS AND A CLINICALLY RELEVANT ABNORMAL
 DURING- OR POST-TREATMENT RESULT BY AGE GROUP AND LABORATORY TEST
 POST-NDA NORTH AMERICAN CEFEPIME COURSES

LABORATORY TEST	Number (%) of Cefepime Courses											
	< 12 years			13 - 64 years			> 65 years			Total		
	N	CLIN.	REL.	N	CLIN.	REL.	N	CLIN.	REL.	N	CLIN.	REL.
HEMATOLOGY												
Hematocrit	34	0		55	1	1.8%	26	1	3.8%	115	2	1.7%
Platelet Ct.	105	1	1.0%	105	1	1.0%	77	0		287	2	0.7%
WBC	113	0		119	2	1.7%	89	0		321	2	0.6%
Neutrophil	116	4	3.4%	119	4	3.4%	79	0		314	8	2.5%
Eosinophil	133	9	6.8%	149	2	1.3%	82	1	1.2%	364	12	3.3%
COAGULATION												
PT				74	3	4.1%	50	4	8.0%	124	7	5.6%
PTT				80	2	2.5%	62	2	3.2%	142	4	2.8%
LIVER FUNCTION												
Alkaline Phos.	77	0		102	1	1.0%	47	0		226	1	0.4%
SGOT/AST	75	1	1.3%	113	8	7.1%	53	2	3.8%	241	11	4.6%
SGPT/ALT	119	1	0.8%	99	11	11.1%	47	1	2.1%	265	13	4.9%
Total Bill.	1	1	0.8%	136	2	1.5%	56	1	1.8%	310	4	1.3%
RENAL FUNCTION												
BUN	33	0		158	2	1.4%	46	0		217	2	0.9%
Creatinine	129	1	0.8%	158	2	1.3%	63	2	3.2%	350	5	1.4%
ELECTROLYTES												
Sodium	116	0		125	1	0.8%	57	0		298	1	0.3%
Potassium	141	9	6.4%	149	5	3.3%	79	0		369	14	3.8%
Calcium	100	2	2.0%	86	3	3.5%	43	0		229	5	2.2%
Phosphorus	69	10	14.5%	90	5	5.5%	50	6	12.0%	209	21	10.0%
IMMUNOLOGY												
Direct Coombs'	57	6	10.5%	87	33	37.9%	47	16	34.0%	191	55	28.8%

Clin. Rel. = Clinically Relevant

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result

**OVERALL CHANGES IN LABORATORY TEST VALUES IN COURSES GIVEN TO PATIENTS HAVING
ABNORMAL PRE-TREATMENT TESTS RESULTS AND A
DURING- OR POST-TREATMENT RESULT THAT WORSENERD TO CLINICALLY RELEVANT
BY AGE GROUP AND LABORATORY TEST
POST-NDA NORTH AMERICAN CEFEPIME COURSES**

LABORATORY TEST	Number (%) of Cefepime Courses											
	< 12 years			13 - 64 years			> 65 years			Total		
	N	CLIN.	REL.	N	CLIN.	REL.	N	CLIN.	REL.	N	CLIN.	REL.
HEMATOLOGY												
Hematocrit	52	9	17.3%	115	18	15.7%	66	3	4.5%	233	30	12.9%
Platelet Ct.	14	1	7.1%	28	8	28.6%	12	1	8.3%	54	10	18.5%
WBC	9	2	22.2%	6	3	50.0%	1	0		16	5	31.3%
Neutrophil	5	1	20.0%	2	1	50.0%	0	0		7	2	28.6%
Eosinophil	21	4	19.0%	15	1	6.7%	1	0		37	5	13.5%
COAGULATION												
PT				17	0		16	4	25.0%	33	4	12.1%
PTT				10	1	10.0%	6	0		16	1	6.3%
LIVER FUNCTION												
Alkaline Phos.	13	2	15.4%	36	2	5.6%	27	4	14.8%	76	8	10.5%
SGOT/AST	32	0		26	3	11.5%	18	1	5.6%	76	4	5.3%
SGPT/ALT	16	1	6.3%	29	8	27.6%	14	3	21.4%	59	12	20.3%
Total Bili.	9	0		18	3	16.7%	17	3	17.6%	44	6	13.6%
RENAL FUNCTION												
BUN	1	0		26	4	15.4%	37	6	16.2%	64	10	15.6%
Creatinine	7	0		18	3	16.7%	25	6	24.0%	50	9	18.0%
ELECTROLYTES												
Sodium	45	0		52	0		33	0		130	0	
Potassium	19	1	5.3%	29	1	3.4%	11	0		59	2	3.4%
Calcium	33	2	6.1%	67	2	3.0%	35	1	2.9%	135	5	3.7%
Phosphorus	19	6	31.6%	26	2	7.6%	17	5	29.4%	62	13	21.0%

Clin. Rel. = Clinically Relevant

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS HAVING
NORMAL PRE-TREATMENT TEST RESULTS
AND A CLINICALLY RELEVANT DURING OR POST-TREATMENT RESULT
BY AGE GROUP AND LABORATORY TEST IN CLINICAL STUDIES
WHERE CEFEPIME WAS COMPARED TO CEFTAZIDIME
POST-NDA NORTH AMERICAN PATIENTS**

FOR CEFEPIME

LABORATORY TEST	Number (%) of Cefepime Courses (N = 273)											
	< 12 years			13 - 64 years			> 65 years			Total		
	N	CLIN.	REL.	N	CLIN.	REL.	N	CLIN.	REL.	N	CLIN.	REL.
HEMATOLOGY												
Hematocrit	1	0		33	1	3.0%	25	1	4.0%	59	2	3.4%
Platelet Ct.	8	0		73	1	1.4%	74	0		155	1	0.6%
WBC				87	0		86	0		173	0	
Neutrophil	3	3	100%	84	0		76	0		163	3	1.8%
Eosinophil	26	0		98	1	1.0%	77	0		201	1	0.5%
COAGULATION												
PT				53	2	3.8%	46	4	8.7%	99	6	6.1%
PYT				60	1	1.7%	58	2	3.4%	118	3	2.5%
LIVER FUNCTION												
Alkaline Phos.				62	1	1.6%	43	0		105	1	1.0%
SGOT/AST				67	5	7.5%	50	2	4.0%	117	7	6.0%
SGPT/ALT	17	0		63	11	17.5%	45	1	2.2%	125	12	9.6%
Total Billi.	26	1	3.8%	84	1	1.2%	33	1	1.9%	163	3	1.8%
RENAL FUNCTION												
BLN	1	0		89	2	2.2%	43	0		133	2	1.5%
Creatinine	27	0		100	1	1.0%	58	2	3.4%	185	3	1.6%
ELECTROLYTES												
Sodium	25	0		85	1	1.2%	54	0		164	1	0.6%
Potassium	28	0		94	3	3.2%	75	0		197	3	1.5%
Calcium	10	0		47	2	4.3%	39	0		96	2	2.1%
Phosphorus				56	4	7.1%	46	5	10.9%	102	9	8.8%
IMMUNOLOGY												
Direct Coombs'	20	3	15.0%	61	20	32.8%	44	14	31.8%	125	37	29.6%

Clin. Rel. = Clinically Relevant

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS HAVING
NORMAL PRE-TREATMENT TEST RESULTS
AND A CLINICALLY RELEVANT DURING OR POST-TREATMENT RESULT
BY AGE GROUP AND LABORATORY TEST IN CLINICAL STUDIES
WHERE CEFEPIME WAS COMPARED TO CEFTAZIDIME
POST-NDA NORTH AMERICAN PATIENTS**

FOR CEFTAZIDIME

LABORATORY TEST	Number (%) of Ceftazidime Courses (N = 276)											
	< 12 years			13 - 64 years			> 65 years			Total		
	N	CLIN.	REL.	N	CLIN.	REL.	N	CLIN.	REL.	N	CLIN.	REL.
HEMATOLOGY												
Hematocrit				38	0		32	2	6.3%	70	2	2.9%
Platelet Ct.	7	0		67	1	1.5%	78	1	1.3%	152	2	1.3%
WBC				82	2	2.4%	96	0		178	2	1.1%
Neutrophil	6	4	66.7%	77	0		90	0		173	4	2.3%
Eosinophil	30	0		80	1	1.3%	90	2	2.2%	200	3	1.5%
COAGULATION												
PT				54	3	5.6%	43	1	2.3%	97	4	4.1%
PTT				61	1	1.6%	57	2	3.5%	118	3	2.5%
LIVER FUNCTION												
Alkaline Phos.				63	1	1.6%	45	1	2.2%	108	2	1.9%
SGOT/AST				60	3	5.0%	43	0		103	3	2.9%
SGPT/ALT	20	0		53	5	9.4%	45	2	4.4%	118	7	5.9%
Total Bill.	32	1	3.1%	57	1	1.8%	60	0		149	2	1.3%
RENAL FUNCTION												
BUN	1	0		84	1	1.2%	46	0		131	1	0.8%
Creatinine	32	0		89	1	1.1%	55	1	1.8%	176	2	1.1%
ELECTROLYTES												
Sodium	24	0		71	0		65	0		160	0	
Potassium	26	0		79	1	1.3%	75	0		180	1	0.6%
Calcium	8	0		36	0		42	2	4.8%	86	2	2.3%
Phosphorus				46	3	6.5%	46	9	19.6%	92	12	13.0%
IMMUNOLOGY												
Direct Coombs'	30	6	20.0%	51	4	7.8%	54	7	13.0%	135	17	12.6%

Clin. Rel. = Clinically Relevant

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS HAVING ABNORMAL
PRE-TREATMENT TEST RESULTS AND A
CLINICALLY RELEVANT DURING- OR POST-TREATMENT RESULT,
BY AGE GROUP AND LABORATORY TEST IN CLINICAL STUDIES
WHERE CEFEPIME WAS COMPARED TO CEFTAZIDIME
POST-NDA NORTH AMERICAN PATIENTS**

FOR CEFEPIME

LABORATORY TEST	Number (%) of Cefepime Courses (N = 273)											
	< 12 years			13 - 64 years			> 65 years			Total		
	N	CLIN.	REL.	N	CLIN.	REL.	N	CLIN.	REL.	N	CLIN.	REL.
HEMATOLOGY												
Hematocrit	13	3	23.1%	77	13	16.9%	62	2	3.2%	152	18	11.8%
Platelet Ct.	6	0		24	7	29.2%	11	1	9.1%	41	8	19.5%
WBC	5	2	40.0%	5	2	40.0%	1	0		11	4	36.4%
Neutrophil	1	1	100%	1	0					2	1	50.0%
Eosinophil	5	0		4	0		1	0		10	0	
COAGULATION												
PT				17	0		16	4	25.0%	33	4	12.1%
PTT				9	1	11.1%	5	0		14	1	7.1%
LIVER FUNCTION												
Alkaline Phos.				28	2	7.1%	26	4	15.4%	54	6	11.1%
SGOT/AST				23	2	8.7%	16	1	6.3%	39	3	7.7%
SGPT/ALT	7	0		22	4	18.2%	12	2	16.7%	41	6	14.6%
Total Bili.	4	0		14	3	21.4%	15	2	13.3%	33	5	15.2%
RENAL FUNCTION												
BUN				20	3	15.0%	35	6	17.1%	55	9	16.4%
Creatinine				12	2	16.7%	25	6	24.0%	37	8	21.6%
ELECTROLYTES												
Sodium	5	0		33	0		31	0		69	0	
Potassium	2	0		25	1	4.0%	10	0		37	1	2.7%
Calcium	14	1	7.1%	51	2	3.9%	34	1	2.9%	99	4	4.0%
Phosphorus				22	1	4.5%	17	5	29.4%	39	6	15.4%

Clin. Rel. = Clinically Relevant

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result

(continued)

**OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS HAVING ABNORMAL
PRE-TREATMENT TEST RESULTS AND A
CLINICALLY RELEVANT DURING- OR POST-TREATMENT RESULT
BY AGE GROUP AND LABORATORY TEST IN CLINICAL STUDIES
WHERE CEFEPIME WAS COMPARED TO CEFTAZIDIME
POST-NDA NORTH AMERICAN PATIENTS**

FOR CEFTAZIDIME

LABORATORY TEST	Number (%) of Cefepime Courses (N = 276)											
	< 12 years			13 - 64 years			> 65 years			Total		
	N	CLIN.	REL.	N	CLIN.	REL.	N	CLIN.	REL.	N	CLIN.	REL.
HEMATOLOGY												
Hematocrit	22	6	27.3%	60	7	11.7%	62	3	4.8%	144	16	11.1%
Platelet Ct.	13	2	15.4%	24	6	25.0%	16	2	12.5%	53	10	18.9%
WBC	2	0		4	1	25.0%	1	0		7	1	14.3%
Neutrophil												
Eosinophil	8	0		6	0		1	0		15	0	
COAGULATION												
PT				15	0		19	2	10.5%	34	2	5.9%
PTT				8	1	12.5%	11	3	27.3%	19	4	21.1%
LIVER FUNCTION												
Alkaline Phos.				17	0		29	1	3.4%	46	1	2.2%
SGOT/AST				17	1	5.9%	32	4	12.5%	49	5	10.2%
SGPT/ALT	12	1	8.3%	18	3	16.7%	19	2	10.5%	49	6	12.2%
Total Bili.	1	0		16	3	18.8%	15	1	6.7%	32	4	12.5%
RENAL FUNCTION												
BUN				17	2	11.8%	30	3	10.0%			
Creatinine	1	0		13	0		27	0		47	5	10.6%
ELECTROLYTES												
Sodium	11	0		32	0		27	0		70	0	
Potassium	8	0		25	0		17	0		50	0	
Calcium	18	0		44	3	6.8%	38	4	10.5%	100	7	7.0%
Phosphorus				24	1	4.2%	31	1	3.2%	55	2	3.6%

Clin. Rel. = Clinically Relevant

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result

European trials

There were 192 patients treated with cefepime in post-NDA European trials. Eighty of these patients received treatment with cefepime/amikacin and two received treatment with cefepime/metronidazole.

OVERALL CHANGES IN LABORATORY TEST VALUES IN PATIENTS HAVING NORMAL PRE-TREATMENT TEST RESULTS AND A CLINICALLY RELEVANT DURING- OR POST-TREATMENT RESULT BY LABORATORY TEST IN CLINICAL STUDIES POST-NDA EUROPEAN PATIENTS

LABORATORY TEST	Number (%) of Patients ^a					
	Cefepime			Cefepime/Amikacin		
	N	CLIN.	REL. ^b	N	CLIN.	REL. ^b
HEMATOLOGY						
Hematocrit	54	0		7	0	
Platelet Ct.	77	0		56	0	
WBC	79	0		72	0	
Neutrophil	77	1	1.3%	62	0	
Eosinophil	72	0		57	1	1.8%
COAGULATION						
PT	5	0		21	1	4.8%
PTT	44	0		0	0	
LIVER FUNCTION						
Alkaline Phos.	68	0		45	4	8.9%
SGOT/AST	80	3	3.8%	32	4	12.5%
SGPT/ALT	80	3	3.8%	46	7	15.2%
Total Bill.	71	1	1.4%	44	1	2.3%
RENAL FUNCTION						
BUN	75	0		47	2	4.3%
Creatinine	84	1	1.2%	59	1	1.7%
ELECTROLYTES						
Sodium	73	0		52	0	
Potassium	76	0		56	0	
Calcium	9	0		19	1	5.3%
Phosphorus	6	0		36	1	2.8%

^a This table compares cefepime monotherapy (multiple protocols) to cefepime/amikacin combination therapy (single protocol).

^b = Clinically Relevant result

NOTE: N = number of cefepime courses with normal pretreatment values and at least one during- or post-treatment result

From the table above, it appears that the primary concentration of laboratory abnormalities appear in the liver function studies. There were too few patients with abnormal baseline test results to detect meaningful trends. No patients on cefepime/metronidazole developed clinically relevant laboratory abnormalities.

Other Patients

There were no additional pharmacokinetic patients enrolled after the first safety update. (See discussion under the first safety update.)

Post NDA, there were 24 patients who received cefepime under individual compassionate use protocols. Nineteen of these patients were neonates infected with a multi-resistant Group B *Salmonella* species. For those patients with normal pre-treatment values, the laboratory tests that worsened were

a clinically relevant decreased platelet count in two of five patients; the development of eosinophilia in one of four patients; and hypocalcemia in two of six patients. In the group that began with abnormal pre-treatment laboratory values, 2 of seven patients developed hypocalcemia. One patient with pre-existing renal and hepatic dysfunction worsened with cefepime therapy.

There were forty patients enrolled in blinded (A1411-160) studies post-NDA. Overall, there were few clinically relevant abnormalities that developed in patients with either normal or abnormal pre-treatment values.

OVERALL CHANGES IN LABORATORY TEST VALUES
POST-NDA BLINDED STUDIES

LABORATORY TEST	Number (%) of Patient Courses					
	Normal Pre			Abnormal Pre		
	N ^a	CLIN.	REL ^b	N ^a	CLIN.	REL.
HEMATOLOGY						
Hematocrit	8	1	13%	30	5	17%
Platelet Ct.	28	1	4%	10	0	
WBC	36	0		2	0	
Neutrophil	37	0		0	0	
Eosinophil	35	3	9%	2	0	
COAGULATION						
PT	11	1	5%	17	0	
PTT	26	0		2	0	
LIVER FUNCTION						
Alkaline Phos.	22	1	5%	9	1	11%
SGOT/AST	17	2	12%	13	1	8%
SGPT/ALT	10	0		5	0	
Total Bill.	19	1	5%	12	2	17%
RENAL FUNCTION						
BUN	24	0		11	1	9%
Creatinine	24	0		11	1	9%
ELECTROLYTES						
Sodium	25	0		9	0	
Potassium	30	0		4	0	
Calcium	10	1	10%	21	0	
Phosphorus	23	2	9%	8	1	13%
IMMUNOLOGY						
Direct Coombs'	9	5	56%	-	-	

- ^a N = number of patients with normal pre-treatment values on at least one during or post-treatment result
- ^b N = number of study drug patients with abnormal but not clinically relevant pre-treatment values and at least one during or post-treatment result.
- ^c = Clinically Relevant result

The blind has not been broken in these patients. However, the clinically relevant results are not different than those seen in the previously discussed studies.

SPECIAL PATIENTS

In the second safety update, there were no new patients identified with neutropenia. Thus, there were a total of three (see first safety update comments) patients who developed neutropenia of the 26 post-NDA patients who had received cefepime therapy in excess of three weeks. This rate is $(8+3)/(112+26) = 7.9\%$ for patients in the NDA and post-NDA studies.

FINAL SAFETY UPDATE

There was no additional laboratory information presented in this update.

FDA ANALYSIS

As previously noted, the applicant supplied the FDA reviewers with SAS data (electronic format) for all NDA patients enrolled in North American comparative trials who began a clinical trial with normal pretreatment laboratory values. The FDA statistician and the two medical reviewers examined the laboratory parameters with respect to gender, age, severity, dose and formulation. The results are presented in tabular form as follows:

1. Definitions of Laboratory Abnormalities

With two exceptions, the definitions of abnormality were identical to the applicant's.

IV FORMULATION:**2. Effect of Gender, IV formulation**

With the exceptions of eosinophilia and increased liver transaminases, changes in laboratory abnormalities in cefepime patients were similar for men and women. Overall, the changes in laboratory values were similar for cefepime and ceftazidime.

3. Effect of Age, IV formulation

There were more patients with an abnormal BUN in the over 65 years of age population. This is not surprising; the elderly are more easily dehydrated with illness. With regard to the other laboratory parameters, patients below and above 65 years of age exhibited similar trends of abnormal laboratory results.

4. Severity, IV formulation

For cefepime, clinically relevant (class IV) laboratory abnormalities of greater than or equal to 1% are: SGOT, SGPT, Total Bilirubin, absolute eosinophil count, platelets (not thrombocytopenia), PT, PTT, calcium and phosphorus.

For ceftazidime, clinically relevant (class IV) laboratory abnormalities of greater than or equal to 1% are: alkaline phosphatase, SGOT, SGPT, Total Bilirubin, hematocrit, WBC, absolute neutrophil count, absolute eosinophil count, platelets, PT, PTT, potassium and phosphorus.

5. Effect of Dosage, IV formulation

The effects of dosage, if present, are not well demonstrated here.

IM FORMULATION: The numbers are too small to draw meaningful conclusions

6. Effect of Gender, IM formulation**7. Effect of Age, IM formulation****8. Severity, IM formulation****9. Effect of Dosage, IM formulation**

Cefepime Laboratory Safety
North American Comparative Trials
FDA Definitions of Abnormalities

Test	Units	Test Result Classification			
		Class I	Class II	Class III	Class CR ¹
BUN	mg/dL	Normal	>UNL ² , <150% UNL	>150%UNL, <50	≥50
Creatinine	mg/dL	≤0.5	>0.5, ≤1.0	>1.0, ≤2.0	>2.0 ⁵
Alk Phos.	U/L	Normal	>UNL, <200% UNL	>200%UNL, <300%UNL	≥300%UNL
SGOT	U/L	1	>UNL, <200% UNL	>200%UNL, <300%UNL	≥300%UNL
SGPT	U/L	Normal	>UNL, <200% UNL	>200%UNL, <300%UNL	≥300%UNL
Bilirubin	mg/dL	Normal	>UNL, ≤150%UNL	>150%UNL, ≤300%UNL	≥3.0
Hematocrit	%	Normal	<LNL ³ , ≥30	<30, ≥24	<24
WBC	1000/MM ³	Normal	<LNL, >3.0	≤3.0, >2.0	≤2.0
ANC ⁴	cells/MM ³	Normal	<LNL, >1000	≤1000, >500	≤500
AEC ⁵	cells/MM ³	Normal	>UNL, ≤600	>600, ≤1000	>1000
Platelet	cells/MM ³ x 10 ³	Normal	UNL-400, 101-LNL	401-800, 51-100	≥800 ⁵ , ≤50
Pro Time	Secs.	Normal	>UNL-15.0	--	>15.0
APTT	Secs	Normal	>UNL-45.0	--	>45.0
WBC	Meq/L	Normal	126 to LNL UNL to 155	120-125, 156-159	≤119, ≥160
Potassium	Meq/L	Normal	3.0 to LNL UNL to 5.9	2.5-2.9, 6.0-6.4	≤2.4 ≥6.5
Calcium	Meq/L	Normal	7.6 - LNL, UNL - 11.4	7.5-7.1, 11.5-11.9	≤7.0 ≥12.0
Phosphorus	Meq/L	Normal	2.1 - LNL, UNL - 4.9	1.8-2.1, 5.0-6.0	≤1.7, ≥6.1

1- UNL=Upper limit of normal.

2- LNL=Lower Limit of normal.

3- ANC=Absolute neutrophil count.

4- AEC=Absolute eosinophil count.

5- Clinically relevant values different from the applicant's.

Cefepime Laboratory Safety
North American Comparative Trials
Intravenous Administration
Effect of Gender on Laboratory Test Abnormalities
FDA Table

Test	Females		Males		Overall	
	Cefepime	Ceftaz.	Cefep	Ceftaz	Cefep	Ceftaz
BUN	45/375 (12)	21/178 (8)	71/636 (11)	46/445 (10)	116/1015 (11)	67/723 (9)
Creat.	8/416 (2)	1/291 (0)	9/665 (1)	8/446 (2)	17/1081 (2)	9/743 (1)
Alk Phos	48/314 (15)	30/222 (14)	77/531 (15)	42/353 (12)	125/845 (15)	72/575 (13)
SGOT	68/339 (20)	48/249 (19)	132/540 (24)	74/351 (21)	200/879 (23)	122/600 (20)
SGPT	20/320 (16)	43/283 (18)	118/535 (22)	64/338 (19)	168/855 (20)	107/571 (19)
T. Bili.	10/407 (2)	5/289 (2)	26/623 (4)	15/420 (4)	36/1030 (4)	20/709 (3)
Hematocrt	128/252 (51)	81/164 (49)	176/361 (49)	106/258 (41)	304/613 (50)	187/422 (44)
WBC	31/479 (6)	31/353 (9)	51/812 (6)	38/574 (7)	82/1291 (6)	69/927 (7)
ANC	30/432 (7)	32/320 (10)	43/745 (6)	38/537 (7)	73/1177 (6)	70/857 (8)
AEC	36/383 (9)	55/295 (19)	111/666 (17)	77/488 (16)	147/1049 (14)	132/783 (17)
Platelet	145/402 (36%)	126/304 (41%)	248/706 (35%)	196/509 (39%)	393/1108 (35%)	322/810 (40%)
Pro Time	21/302 (7)	17/219 (8)	44/519 (8)	33/357 (9)	65/821 (8)	50/576 (9)
PTT	20/337 (6)	16/244 (7)	33/570 (6)	28/384 (7)	53/907 (6)	44/628 (7)
Sodium	54/346 (16)	47/256 (18)	95/601 (16)	80/430 (19)	149/947 (16)	127/686 (19)
Potas.	68/396 (17)	47/274 (17)	116/627 (17)	91/489 (19)	184/1083 (17)	138/763 (18)
Calcium	66/240 (28)	55/172 (32)	122/444 (27)	95/312 (30)	188/684 (27)	150/484 (31)
Phos.	70/309 (23)	52/229 (23)	112/529 (21)	69/364 (19)	182/838 (22)	121/593 (20)

**Cefepime Laboratory Safety
North American Comparative Trials
Intravenous Administration
Effect of Age on Laboratory Test Abnormalities
FDA Table**

Test	≤ 65 years		> 65 years		Overall	
	Cefepime	Ceftaz.	Cefep	Ceftaz	Cefep	Ceftaz
BUN	48/692 (7)	28/491 (6)	68/319 (21)	39/232 (17)	116/1015 (11)	67/723 (9)
Creat.	10/701 (1)	6/480 (1)	7/380 (2)	3/263 (1)	17/1081 (2)	9/743 (1)
Alk Phos	85/522 (16)	40/349 (11)	43/323 (13)	32/226 (14)	125/845 (15)	72/575 (13)
SGOT	119/519 (23)	72/338 (21)	81/360 (23)	50/262 (19)	200/879 (23)	122/600 (20)
SGPT	113/521 (22)	68/317 (22)	55/334 (16)	39/254 (15)	168/855 (20)	107/571 (19)
T. Bili.	22/621 (4)	16/423 (4)	14/409 (3)	4/286 (1)	36/1030 (4)	20/709 (3)
Hematcrt	199/409 (49)	100/247 (40)	105/204 (51)	87/175 (50)	304/613 (50)	187/422 (44)
WBC	59/792 (7)	52/542 (10)	56/499 (5)	17/385 (4)	82/1291 (6)	69/927 (7)
ANC	57/729 (8)	54/501 (11)	16/448 (4)	16/356 (4)	73/1117 (6)	70/857 (8)
AEC	88/641 (14)	75/450 (17)	59/408 (14)	57/333 (17)	147/1049 (14)	132/783 (17)
Platelet	243/702 (35%)	185/483 (38%)	150/406 (37%)	137/327 (42%)	393/1102 (35%)	22/810 (40%)
Pro Time	34/502 (7)	25/337 (7)	31/319 (10)	25/239 (10)	65/821 (8)	50/576 (9)
PTT	36/561 (6)	24/368 (7)	17/346 (5)	20/260 (8)	53/907 (6)	44/628 (7)
Sodium	84/597 (14)	59/410 (14)	65/350 (19)	68/276 (25)	149/947 (16)	127/686 (19)
Potas.	82/660 (12)	75/448 (17)	102/423 (24)	63/315 (20)	184/1083 (17)	138/763 (18)
Calcium	97/420 (23)	76/277 (27)	91/264 (34)	74/207 (36)	188/684 (27)	150/484 (31)
Phos.	103/516 (20)	83/355 (23)	79/325 (24)	38/238 (16)	182/830 (22)	121/593 (20)

Cefepime Laboratory Safety
North American Comparative Trials
Intravenous Administration
Severity of Laboratory Test Abnormalities
FDA Table

Test	#Abnormal/#Tested (Percent)							
	Class II ¹		Class III ¹		Class IV ¹		Overall	
	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz
BUN	88/1015 (9%)	54/723 (7%)	25/1015 (2%)	10/723 (1%)	1/1015 (<1%)	3/723 (<1%)	116/1015 (11%)	67/723 (9%)
Creat.	15/1081 (1%)	4/743 (1%)	2/1081 (<1%)	5/743 (1%)	0/1081 (0%)	0/743 (0%)	17/1081 (2%)	9/743 (1%)
Alk Phos.	114/845 (13%)	66/575 (11%)	10/845 (2%)	2/575 (<1%)	1/845 (<1%)	4/575 (1%)	125/845 (15%)	72/575 (13%)
SGOT	158/879 (18%)	99/600 (17%)	27/879 (3%)	13/600 (2%)	15/879 (2%)	10/600 (2%)	200/879 (23%)	122/600 (20%)
SGPT	125/855 (15%)	83/571 (15%)	27/855 (3%)	18/571 (3%)	16/855 (2%)	5/571 (1%)	168/855 (20%)	107/571 (19%)
Tot. Bili.	19/1030 (2%)	9/709 (1%)	9/1030 (1%)	7/709 (1%)	8/1030 (1%)	4/709 (1%)	36/1030 (4%)	20/709 (3%)
Hematcrt.	280/613 (46%)	173/422 (41%)	21/613 (3%)	9/422 (2%)	3/613 (<1%)	5/422 (1%)	304/613 (50%)	187/422 (44%)
WBC	75/1291 (6%)	60/927 (6%)	4/1291 (<1%)	4/927 (<1%)	3/1291 (<1%)	5/927 (1%)	82/1291 (6%)	69/927 (7%)
ANC	68/1177 (6%)	62/857 (7%)	3/1177 (<1%)	2/857 (<1%)	2/1177 (<1%)	6/857 (1%)	73/1177 (6%)	80/857 (8%)
AEC	114/1049 (11%)	83/783 (11%)	26/1049 (2%)	35/783 (4%)	7/1049 (1%)	14/783 (2%)	147/1049 (14%)	132/783 (17%)

Cefepime Laboratory Safety
Severity of Laboratory Test Abnormalities - Continued
North American Comparative Trials
Intravenous Administration
FDA Table

Test	#Abnormal/#Tested (Percent)							
	Class II ¹		Class III ¹		Class IV ¹		Overall	
	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz
Platelet	79/1164 (7%)	50/844 (6%)	332/1164 (29%)	269/844 (32%)	15/1164 ² (1%)	16/844 (2%)	426/1164 (37%)	335/844 (40%)
P.T.	55/821 (7%)	43/576 (7%)	0/821 (0%)	0/576 (0%)	10/821 (1%)	7/576 (1%)	65/821 (8%)	50/576 (9%)
A.P.T.T.	33/907 (4%)	27/628 (4%)	0/907 (0%)	0/628 (0%)	20/907 (2%)	17/628 (3%)	53/907 (6%)	44/628 (7%)
Sodium	145/947 (15%)	123/686 (28%)	3/947 (<1%)	2/686 (<1%)	1/647 (<1%)	2/686 (<1%)	149/947 (16%)	127/686 (19%)
Potass.	158/1073 (15%)	126/763 (17%)	22/1083 (2%)	8/763 (1%)	4/1083 (<1%)	4/763 (1%)	184/1083 (17%)	138/763 (18%)
Calcium	180/684 (26%)	138/484 (29%)	4/684 (1%)	11/484 (2%)	4/684 (1%)	1/484 (<1%)	188/684 (27%)	150/484 (31%)
Phosphor.	103/838 (12%)	79/593 (13%)	55/838 (6%)	33/593 (6%)	24/838 (3%)	9/593 (2%)	182/838 (22%)	121/593 (20%)

1- Please see table #1 for definition of the abnormality classes.

2- Platelet: 5/1164 = 0.4% had thrombocytopenia

Cefepime Laboratory Safety
North American Comparative Trials
Intravenous Administration
Effect of Dosage on Laboratory Test Abnormalities
FDA Table

Test	# Abnormal/#Tested (Percent)							
	Cefepime Dose							
	500 mg BID		1.0 Gram BID		22.0 Grams BID		Overall ¹	
	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz
BUN	16/234 (7%)	12/129 (9%)	50/378 (13%)	14/232 (6%)	44/355 (12%)	41/329 (12%)	116/1015 (11%)	67/723 (9%)
Creat.	2/243 (1%)	1/121 (1%)	5/398 (1%)	2/227 (1%)	10/379 (3%)	2/338 (1%)	17/1081 (2%)	9/743 (1%)
Alk Phos	16/211 (8%)	9/110 (8%)	43/311 (14%)	20/188 (11%)	62/275 (23%)	36/238 (15%)	125/845 (15%)	72/575 (13%)
SGOT	38/200 (19%)	20/106 (19%)	72/320 (23%)	39/185 (21%)	82/311 (26%)	56/278 (20%)	200/879 (23%)	122/600 (20%)
SGPT	26/216 (12%)	11/110 (10%)	61/338 (18%)	28/185 (15%)	79/277 (29%)	62/254 (24%)	168/855 (20%)	107/571 (19%)
Tot. Bili.	4/231 (2%)	3/116 (3%)	12/371 (3%)	2/218 (1%)	17/370 (5%)	11/333 (3%)	36/1030 (4%)	20/709 (3%)
Hematcrt.	75/153 (49%)	28/69 (41%)	121/263 (46%)	62/154 (40%)	93/160 (58%)	91/176 (52%)	304/613 (60%)	187/422 (44%)
WBC	25/287 (9%)	18/142 (13%)	30/492 (6%)	15/291 (5%)	23/453 (5%)	31/460 (7%)	82/1291 (6%)	69/327 (7%)
Neutroph.	14/262 (5%)	5/133 (4%)	19/436 (4%)	19/263 (7%)	34/421 (8%)	37/425 (9%)	73/1177 (6%)	80/857 (8%)

Cefepime Laboratory Safety
North American Comparative Trials
Intravenous Administration
Effect of Dosage on Laboratory Test Abnormalities - Continued
FDA Table

Test	#Abnormal/#Tested (Percent)							
	Cefepime Dose							
	500 mg BID		1.0 Grams BID		≥2.0 Grams BID		Overall ¹	
	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz
Eosinoph.	17/196 (9%)	14/106 (13%)	56/409 (14%)	34/250 (14%)	65/389 (17%)	75/386 (19%)	147/1049 (14%)	132/783 (17%)
Platelet	74/253 (29%)	46/133 (35%)	169/444 (38%)	107/275 (39%)	150/411 (37%)	169/402 (42%)	393/1108 (35%)	322/810 (40%)
P.T.	25/187 (13%)	15/95 (15%)	15/351 (4%)	8/201 (4%)	22/238 (9%)	21/243 (8%)	65/821 (8%)	50/576 (9%)
A.P.T.T.	7/232 (3%)	9/116 (8%)	21/356 (6%)	10/201 (5%)	24/270 (9%)	21/276 (8%)	53/907 (6%)	44/628 (7%)
Sodium	39/220 (18%)	18/107 (17%)	47/356 (13%)	37/215 (17%)	44/355 (12%)	41/329 (12%)	149/947 (16%)	127/686 (19%)
Potass.	29/234 (12%)	18/130 (14%)	75/412 (18%)	40/240 (17%)	70/373 (19%)	75/351 (21%)	184/1083 (17%)	138/763 (18%)
Calcium	37/181 (20%)	24/98 (24%)	64/206 (31%)	37/129 (29%)	71/249 (29%)	79/220 (36%)	188/684 (27%)	150/484 (31%)
Phosphor.	39/207 (19%)	13/102 (13%)	67/281 (24%)	39/167 (23%)	70/311 (23%)	54/285 (19%)	182/838 (22%)	121/593 (20%)

1- Dosage information was not supplied for all patients, therefore, overall totals do not reflect the sum of individual dosage groups.

Cefepime Laboratory Safety
North American Comparative Trials
Intramuscular Administration
Effect of Gender on Laboratory Test Abnormalities
FDA Table

Test	Females		Males		Overall	
	Cefepime	Ceftaz.	Cefep	Ceftaz	Cefep	Ceftaz
BUN	4/37 (11%)	3/23 (13%)	1/14 (7%)	1/7 (14%)	5/51 (10%)	4/30 (13%)
Creat.	1/39 (3%)	0/25 (0%)	1/15 (7%)	0/7 (0%)	2/54 (4%)	0/32 (0%)
Alk Phos	0/35 (0%)	3/23 (13%)	0/13 (0%)	1/11 (9%)	0/48 (0%)	4/34 (12%)
SGOT	5/36 (14%)	2/24 (8%)	4/12 (33%)	1/12 (8%)	9/48 (19%)	3/36 (8%)
SGPT	4/37 (11%)	4/23 (17%)	3/12 (25%)	2/10 (20%)	7/49 (14%)	6/33 (18%)
T. Bili.	No Abnormalities in Bilirubin were detected					
Hematcrt	5/30 (17%)	2/24 (8%)	3/9 (33%)	1/7 (14%)	8/39 (21%)	3/31 (10%)
WBC	2/42 (5%)	0/29 (0%)	2/20 (10%)	0/12 (0%)	4/62 (6%)	0/41 (0%)
ANC	4/34 (12%)	4/25 (16%)	2/18 (11%)	1/12 (8%)	6/52 (12%)	5/37 (14%)
AEC	1/38 (3%)	3/27 (11%)	6/18 (33%)	1/12 (8%)	7/56 (13%)	4/39 (10%)
Platelet	12/48 (25%)	2/28 (7%)	2/15 (13%)	2/9 (22%)	14/63 (22%)	4/37 (11%)
Pro Time	2/36 (6%)	2/25 (8%)	1/16 (6%)	2/11 (18%)	3/52 (6%)	4/36 (11%)
PTT	7/33 (21%)	6/22 (27%)	1/17 (6%)	1/8 (13%)	8/50 (20%)	7/30 (23%)
Sodium	4/32 (13%)	2/20 (10%)	6/14 (43%)	2/10 (20%)	10/46 (22%)	4/30 (13%)
Potas.	8/31 (26%)	4/23 (17%)	3/16 (19%)	1/8 (13%)	11/47 (23%)	5/31 (16%)
Calcium	5/38 (13%)	4/23 (17%)	1/12 (8%)	2/10 (20%)	6/50 (12%)	6/33 (18%)
Phos.	10/42 (24%)	2/25 (8%)	2/16 (13%)	0/9 (0%)	12/58 (21%)	2/34 (6%)

Cefepime Laboratory Safety
North American Comparative Trials
Intramuscular Administration
Effect of Age on Laboratory Test Abnormalities
FDA Table

Test	≤65 years		>65 years		Overall	
	Cefepime	Ceftaz.	Cefep	Ceftaz	Cefep	Ceftaz
BUN	1/34 (3%)	2/21 (10%)	4/17 (24%)	2/9 (22%)	5/51 (10%)	4/30 (13%)
Creat.	2/37 (5%)	0/20 (0%)	0/17 (0%)	0/12 (0%)	2/54 (4%)	0/32 (0%)
Alk Phos	0/29 (0%)	2/21 (10%)	0/19 (0%)	2/13 (15%)	0/48 (0%)	4/34 (12%)
SGOT	5/30 (17%)	3/22 (14%)	4/18 (22%)	0/14 (0%)	9/48 (19%)	3/36 (8%)
SGPT	4/30 (13%)	3/19 (16%)	3/16 (16%)	3/14 (21%)	7/49 (14%)	6/33 (18%)
T. Bili.	No abnormalities in bilirubin were observed					
Hematcrt	5/26 (19%)	2/18 (11%)	3/13 (23%)	1/13 (8%)	8/39 (21%)	3/31 (10%)
WBC	3/40 (8%)	0/22 (0%)	1/22 (5%)	0/19 (0%)	4/62 (6%)	0/41 (0%)
ANC	5/37 (14%)	1/21 (5%)	1/15 (7%)	4/16 (25%)	6/52 (12%)	5/37 (14%)
AEC	5/38 (13%)	1/23 (4%)	2/18 (11%)	3/16 (19%)	7/56 (13%)	4/39 (10%)
Platelet	8/37 (22%)	1/21 (5%)	6/26 (23%)	3/16 (19%)	14/63 (22%)	4/37 (11%)
Pro Time	2/34 (6%)	1/21 (5%)	1/18 (6%)	3/15 (20%)	3/52 (6%)	4/36 (11%)
PTT	5/32 (16%)	3/15 (20%)	3/18 (17%)	4/15 (27%)	8/50 (20%)	7/30 (23%)
Sodium	7/33 (21%)	1/19 (5%)	3/13 (23%)	3/11 (27%)	10/46 (22%)	4/30 (13%)
Potass.	8/31 (26%)	1/18 (6%)	3/16 (19%)	4/13 (31%)	11/47 (23%)	5/31 (16%)
Calcium	3/31 (10%)	3/18 (17%)	3/19 (16%)	3/15 (20%)	6/50 (12%)	6/33 (18%)
Phos.	8/38 (21%)	1/20 (5%)	4/20 (20%)	1/14 (7%)	12/58 (21%)	2/34 (6%)

Cefepime Laboratory Safety
North American Comparative Trials
Intramuscular Administration
Severity of Laboratory Test Abnormalities
FDA Table

Test	#Abnormal/#Tested (Percent)							
	Class II		Class III		Class IV		Overall	
	Cefep	Ceftas	Cefep	Ceftas	Cefep	Ceftas	Cefep	Ceftas
EUN	5/51 (10%)	4/30 (13%)	--	--	--	--	5/51 (10%)	4/30 (13%)
Creat.	2/54 (4%)	0/32 (0%)	--	--	--	--	2/54 (4%)	0/32 (0%)
Alk Phos.	0/48 (0%)	4/34 (12%)	--	--	--	--	0/48 (0%)	4/34 (12%)
SGOT	8/48 (17%)	3/36 (8%)	1/48 (2%)	0/36 (0%)	--	--	9/48 (19%)	3/36 (8%)
SGPT	6/49 (12%)	6/33 (18%)	1/49 (2%)	0/33 (0%)	--	--	7/49 (14%)	6/33 (18%)
Tot. Bill.	No abnormalities of bilirubin were observed							
Hematcrt.	8/39 (21%)	3/31 (10%)	--	--	--	--	8/39 (21%)	3/31 (10%)
WBC	3/62 (5%)	0/41 (0%)	1/62 (2%)	--	--	--	4/62 (6%)	0/41 (0%)
ANC	3/21 (14%)	1/14 (7%)	--	--	--	--	3/21 (14%)	1/14 (7%)
AEC	2/56 (4%)	1/39 (3%)	3/56 (5%)	3/39 (8%)	2/56 (4%)	0/39 (0%)	7/56 (13%)	4/39 (10%)

Cefepime Laboratory Safety
Severity of Laboratory Test Abnormalities - Continued
North American Comparative Trials
Intramuscular Administration
FDA Table

Test	#Abnormal/#Tested (Percent)							
	Class II ¹		Class III ¹		Class IV ¹		Overall	
	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz	Cefep	Ceftaz
Platelet	1/63 (2%)	2/39 (5%)	13/63 (21%)	4/39 (10%)	1/63 (2%)	0/39 (0%)	15/63 (24%)	6/39 (15%)
P.T.	3/52 (6%)	2/38 (6%)	--	--	0/52 (0%)	2/36 (6%)	3/58 (6%)	4/36 (11%)
A.P.T.T.	7/50 (14%)	6/30 (20%)	--	--	1/50 (2%)	1/30 (3%)	8/50 (16%)	17/30 (23%)
Sodium	10/46 (21%)	4/30 (13%)	--	--	--	--	10/46 (21%)	4/30 (13%)
Potass.	8/47 (17%)	5/31 (16%)	2/47 (4%)	0/31 (0%)	1/47 (2%)	0/31 (0%)	11/47 (23%)	5/31 (16%)
Calcium	6/50 (12%)	6/33 (18%)	--	--	--	--	6/50 (12%)	6/33 (18%)
Phosphor.	6/58 (10%)	2/34 (6%)	4/58 (7%)	0/34 (0%)	2/58 (3%)	0/39 (0%)	12/58 (21%)	2/34 (6%)

1- Please see table #1 for definition of the abnormality classes.

North American Comparative Trials
Intravenous Administration
Effect of Dosage on Laboratory Test Abnormalities - Continued
FDA Table

The majority of patients who were treated with cefepime or the control agent via the intramuscular route received 500 mg BID of cefepime or an equivalent regimen of the comparator agent. Therefore, no new information would be obtained from a dose-effect analysis in intramuscular patients.

URINALYSIS

The applicant did not specifically address the urinalysis data that were collected from the study patients. The clinical reviewer discussed this issue with the applicant and additional information was submitted. The FDA reviewer's report appears on the following pages.

URINALYSIS

(reviewed by William Erhardt, MD)

Material Reviewed: The subject of this review is safety data regarding the effect of cefepime hydrochloride on the urinary sediment. The submission includes data generated during the study of the safety and efficacy of Maxipime® (cefepime hydrochloride) for the purposes of a new drug application (NDA:50-679). The material reviewed was contained in three amendments to the original NDA.

Background Information: Cefepime is a parenterally administered, semisynthetic cephalosporin. According to the manufacturer, the drug, when compared with ceftazidime, has equivalent *in-vitro* activity against *Pseudomonas aeruginosa* and fourfold greater *in-vitro* activity against *S. aureus*.

The total body clearance of cefepime is 120 mL/min. The average renal clearance of cefepime is 110 mL/min, therefore, the compound is eliminated almost exclusively by renal mechanisms, primarily glomerular filtration. Approximately 85% of the dose of cefepime may be recovered unchanged in the urine.

The assessment of the potential urotoxicity of a drug through examination of the urinalysis is traditionally included as part of a new drug application. Beam, in the IDSA guideline, "General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products," states that all patients should undergo a routine urinalysis.

Although a routine urinalysis was requested and performed for many patients in the cefepime database the data was not analyzed as part of the integrated summary of laboratory safety by the applicant. The DAIDP requested the applicant conduct an analysis of the effect of cefepime on the urine, this analysis resulted in the submission of the amendments mentioned above.

Analysis Plan:

The applicant and the medical officer identified eight parameters as most indicative of potential urotoxicity. These parameters included a chemical analysis of the urine for protein, glucose and hemoglobin and a microscopic analysis of the urine for red blood cells, white blood cells, casts and crystals. Abnormal values for each parameter were defined and are presented in Table I.

Table I
Definitions of Abnormalities in Urinalysis Parameters

Test	Abnormal Value
Urine Chemistries	
Protein	> 2 +
Glucose	> trace
Hemoglobin	> trace
Urine Microscopy	
RBC	≥ 5 RBC/HPF
WBC	> 5 WBC/HPF
Crystals	> 0
Casts	> 0

To be included in this evaluation, patients had to have at least one value recorded before therapy and one value during treatment or during the follow-up period. The applicant performed an analysis on all patients except those treated for a urinary tract infection. The UTI population was excluded because their underlying disease would make interpretation of any observed urinary abnormalities difficult.

Results:

Table II summarizes the results of the urinalysis data. Hematuria occurred more frequently in the cefepime treatment group than in the ceftazidime treatment group (15% versus 9%, p = 0.002). There was also a higher incidence of glycosuria in cefepime patients (5% with cefepime versus 2% with ceftazidime, p = 0.025). None of the other parameters that were analyzed showed any difference between cefepime and ceftazidime.

Table II
Effect of Cefepime and Control Drug Treatment
on Common Indices of Urotoxicity
(According to the Applicant)

Test	#Abnormal/#Tested (Percent)		
	All Cefepime Courses	Comparative Studies	
		Cefepime	Ceftazidime
Protein	66/1355 (5%)	19/538 (4%)	18/375 (5%)
Glucose	54/1193 (5%)	25/461 (5%)	6/312 (2%)
Red Blood Cells	186/1259 (15%)	76/523 (15%)	29/346 (9%)
RBC > 50	43/1262 (3%)	11/523 (2%)	6/346 (2%)
White Blood Cells	160/1198 (13%)	67/473 (14%)	42/317 (13%)
Crystals	117/1270 (9%)	51/532 (10%)	29/359 (8%)
Casts	165/1469 (4%)	62/518 (12%)	38/34 (11%)

The highest incidence of glycosuria was seen among patients treated with low cefepime doses. Of interest the difference in glycosuria rates between cefepime and ceftazidime was only noted among patients treated for SSTI

Table III
Incidence of Glycosuria

Group	# with Abnorm. Glucose/# Tested (Percent)		
	All Cefepime Courses	Comparative Trials	
		Cefepime	Ceftazidime
Low Dose ¹	23/473 (5%)	17/270 (6%)	3/144 (2%)
High Dose ²	28/662 (4%)	5/168(3%)	2/144 (1%)
Other Doses ³	5/58 (8%)	3/23 (13%)	1/24 (4%)
LRTI	21/409 (5%)	12/218 (5%)	5/126 (4%)
SSTI	13/387 (3%)	10/216 (5%)	0/162 (0%)
Septicemia	5/96 (5%)	4/42 (10%)	0/27 (0%)
Peritonitis	6/41 (15%)	---	---
Biliary Infect.	6/134 (2%)	---	---

¹ Patients treated with daily doses $\leq$ 2 grams per day

² Patients treated with daily doses $>$ 2 grams per day

³ Includes patients with fever and neutropenia who received 6 grams/day.

The most significant finding is the increased incidence of hematuria seen in the cefepime treatment group. The effect is a dose related phenomena, with increasing percentages of patients developing hematuria at higher doses. In addition, hematuria occurred more frequently in patients who had mild abnormalities of the urinary sediment at the baseline evaluation. The effect, however, was not related to the indication treated. (See table IV).

Table IV
Incidence of Hematuria
(According to the Applicant)

Group	# with Urine RBC/# Tested (Percent)		
	All Cefepime Courses	Comparative Trials	
		Cefepime	Ceftazidime
All Patients	186/1262 (15%)	76/523 (15%)	29/346 (8%)
Dose of Cefepime			
Low Dose ¹	57/543 (10%)	41/311 (13%)	12/162 (7%)
High Dose ²	115/655 (18%)	27/183 (15%)	15/156 (10%)
Neutropenia ³	9/37 (24%)	4/19 (21%)	1/16 (6%)
Renal Impaired	5/17 (29%)	4/10 (40%)	1/11 (9%)
Indication			
LRTI	52/419 (12%)	33/216 (15%)	11/118 (9%)
SSTI	52/489 (11%)	37/281 (13%)	15/198 (8%)
Septicemia	19/95 (20%)	8/44 (18%)	3/31 (10%)
Peritonitis	7/37 (19%)	---	---
Biliary Infect.	26/114 (23%)	---	---
Pre-Treatment Urine RBC			
No RBC	86/745 (12%)	28/295 (9%)	15/195 (8%)
1-4 RBC	100/517 (19%)	48/228 (21%)	14/151 (9%)

¹ Patients treated with daily doses $\leq$ 2 grams per day

² Patients treated with daily doses $>$ 2 grams per day

³ Includes patients with fever and neutropenia who received 6 grams/day.

The patients at greatest risk for significant hematuria are those patients who had mild abnormalities of the urinary sediment at the pre-enrollment evaluation. Hematuria is an age related phenomena among patients in the group at greatest risk; hematuria occurs with the highest incidence among elderly patients exposed to cefepime. (See table V)

Table V
 Effect of Age on Hematuria in Patients with 1-4 RBC/HPF at Baseline
 (According to the Applicant)

Group	# with Urine RBC/# Tested (Percent)		
	All Cefepime Courses	Comparative Trials	
		Cefepime	Ceftazidime
Pediatric	1/12 (8%)	---	---
13 - 64 years	63/363 (17%)	20/152 (13%)	9/91 (10%)
≥ 65 years	36/142 (25%)	28/76 (37%)	5/60(8%)

To better characterize the group of patients at risk for hematuria, the medical officer chose the group with the highest incidence of hematuria (≥ 65 years) to examine in greater detail; the medical officer will refer to this group as the "high-risk group" in the remainder of the review.

Among patients in the high-risk group, males and females were equally affected. There was no difference between the two treatment groups in exposure to common risk factors for hematuria (e.g., catheters, bladder cancer, etc.). Most patients, in the high-risk group had low-grade hematuria (<10 RBC/HPF). However, 11/36 patients had > 10 RBC/HPF and 5/36 had > 50 RBC/HPF.

Medical Officer's Comments: Of note, no patients in the ceftazidime treatment group developed > 50 RBC/HPF.

The medical officer reviewed the case report forms of the 11 high risk patients who developed significant hematuria (>10 RBC/HPF) to learn if any other clinical or laboratory abnormalities were associated with the hematuria.

Most of the high-risk patients who developed severe hematuria were treated (7/11 patients). The mean duration of ... in these patients was 7.5 days. 3/11 high-risk patients died.

There were no significant concomitant changes in other indices of renal function (BUN, creatinine) in high-risk patients who developed severe hematuria. There were no significant concomitant abnormalities of the urinary sediment. There were also no significant changes noted in hematologic or coagulation parameters in these patients.

Conclusions:

In comparative studies of cefepime and ceftazidime patients in the cefepime treatment group experienced both hematuria and glycosuria at a significantly higher rate than patients in the ceftazidime treatment group.

Glycosuria occurred in patients who were treated for SSTI:

Also, there was a greater incidence of glycosuria in patients who received low-dose cefepime compared with high-dose cefepime. If glycosuria were truly a toxic effect of the drug, then it should occur in patients treated for all indications. Also, if glycosuria were a toxicity of cefepime it should occur in a dose-related or dose-independent fashion but not in the inverse dose-related manner in which it was observed. Glycosuria can occur in severely ill, hospitalized patients for multiple iatrogenic and disease-related reasons. For example, glycosuria may occur due to the administration of large volumes of glucose containing intravenous fluids or due to stress-induced hyperglycemia. Therefore, the medical officer is not convinced that the observed glycosuria was attributable to cefepime.

In contrast, hematuria was significantly more common in the cefepime treatment group in all indications studied in comparative studies. Also, the incidence of hematuria increased with increasing doses of cefepime. Hematuria occurred most commonly in elderly individuals, however, all age groups were affected. Frequently, the hematuria was low-grade, however, in some instances severe hematuria was noted. In general, the observed hematuria was not associated with any other significant clinical or laboratory abnormalities.

Currently, two other cephalosporin anti-microbials (cephalexin and ceftriaxone) mention hematuria as a potential adverse event in their approved package insert.

Recommendations:

Hematuria (in 15% of patients studied in comparative trials) should be included as an adverse event in the approved package insert for cefepime.

FINAL SAFETY COMMENTS AND RECOMMENDATIONS FOR LABELLING

1. SAFETY SUBMISSIONS

Because of the many exceptions presented in the safety summaries, it was very difficult to determine the denominators of an item of interest and therefore difficult to determine the incidence of such an item. The applicant often had two denominators for the same event. The denominator could either be the number of "courses" or the number of "patients." A single patient could receive more than one "course" of therapy. Many times the applicant referred to "X event (Y%)" without further clarification of denominator. This provided a significant amount of confusion for the reviewer. An example of this problem is illustrated in the applicant's text below:

A total of 4,419 patients were treated initially with cefepime as described in the individual study reports. Some patients in Study 411-143 received more than one course of cefepime as allowed by protocol, contributing an additional 24 courses of cefepime. There were 26 additional patients who were not initially randomized to cefepime who nevertheless contributed 26 more courses of cefepime, either as a second course of study therapy or concomitantly with their randomized treatment therapy. Thus, 4,445 patients received a total of 4,469 courses of cefepime. (volume 286, p. 19)

...

Discrepancies exist between certain patient numbers in the ISS and this 4 month Safety Update. The ISS previously submitted with the June 30, 1992 NDA summarized the safety of the first 6,649 patients. The 4-Month Safety Update presents the NDA patient number count as 6,646. At the time the ISS was written, three of the patients had received a second course of cefepime; however, these three patients had been counted as six patients instead of six courses of therapy. The ISS total of 6,649 cefepime patients is actually the Update number of 6,646 patients. This same discrepancy appears in the ISS discussion of the safety experience of 4,445 cefepime patients in all clinical efficacy studies. Since three of those patients were actually counted twice, the true number of ISS patients is 4,442, as is presented in the Update. (volume 24.1, p. 21)

Is the value "26" given in paragraph one, now 23? The actual number of patients versus the number of courses has a tremendous impact on the ultimate percentages of safety events.

Second, there were many sub-populations: the NDA (European and North American) population, the post-NDA (European and North American) update population, the comparative sub-population, the individual use population, the blinded population, the pharmacokinetic population and the Japanese population (and the excluded Japanese patient subset). The length of the FDA safety review is a reflection of this complexity. In particular, when errors were corrected by the applicant in a safety update; it was often difficult to determine the final "N" of a sub-population.

Recommendation: The concept of "courses" should be eliminated; the incidence of an event should be reported in a specific number of patients. Denominators should be clear (x patients from the NDA, y patients from the first safety update, z patients from the second safety update for a total yield of "n" patients.) Cumulative tallies should itemize all components.

2. DEATHS

Although there were many deaths and many of these deaths were the result of drug failure, there were NO deaths that appeared to be a direct, toxic consequence of the drug.

3. DISCONTINUATIONS

During the clinical trials, most discontinuations were the result of an adverse clinical event. In both North American and European populations, the incidence of discontinuation was dose dependent.

From the over four thousand cefepime patients treated worldwide in the NDA studies, the reviewer believes that the following adverse clinical events with regard to their a) import, b) probability of cause and c) frequency of cause deserve consideration for listing in the label in the section entitled adverse events:

Anaphylactoid reaction, chills, fever, headache, hypotension, pain, diarrhea, dyspepsia, nausea, vomiting, pruritus, rash, and urticaria.

Cefepime was discontinued due to laboratory abnormalities in 0.4% of all 4,442 patients in the NDA. Consideration of inclusion in the adverse events section of the label should be given to the laboratory events listed below that required discontinuation at least two times or more and that were of probable or possible relationship to cefepime administration. These include:

Eosinophilia; elevations in alanine aminotransferase (SGPT) and aspartate aminotransferase (SGOT), alkaline phosphatase, bilirubin, creatinine; neutropenia and leukopenia

Recommendation: A phrase with reference to discontinuation should be included in the adverse reactions section of the label which lists the above events as reasons for discontinuation. This might be stated as follows: During the clinical investigations, MAXIPIME was administered to over 4,442 patients worldwide. In 2.6% of the courses administered, MAXIPIME was discontinued because of adverse clinical events involving the body as a whole (0.6%), including headache and fever; the gastrointestinal system (0.5%) including diarrhea and nausea; and the integument (1.6%) including pruritus, rash and urticaria. Discontinuation of MAXIPIME therapy due to the development of laboratory abnormalities was infrequent (0.4%).

4. LOCAL TOLERANCE

Most patients tolerated cefepime by both the intravenous and the intramuscular routes. The most frequently reported problems with the intravenous route were infiltration, inflammation and phlebitis. Infiltration is a mechanical problem and does not require clarification; phlebitis is more significant. The incidence of local intolerance for all 4224 intravenous courses of cefepime administered during the NDA period was (283/4224) 6.7%. The incidence of phlebitis was 121/4224 = 2.8%. For the intramuscular route, there were 4 reports of local intolerance among 195 (2.0%) patients administered cefepime by this route. In the post-NDA studies, the patient population received infusions usually three times daily. The rate of intolerance increased accordingly. In the post-NDA North American maximum dose (2g TID) studies, 70/314 (20.5%) patients expressed discomfort with the intravenous infusion. There were too few intra-muscular patients post-NDA to comment.

Recommendation: The label should include a statement such as: The incidence of local intolerance for 4224 intravenous courses of cefepime therapy administered worldwide in

clinical trials was 6.7%. The incidence of phlebitis was 2.8%. Among the 195 patients who received MAXIPIME by the intramuscular route, there were only four reports of pain/inflammation. Local reactions required discontinuation in 0.3% of patient courses.

5. ADVERSE CLINICAL EVENTS

For the 4,442 patients who received cefepime therapy before the NDA cut-off date, the following adverse clinical events of either probable or unknown relationship were reported at a frequency of greater than or equal to 0.3%: asthenia (0.3%), fever (0.4%), headache (2.3%), pain (0.4%), chest pain (0.3%), constipation (0.9%), diarrhea (2.4%), dyspepsia (0.4%), nausea (2.0%), abdomen pain (0.7%), vomiting (1.5%), anxiety (0.3%), dizziness (0.6%), insomnia (0.6%), paresthesia (0.3%), pruritus (0.9%), rash (2.1%), and sweating (0.3%). (Moniliasis should be added to this list as well, because there were 2 reports of moniliasis, 10 reports of oral moniliasis, and 5 reports of vaginal moniliasis. All were either probably or of unknown relationship to study drug. This yields an incidence of 0.4%)

Of the 3587 courses administered to adults in North America including the NDA and the first two safety updates, the following adverse clinical events of either probable or unknown relationship were reported at a frequency of greater than or equal to 0.3%: asthenia (0.5%), fever (0.7%), headache (3.4%), pain (0.6%), back pain (0.3%), chest pain (0.6%), tachycardia (0.4%), constipation (1.4%), diarrhea (3.6%), dyspepsia (0.5%), nausea (3.0%), abdomen pain (1.2%), vomiting (2.3%), peripheral edema (0.3%), anxiety (0.4%), confusion (0.4%), dizziness (0.9%), insomnia (1.0%), paresthesia (0.4%), cough (0.3%), dyspnea (0.3%), throat pain (0.3%), pruritus (1.3%), rash (2.8%), sweating (0.4%) and infection (0.3%). (Moniliasis in various body sites totaled 0.5%.)

Anaphylaxis occurred in 7/7362 (0.09%) of patients. Seizures occurred in 16/5162 (0.3%) patients. The majority of the seizures were not attributed to cefepime therapy according to the investigator.

Recommendation: The applicant in their proposed label chose to list all adverse events (in excess of 0.3%) and their respective incidence from the database of adult North American cefepime treated patients (N = 3587) that had been reported until December 31, 1992 (NDA and two safety updates). The disadvantage of using this population is that many patients from the post-NDA experience received maximum dose therapy ($\geq 6\text{g/day}$). The impact of the inclusion of these patients is that the incidence of a given clinical event will be inflated as a result of the expected dose related response. The applicant's decision is acceptable to the reviewer, because it depicts the "worst case scenario."

Therefore, the following adverse clinical events of either probable or unknown relationship should be included in the label: asthenia, fever, headache, pain, back pain, chest pain, tachycardia, constipation, diarrhea, dyspepsia, nausea, abdomen pain, vomiting, peripheral edema, anxiety, confusion, dizziness, insomnia, paresthesia, cough, dyspnea, throat pain, pruritus, rash, and sweating. Moniliasis should also be added for reasons stated above.

Infection should not be included, because it has no clinical meaning. Although less than reported in less than 0.3%, a statement with regard to seizure and anaphylaxis should be included because of their importance.

6. LABORATORY ABNORMALITIES

The most commonly occurring laboratory abnormality was a Coombs' positive test. The next most frequently reported abnormalities were elevations of the liver transaminases.

For the over four thousand patients treated with cefepime summarized in the NDA whose pretreatment values were normal, the incidence of developing a clinically relevant laboratory value during cefepime treatment was as follows:

Hematocrit	5/1886 = 0.2%	Alkaline Phosphatase	16/2413 = 0.7%
Platelets	13/3146 = 0.4%	AST/SGOT	57/2640 = 2.2%
WBC	17/3706 = 0.5%	ALT/SGPT	70/2512 = 2.8%
Neutrophils	24/3230 = 0.7%	Total Bilirubin	26/2923 = 0.9%
Eosinophils	44/3045 = 1.4%	BUN	11/2716 = 0.4%
PT	24/1651 = 1.5%	Creatinine	8/3272 = 0.2%
PTT	39/2323 = 1.6%	Sodium	5/2797 = 0.2%
Coombs' test	136/891 = 15.3%	Potassium	10/3105 = 0.3%
		Calcium	12/1661 = 0.7%
		Phosphorus	67/1912 = 3.5%

The values listed above are the percentage of NDA patients treated with cefepime who had a normal pretreatment value and developed a clinically relevant value either during or post treatment. The reviewer believes that those tests that are 0.7% or greater are meaningful.

The FDA conducted its own analysis of the North American NDA patients in comparative trials, the incidence of developing a clinically relevant value was as follows:

Hematocrit	3/613 = 0.5%	Alkaline Phosphatase	1/845 = 0.1%
Platelets	5/1164 = 0.4%	AST/SGOT	15/879 = 1.7%
WBC	3/1291 = 0.2%	ALT/SGPT	16/855 = 1.9%
Neutrophils	2/1177 = 0.2%	Total Bilirubin	8/1030 = 0.8%
Eosinophils	7/1049 = 0.7%	BUN	1/1015 = 0.1%
PT	10/821 = 1.2%	Creatinine	0/1081 = 0.0%
PTT	20/907 = 2.2%	Sodium	1/647 = 0.2%
		Potassium	4/1083 = 0.4%
		Calcium	4/684 = 0.6%
		Phosphorus	24/838 = 2.8%

For the most part, these two summaries show similar trends in laboratory values that became abnormal during therapy.

Dr. Erhardt, in his analysis of the urinary sediment, found that in comparative studies of cefepime and ceftazidime patients; the cefepime treatment group experienced both hematuria and glycosuria at a significantly higher rate than patients in the ceftazidime treatment group. However, a closer scrutiny of glycosuria did not predict consistency. Therefore, Dr. Erhardt did not believe that the finding was attributable to cefepime. False positive reactions for glucose in the urine has been described for other cephalosporins. It is possible that the glycosuria observed by Dr. Erhardt was an example of this phenomenon. On the other hand, hematuria does appear to be related to cefepime administration.

Patients developed neutropenia (8/112 patients in the NDA) at a high percentage (7.1%) rates if they were treated with cefepime in excess of 21 days.

Recommendations: Because the values of over four thousand patients were consistent with the FDA findings, the reviewer recommends listing all laboratory tests that developed clinically relevant values equal to or greater than 0.7% of the time. This includes: eosinophilia, increased PT, increased PTT, increased alkaline phosphatase, increased AST (SGOT), increased ALT (SGPT), increased total bilirubin, changes in calcium and phosphorus. A Coombs' positive test is frequent (15.3%). Hematuria should be included because of its significance. A statement with regard to the development of neutropenia after prolonged cefepime administration should be included. The applicant should determine if cefepime, like other cephalosporins, causes a false positive test for urinary glucose.

Linda Ann Sherman MD

Linda Ann Sherman, MD

- cc: Original NDA
- HFD-340
- HFD-520
- HFD-520/MO/LSHERMAN
- HFD-520/MO/WERHARDT
- HFD-520/SMO/RALBRECHT
- HFD-520/PHARM/MAINIGI
- HFD-520/MICRO/SOPREY
- HFD-520/CHEM/ROY
- HFD-520/CSO/CDEBELLAS

- CONCURRENCE ONLY:
- HFD-520/DEPCTDIR/MLUMPKIN
- HFD-520/DIVDIR/LGAVRILOVICH

*(F) 6/24/94
acc addendum*

AMENDMENT TO THE SAFETY REVIEW

In response to a request made by the FDA Project Manager for updated safety information, the applicant submitted three amendments to the NDA.

Amendment number 95 was submitted on June 15, 1994. Enclosed were the safety sections of the annual report submitted to IND. The submission covered the reporting period from March 9, 1993 to March 8, 1994; all data entries that were recorded and verified as of March 25, 1994 were included. The database also included 95 blinded patients who were treated in 1992, but whose data was not entered in the annual report of the previous year. During the reporting period, the clinical development program focused on two areas. First, there were comparative clinical trials conducted to gain further experience on the safety and efficacy of cefepime in adults with severe and life-threatening infections at dosages to six grams per day. Second, there were comparative studies in pediatric patients with severe infections.

Amendment number 96 was submitted on June 17, 1994. Additional safety information, from the reporting period November 1, 1993 to June 15, 1994, was submitted in a tabular format. The first table listed the frequency of serious adverse events and deaths for studies conducted during the aforementioned reporting interval. Included in this tabulation were all IND and non-IND studies and the Phase IV and post-marketing experience of France. A second table listed those patients who discontinued therapy due to an adverse clinical event from a single study (A1411-186) conducted in Europe during this period.

Amendment number 97 was submitted on June 23, 1994. This submission contained an amended cover letter for the June 17, 1994 submission.

Because the reporting periods of these additional safety amendments overlapped, they are presented separately on the following pages.

Amendment 95:

The following information (Cefepime Annual Report, submission #212 to the IND and Amendment #95 to the NDA) summarizes the serious adverse events and fatalities during the reporting period given above (3/9/93 to 3/8/94). The information is given in two parts: Phase I-III studies (registrational studies) and Phase IIIb studies (non-registrational studies).

Below is a table which lists the most frequent adverse events by body system, irrespective of causality, occurring at an incidence of > 2% (rate chosen by the applicant) reported from 224 cefepime patients treated from January 1, 1993 (including patients not reported in the 1993 Annual report) through March 8, 1994.

MOST FREQUENT ADVERSE EVENTS BY BODY SYSTEM

Phase I, II, III Protocols
Incidence Greater than 2%
1/1/93-3/8/94 (N = 224)

Body as a Whole	number of patients:
Fever	16 (7.1%)
Headache	11 (4.9%)
Pain	5 (2.2%)
Cardiovascular System	number of patients:
Tachycardia	7 (3.1%)
Digestive System	number of patients:
Abdominal Pain	7 (3.1%)
Diarrhea	26 (11.6%)
Nausea	14 (6.3%)
Vomiting	19 (8.4%)
Metabolism and Nutrition	number of patients:
Edema	6 (2.7%)
Peripheral Edema	8 (3.6%)
Nervous system	number of patients:
Confusion	6 (2.7%)
Convulsion	9 (4.0%)
Drowsiness	5 (2.2%)
Insomnia	5 (2.2%)
Respiratory System	number of patients:
Apnea	7 (3.1%)
Cough	5 (2.2%)
Dyspnea	7 (3.1%)
Hyperventilation	9 (4.0%)
Skin and Appendages	number of patients:
Erythema	5 (2.2%)
Rash	16 (7.1%)

MEDICAL OFFICER'S COMMENTS:

This lists is similar to previous lists of adverse clinical events presented in the NDA and other safety updates. The most frequent events are diarrhea, vomiting, fever and rash.

Below is a list of the most serious events that occurred in the same 224 patients from Phase I, II, III protocols described on the previous page. A total of 53 serious adverse events occurred in 31 patients. Some patients had multiple events.

MOST SERIOUS ADVERSE EVENTS BY BODY SYSTEM

Phase I, II, III Protocols

1/1/93-3/8/94 (N = 224 patients)

Body as a Whole number of events:

Allergic reaction	1
Increased chills	1
Increased rigors	1

Cardiovascular System number of events:

Cardiovascular arrest	2
Heart failure	2
Bradycardia	1
Cardiorespiratory arrest	1
Cerebral thrombosis	1
Temporal arteritis	1
Electromagnetic Dissociation	1
Deep vein thrombosis	1
Decreased Blood Pressure	1

Digestive System number of events:

Cholecystitis	1
Nausea	1
Increased Anorexia	1
Emesis	1

Metabolism and Nutrition number of events:

Malnutrition	1
Metabolic Acidosis	1

Musculoskeletal System number of events:

Hip fracture	1

Nervous system number of events:

Seizures	4
Increased lethargy	2
Cerebral empyema	1
Bulging fontanelle	1
Brain tumor	1
Confusion	1
Mental Clouding	1
Unresponsive	1
Mental Status Deterioration	1

MOST SERIOUS ADVERSE EVENTS BY BODY SYSTEM

Phase I, II, III Protocols
1/1/93-3/8/94 (N = 224)
Continued

Respiratory System	number of events:
Respiratory failure	3
Respiratory distress	2
Tachypnea	2
Cough	1
Respiratory Decompensation	1
Respiratory Arrest	1
Purulent sputum	1
Lung infiltrate	1
Shortness of breath	1
Respiratory difficulty	1
ARDS	1

Special Senses	number of events:
Conjunctivitis	1
Iritis	1
Endophthalmitis	1

Urogenital System	number of events:
Renal failure	1

MEDICAL OFFICER'S COMMENTS:

The applicant did not indicate how it judged an event. At least some of the events listed such as increased chills, cough or conjunctivitis are not usually considered "serious" events.

Below is a summary of the most frequent and most serious events reported in the Phase III b studies during the reporting interval of 3/9/93 -3/8/94. There were seven protocols included in the table below: AI411-196 (56 events in 21 patients), AI411-200 (10 events in four patients), AI411-201 (19 events in 11 patients), AI411-202 (0 events in ongoing study), AI411-204 (78 events in 36 patients), AI411-205 (10 events in 7 patients), AI411-206 (14 serious events in 6 patients) and AI411-207 (5 events in 2 patients). The relationship to study drug is unknown.

**SERIOUS AND MOST FREQUENT ADVERSE EVENTS
PHASE IIIb STUDIES
1/1/93-3/8/94 (N = 87 CEFEPIME PATIENTS)**

Body as a Whole	number of events:
Multi-organ failure	3
Malnutrition	1
Gram negative infection	2
Candidiasis	2
Sepsis/Septicemia	10
Septic Shock	1
Fever	4
Lower Extremity Weakness	1
Hypothermia	1
Febrile Neutropenia	5
Hematologic Cancer	5
Other Cancer	3
Fall	1
Head injury	1
Cardiovascular System	number of events:
Cardiovascular arrest	5
Cardiopulmonary arrest	7
Myocardial Infarct	5
Congestive Heart Failure	2
Syncope	1
Ventricular Tachycardia	2
Atrial fibrillation with flutter	1
Atrial fibrillation	2
Hypotension	11
Shock	2
Deep vein thrombosis	1
MI/CHF	1
Tachycardia	1
Cerebral Hemorrhage	1
Cardiovascular Collapse	2
Digestive System	number of events:
C. difficile infection	1
Gastrointestinal bleeding	1
Abnormal Liver Function Tests	1
Duodenal Ulcer	1
Ischemic Bowel	1
Subacute Cholecystitis	1
Hepatic Failure	1

SERIOUS AND MOST FREQUENT ADVERSE EVENTS
PHASE IIIb STUDIES
 1/1/93-3/8/94 (N = 87 CEFEPIME PATIENTS)
continued

Metabolism and Nutrition	number of events:
Respiratory Acidosis	2
Alcohol Intoxication	1
Metabolic Acidosis	1
Hypoglycemia	1
Diabetes	1
Failure to Thrive	1
Hypokalemia	1
Respiratory Acidosis	1
Increased Liver Function Tests	1
Adequate Nutrition Undeliverable	1

Nervous system	number of events:
Seizures	3
Focal seizures	1
Hypertension	1
Anoxic encephalopathy	1
Encephalopathy	1
Global cerebral ischemia	1
Neurological Damage	1
Multi-infarct Dementia	1
Transverse Myelitis	1
Unresponsiveness	1
Altered Mental Status	2
Anxiety	1
Cerebral Hemorrhage	1
Ataxia	1
Spinal Meningitis	1

Respiratory System	number of events:
Respiratory failure	13
Worsening Respiratory function	1
Dyspnea	3
COPD	4
COPD Exacerbation	2
Respiratory Arrest	1
Pleural effusion	2
Hemothorax	1
Aspiration Pneumonia	1
Pulmonary edema	4
ARDS	3
Cardiopulmonary demise	1
Lung cancer	5
Tension Pneumothorax	1
Apnea	2
Respiratory distress	1
Hypoxia	1
Pneumonia	4
Pulmonary Hemorrhage	1
Aspergillosis	1
Candida esophagitis	1

SERIOUS AND MOST FREQUENT ADVERSE EVENTS
PHASE IIIb STUDIES
1/1/93-3/8/94 (N = 87 CEFEPIME PATIENTS)
continued

Heme/Lymphatic	number of events:
Profound Neutropenia	5
Coagulopathy	2
Skin and Skin Appendages	number of events:
Macular rash	1
Urogenital System	number of events:
Renal failure	3
Chronic Renal Failure	1
Acute Renal Failure	1
Anuria	1

DISCONTINUATIONS DUE TO ADVERSE EVENTS

Phase I, II, III Protocols:

The following is a list of all discontinuations due to adverse events for cefepime treated or blinded (*) patients dosed between 1/1/93 and 3/8/94. (The lists also includes patients who were dosed prior to 1/1/93, but who were not included in the 1993 annual report. In addition, some patients listed below were also listed in the third safety update, amendment #83.) Among the total of 287 cefepime (or blinded patients), ten (10/287 = 3.5%) discontinued.

MEDICAL OFFICER'S COMMENTS.

The reviewer presumes the difference in the denominator of this table (287) and the denominator of serious adverse events table (224) is related to the inclusion of the blinded study patients.

<u>Patient Number</u>	<u>Adverse Event</u>	<u>Relatedness</u>
	Fever	Probably
	Seizure	Not Related
	Hip Pain	Not Related
	Oral Moniliasis	Probably
	Rash	Probably
	Pruritus	Probably
	Rash	Probably
	Diarrhea	Not Related
	Pruritus	Unknown
	Erythema	Unknown
	Cholecystitis	Not related
	Nausea	Not related
	Vomiting	Not related
	Decreased appetite	Not related
	Constipation	Not related
	Rash	Unknown
	Diarrhea	Unknown
	Hemorrhage	Not related
	Hemorrhagic pancreatitis	Not related
	Urinary retention	Not related
	Renal failure	Not related
	Hypotension	Not related
	DIC	Not related
	Lactic acidosis	Not related
	Hypothermia	Not related
	Ventricular tachycardia	Not related
	Anaphylactoid Reaction	Probably
	Flank pain	Unknown
	Nausea	Probably
	Rash	Probably
	Nausea	Not related

DISCONTINUATIONS continued**Phase IIIb Protocols:**

The following is a list of all discontinuations due to adverse events for cefepime-treated patients dosed in Phase IIIb trials between 3/9/93 and 3/8/94. Twenty-seven patients (27/87 = 31%) discontinued therapy due to an adverse clinical event in the Phase IIIb trials.

<u>Patient Number</u>	<u>Adverse Event</u>	<u>Relatedness</u>
	Tension pneumothorax	Not related
	Myocardial infarct/death	Not related
	Metastatic lung cancer/death	Not related
	Anoxia/respiratory failure	Not related
	Respiratory failure/death	Not related
	Seizure	Undetermined
	Cardioresp. failure/death	Not related
	Respiratory arrest	Not related
	Respiratory failure	Not related
	Pleuritic pain	Not related
	Fever	Probably
	Cardiogenic shock/death	Not related
	Cardiac arrest/death	Not related
	Respiratory failure/COPD	Not related
	ARDS	Not related
	Respiratory failure/death	Not related
	Profound hypotension	Not related
	Hypotension	Not related
	Epiglottitis	Not related
	Respiratory failure	Not related
	Septic shock/Death	Not related
	Sepsis/Neutropenia	Not related
	Rash	Unknown
	Sepsis/Kidney failure	Not related
	Gastrointestinal bleed	Not related
	Elevated liver function	Probably
	Rash	Unknown

DEATHS

Phase I, II, III Protocols:

The following table catalogues the deaths of cefepime-treated patients (or patients in blinded studies) dosed between 1/1/93 and 3/8/94. There were a total of 18 deaths (13 adults, 2 children and 2 patients in blinded studies). All deaths were determined by their investigator to be non-drug related. None of the case report forms were submitted.

NOTE: Some of the patients listed below also appeared in Amendment #83. The applicant did not indicate which patients were listed previously.

<u>Children:</u>	<u>Patient Number</u>	<u>Cause of Death</u>
		Infection Pneumonia/RSV/Bronchopulmonary Dysplasia

Blinded Study Patients:

ARDS/Pneumonia
Gastrointestinal hemorrhage/Pancreatitis
Head Injury

Adults:

Respiratory failure/Pneumonia
Hepatic cancer
Metastatic prostate cancer
Biliary carcinoma
Cardiomyopathy
Anemia/ASHD
COPD
Bladder carcinoma/Diabetes/hypertension
Myotonic Dystrophy
Uremia/Status epilepticus/COPD/Infection
AIDS/Kaposi's sarcoma/Disseminated Cryptococcosis
ARDS/Renal failure/COPD/Infection
Pulmonary emboli/Coma/Craniopharyngioma

Phase IIIb Protocols:

The following table catalogues the deaths of cefepime-treated patients recorded between 3/9/93 and 3/8/94. There were a total of 55 adult deaths. All deaths were determined by their investigator to be non-drug related. None of the case report forms were submitted.

<u>Adults:</u>	<u>Patient Number</u>	<u>Cause of Death</u>
		Cardiorespiratory arrest
		Cardiorespiratory arrest
		Respiratory failure
		Myocardial infarct
		Metastatic lung carcinoma
		Multi-organ failure
		Respiratory failure

Phase IIIb Protocols/Deaths/continued:

<u>Adults:</u>	<u>Patient Number</u>	<u>Cause of Death</u>
		Anoxic encephalopathy
		ARDS/Respiratory failure
		Renal failure/dementia/Malnutrition
		Cardiorespiratory failure
		CHF
		Respiratory failure/Multi-organ failure
		Cardiac arrest
		Respiratory failure
		Myocardial infarct, ischemic heart disease
		Cardiac arrest
		Respiratory failure
		Cardiogenic shock/Pulmonary edema
		ARDS/Respiratory failure
		Respiratory Failure
		COPD
		ARDS
		Pneumonia/Transverse Myelitis/Pleural effusion
		Old age
		Respiratory failure/Septic shock
		CML
		Large cell lymphoma
		Hypotension
		Hypotension
		Hypotension/Sepsis/Aspergillus
		Metastatic Adenocarcinoma
		Non-Hodgkin's lymphoma
		Renal/lymphoma
		Sepsis
		Lung cancer
		Sepsis
		Metastatic lacrimal gland carcinoma
		Non-Hodgkin's lymphoma
		Acute leukemia/myelodysplastic syndrome
		Esophageal Carcinoma
		Cardiovascular collapse
		Head injury
		Cerebral hemorrhage
		Leukemia/low grade lymphoma
		Head injury/Brain death
		COPD/seizure disorder
		Cardiovascular collapse
		Pulmonary edema/septicemia
		Sepsis
		Cardiopulmonary arrest
		Ischemic bowel/Cardiopulmonary arrest
		Cardiopulmonary arrest
		Hepatic failure/sepsis
		Respiratory failure

Amendments 96, 97:**Deaths/Serious Adverse Events - Final Summary**

Below is a listing of 394 serious adverse events which occurred in 161 cefepime patients (163 courses) from November 1, 1993 to June 15, 1994. This included reports that were spontaneous, from Phase I-IV trials and from reports in the literature. Patients could have experienced more than one event; all events were listed regardless of causal relationship. There were a total of 79 deaths; seventy-six of these deaths occurred within 30 days of discontinuation. None of the deaths were reported by their investigators to be related to cefepime.

CEFEPIME PATIENTS**Body as a Whole****(111 courses)****number of events:**

Death**	79
Sepsis	25
React Aggrav	21
Fever	12
Multi-Organ Failure	8
Infection	7
Pain, Abdominal	3
Cellulitis	1
Headache	1
HIV	1
Hydrocephalus	1
Hypothermia	1
Mucous Membrane Disease	1
Overdose	1
Unevaluable Reaction	1

Cardiovascular System**(49 courses)****number of events:**

Shock	16
Cardiac arrest	13
Hypotension	10
Myocardial Infarct	3
Syncope	3
Atrial Fibrillation	2
Heart Failure	2
Tachycardia	1
Vascular Anomaly	1
Pericardial Effusion	1
Ventricular Fibrillation	1
Left Heart Failure	1

Digestive System**(19 courses)****number of events:**

Cholecystitis	2
Enterocolitis, Pseudomem	2
Liver Function Abnormalities	2
Vomiting	2
Carcinoma of Mouth	1
Colitis Hemorrhagic	1
Colitis Pseudomembranous	1
Dysphagia	1
Gastroenteritis	1
Hemorrhagic, Gastrointestinal	1

Digestive System (cont.) (19 courses)

number of events:

Hematemesis	1
Jaundice	1
Liver Damage	1
Nausea	1
Intestinal Obstruction	1
Rectal Disease	1
Duodenal Ulcer	1
Gastric Ulcer	1

Endocrine System (1 course)

number of events:

Hypothyroidism	1

Heme and Lymphatic System (13 courses)

number of events:

Leukopenia	7
Lymphoma like Reaction	3
Coagulation Disorder	1
Leukemia Acute	1
Leukemia Chronic Myelogenous	1
Splenomegaly	1

Metabolic and Nutritional Disorders (7 courses)

number of events:

Acidosis	3
Respiratory Acidosis	1
Alcoholic Intolerance	1
Bilirubinemia	1
Creatinine Increased	1
Edema	1
Edema General	1
Hyperglycemia	1
Hypernatremia	1
SGOT increased	1

Musculoskeletal System (1 course)

number of events:

Arthrosis	1

Nervous System (35 courses)

number of events:

Convulsion	5
Neuropathy	4
Coma	3
Hemiplegia	3
Ataxia	2
Edema Brain	2
Meningitis	2
Paralysis	2
Stupor	2
Congenital Anomaly CNS	1
Anxiety	1
Cerebrovascular Accident	1

Nervous System (cont.)	(35 courses)
	<i>number of events:</i>
Delirium	1
Encephalopathy	1
Cerebral Hemorrhage	1
Hypertension	1
Hypotonia	1
Myelitis	1
Neoplasm CNS	1
Multiple Sclerosis	1
Thinking Abnormality	1

Respiratory System	(40 events)
	<i>number of events:</i>
Apnea	10
Dyspnea	6
Respiratory Disorder	6
Pneumonia	5
Lung Disorder	4
Carcinoma of Lung	3
Hypoxia	3
Edema lung	2
Hemorrhage Lung	2
Pharyngitis	2
Pneumothorax	2
Atelectasis	1
Pleural Effusion	1
Pulmonary Embolism	1
Aspiration Pneumonia	1
Sputum Increased	1

Skin and Appendages	(5 events)
	<i>number of events:</i>
Rash	2
Atrophy skin	1
Herpes Simplex	1
Rash Maculopopular	1

Special Senses	(11 events)
	<i>number of events:</i>
Deaf	9
Congenital Anomaly SS	2

Urogenital System	(18 events)
	<i>number of events:</i>
Kidney Function Abnormality	8
Kidney Failure	4
Kidney Failure Acute	4
Anuria	2
Hepatorenal Syndrome	1

MEDICAL OFFICER'S COMMENTS:

The adverse events are consistent with progression of severe illness and similar to those events reported in the previous post-NDA reports. The relationship of the reported events to cefepime therapy was not submitted. The absolute number of deaths is high; this is probably a reflection of the seriously ill patient population. Because there was not an overall denominator, it was not possible to determine the rate of death

The following table is from a single study A1411-186 conducted during this reporting period.

Discontinuations Due to Adverse Clinical Event

The following table lists the reasons for discontinuation of study therapy during Study A1411-186 (non-IND study). The study, conducted in Europe, was a comparative trial of cefepime and ceftazidime/amikacin in the treatment of patients with fever and neutropenia. The study was completed in 1994. All discontinuations are listed irrespective of causal relationship to cefepime. Sixteen of 242 (6.6%) cefepime patients discontinued therapy as compared to four of 111 (3.6%) ceftazidime/amikacin patients who discontinued treatment.

<u>Reason for Discontinuation</u>	<u>Cefepime</u>	<u>CTZ/Amikacin</u>
Allergy	4 (1.7%)	
Cerebral Hemorrhage	1 (0.4%)	
Erythema	3 (1.2%)	1 (0.9%)
Infection	1 (0.4%)	
Rash	4 (1.7%)	3 (2.7%)
Renal Function, impaired	1 (0.4%)	
Respiratory Distress	1 (0.4%)	
Shock	1 (0.4%)	
Thrombocytopenia	1 (0.4%)	
Veno-occlusive Liver Disease	1 (0.4%)	

MEDICAL OFFICER'S COMMENTS:

Cutaneous reactions and allergy were the most common reasons for discontinuation for both groups.

FINAL COMMENT

These safety reports were abbreviated as was the third safety update (amendment 83). Neither amendments number 83 nor 95-97 included information with regard to administration tolerance or laboratory abnormalities. The deaths were many; no death was reported to be related to the administration of cefepime. Case report forms for patients who died or discontinued therapy were not submitted for either the final safety update (#83) nor the current safety updates (#95-97). The list of adverse clinical events did not reveal any new trends or findings. Based on the limited information provided, the reviewer does not recommend any additional revisions of the proposed label.

Pharm/Tax

FEB 1 1993

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS, HFD-520

NDA #50-679 (Original Submission dated 07-01-92)

Drug: Cefepime Hydrochloride (BMY-28142)

Sponsor: Bristol-Myers Squibb Company
Pharmaceutical Research Institute
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660
203-284-7879

Number of Volumes: Fifty-two (52)

Date CDER Received: 07-01-1992

Date Assigned: 07-07-92

Date Review Started: 10-05-92

Date First Draft Completed: 11-03-92

Date Review Accepted by Supervisor: *January 26, 1993*

Dosage and Route of Administration: Intramuscular or intravenous injection (0.5, 1.0, 2.0 g vials)

Category: Cephalosporin Antibiotic

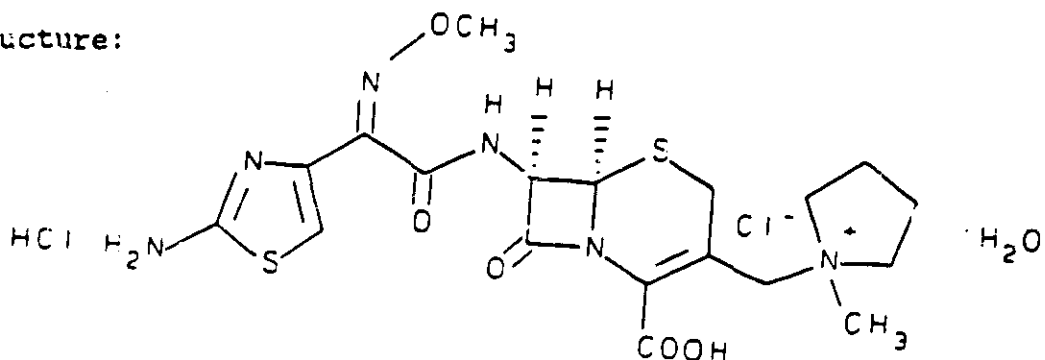
Indication: urinary tract infections, skin and skin structure infections,

Review Objectives: To evaluate the safety of the proposed drug to get approval for marketing in the United States:

Chemical Name: Pyrrolidinium, 1-[[[7-[[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-chloride, monohydrochloride, monohydrate, [6R-[6 α , 7 β (Z)]]

Code Name: BMY-28142

Chemical Structure:



INDEX OF STUDIES

STUDIES SUBMITTED IN NDA-50-679

1. Neonatal toxicity in rats
2. Mouse micronucleus assay
3. Distribution of radioactivity in rodent brains following administration of parent drug and its metabolite

STUDIES SUBMITTED UNDER SUPPLEMENTS (IND

4. Subacute (I.P.) toxicity in rats
5. Pharmacokinetics (I.P.) in rats
6. Effects on arterial and venous pressure in rats
7. Cardiovascular effects of cefepime and cephaloridine in rats
8. Cardiovascular evaluation in dog
9. Effect on isolated rat heart
10. Ames Assay
11. Acute toxicity in rats
12. Subcutaneous pilot study in rats
13. Urinary excretion studies in monkeys

NOTE: A number of studies included in the current submission were reviewed under IND's (Drs. Debbas and Coulter; appendices I, II), and (Drs. Coulter, Mainigi, Morseth, and Snipes; appendices III-VIII).

NDA 58679

11 OF 13

RELATED SUBMISSIONS

IND
IND

BACKGROUND INFORMATION

Cefepime hydrochloride is a semi-synthetic broadspectrum cephalosporin antibiotic for parenteral administration. The initial preclinical toxicity studies of cefepime were conducted using _____ or the lyophilized formulation containing sodium chloride. The latter formulation was used in Phase II clinical trials under IND _____. Reportedly, _____ formulation was not scable enough to meet criteria for a commercially acceptable dosage form of ambient conditions. Therefore, under IND _____ cefepime di HCl/L-arginine, which appeared to be a more suitable formulation, was evaluated. The L-arginine, at an approximate concentration of 725 mg/g of cefepime, is added to control the pH of the constituted solution at 4.0 to 6.0.

PRECLINICAL PHARMACOLOGY

1. _____ Effects _____ on Arterial and Venous Pressure when Administered Arterially and Intravenously to Conscious Sprague-Dawley Rats (DAVI-TJ-20268; March 1986).

Facility:

STUDY DESIGN

Test material was administered by intra-arterial or intravenous injection to 9-11 weeks old rats (259-304 g; sex not mentioned) at the rate of 0.05 mL/second via the right femoral artery or vein. Dose levels of 200, 400, 800 and 1000 mg/kg were

administered to one rat by each route of administration. Controls received volume of saline equivalent to 1000 mg/kg dose. Average pressures were recorded from the left femoral artery and vein every 6 seconds or every 1 minute for 15 minutes post treatment.

RESULTS/CONCLUSIONS

Following the intravenous injection, a transient dose-dependent pressor response developed within 12-30 seconds. At the highest dose level, the initial pressor response was followed by a rapid systemic arterial collapse and death.

Following the intra-arterial injection, pressor responses at all dose levels except 200 mg/kg, were observed within 1-3 minutes. Changes in venous pressure were inconsistent and were not considered evaluable. It was inferred that the drug may have significant cardiovascular effects contributing to the lethality at 1000 mg/kg dose level.

2. A Comparison of the Cardiovascular Effects of Cephaloridine Following Rapid Intravenous Infusion in Anesthetized Rats (HAYE-DC-11256, December 1985).

Study was conducted by the sponsor.

STUDY DESIGN

Anesthetized male S-D rats (251-275 g; 5 rats/group) received rapid intravenous infusion (3 mL/minute) of cephaloridine at doses of 200, 500 and 1000 mg/kg. Pulse rate, mean arterial blood pressure (MABP), and heart rate (HR) were recorded for 5 minutes after the start of infusion.

RESULTS/CONCLUSIONS

No changes were observed in saline infused controls. killed all the rats in the mid- and high-dose groups. Cephalexin killed all the rats in the high-dose group and 1/5 in the mid-dose group. In all cases, an immediate collapse in MABP following the pressor response was observed. This led to a fall in HR, cessation of respiration and death within 2 minutes. Both drugs caused some cardiovascular effects including a small transient pressor response in every rat at each dose level about 10 seconds after the start of infusion. At the low-dose level, MABP and HR stabilized slightly lower than the starting levels following the initial rise in pressure. Although the cardiovascular effects for two drugs appeared to be similar BMX, 28142 was more toxic in this rat model.

3. Ceftazidime and Cephalexin: Comparative Cardiovascular Evaluation in the Conscious Dog (DAVI-TJ-20303; March 1986).

Facility:

STUDY DESIGN

Three antibiotics were administered by intravenous bolus injection (7.6 mL/minute) to one male and one female beagle dogs (about 22 kg). Dose levels were 0, 2, 20, 200 and 500 mg/kg for ceftazidime, and 0, 238 and 500 mg/kg for cephalexin. The following parameters were measured: arterial, right ventricular, pulmonary artery and left ventricular pressures, left ventricular dp/dt, heart rate, total

BIODISPOSITION

5. Pharmacokinetics of [Intraperitoneal Toxicity Study in Rats (#86052; February 1987)].

Study was conducted by the sponsor.

STUDY DESIGN

Animals: Male (212-277 g) and female (177-220 g) Sprague-Dawley (Cr1:CD(SD)BR) rats.

At the initiation of dosing, a catheter was implanted in the jugular vein of each rat. The following day, groups of rats (3 rats/sex/dose level) received a single intraperitoneal dose of 500, 1000, or 1500 mg/kg. Blood samples were drawn from each rat.

In the multiple dose study, groups of rats (3 rats/sex/dose level) received daily doses of 500, 1000, or 1500 mg/kg for one month. Then all animals were catheterized for serial blood sampling.

In both studies, plasma concentrations were determined with an HPLC/UV method, and evaluated by noncompartmental pharmacokinetic methods.

RESULTS

In the single-dose study, drug absorption from the peritoneal cavity into the blood was rapid but apparently a saturable process. Plasma levels were near maximal 6 to 15 minutes after dosing thereafter a plateau was observed. C_{max} was about 1/5 of the value expected for 15 minute i.v. infusion. Regression analyses indicated a significant deviation from a linear relationship between C_{max} and dose, and between AUC and dose; the

1500 mg/kg parameters were lower than expected. Bioavailability data indicated nearly total systemic absorption at the two lower levels. Two of the 18 rats had negligible plasma levels.

Only 7/8 rats receiving multiple doses had detectable plasma drug concentrations. The values for several pharmacokinetic parameters for 7 animals were comparable to those in single dose study. Data suggested an absence of drug accumulation during one month study.

6. Urinary Excretion of Radiolabeled Compounds After i.v. Administration of ¹⁴C-Cefepime to Cynomolgus Monkeys (FORG-ST-20700; March, 1988).

Study was conducted by the sponsor.

STUDY OBJECTIVE/DESIGN

The sole objective of this study was to determine the extent to which N-methyl-pyrrolidine (NMP) formed from catabolism of cefepime is metabolized to its N-oxide by the monkey.

Two female cynomolgus monkeys (3.9-5.6 kg) received 31.6 mg/kg dose of ¹⁴C-cefepime specific activity, 0.5/uc1/mg) as a 5 minute i.v. infusion. The total urine output was collected via the bladder catheter for first 8 hours, and for 16 hour thereafter. Urine samples were subjected to HPLC determination of metabolites.

RESULTS/CONCLUSIONS

The urinary recovery of total radioactivity in two monkeys was 78 and 104% of the administered dose respectively. The amounts of

radioactivity attributable to cefepime, NMP, and N-oxide were virtually the same in both animals, and were 88, 1.6, and 8.9% of the recovered radioactivity, respectively; the chemical nature of the rest of the fraction was not identified. The rates of excretion for NMP and cefepime were similar. It was inferred that like in rat, NMP was extensively metabolized to its N-oxide.

7. Distribution of Radioactivity to Brains of Rats and Mice After Bolus I.V. Injection of ¹⁴C-cefepime and ¹⁴C-NMP (FORG-TS-20206; December, 1985)

Study was conducted by the sponsor.

STUDY OBJECTIVE/DESIGN

These studies were conducted 1) to detect any major differences between rat and mouse with respect to distribution of radioactivity following the bolus, i.v. administration of toxicologic doses of cefepime and 2) to determine if extensive release of N-methyl-pyrrolidine (NMP) moiety of cefepime within the CNS could account for toxicologic signs in rats.

Animals: Male and female Sprague-Dawley rats (181-316 g)

Swiss-Webster mice (23-23 g; sex not mentioned)

Animals were injected with 464-600 mg/kg ¹⁴C-cefepime or 26 mg/kg ¹⁴C-NMP and were decapitated 1-5 minutes thereafter. The bolus i.v. doses were chosen to be slightly below the LD₅₀ (700 mg/kg) value for rats. Lungs, heart, liver, blood, and brain tissues were analyzed for radioactivity. Brain homogenates and plasma of drug-treated animals were subjected to HPLC analysis.

RESULTS/CONCLUSIONS

No significant species difference in the distribution of parent drug to the brain was observed. Brain concentrations uncorrected for blood contamination, were about 2% of the plasma levels. In contrast, the distribution of ¹⁴C-NMP to tissues was rapid and extensive. The tissue ¹⁴C levels for NMP-dosed animals were higher than the plasma levels, indicating rapid penetration of NMP into the CNS.

Two rats died 1.3 minutes after receiving rest exhibited signs of toxicity (e.g. hypoactivity, prostration). None of the mice were affected. Although toxicity was apparent in rats following administration of either compounds, NMP equivalent concentrations in brains of NMP-dosed rats were about an order of magnitude higher than for rats treated with BMY-28142. Therefore, it was inferred that the acute toxicity in the rat was not due to NMP in the brain.

TOXICITY STUDIES

8. Cefepime Intravenous Single-Dose
Lethality Study in Rats (DAVI-RJ-20579; September, 1987)

Study was conducted by the sponsor.

STUDY DESIGN

Animals: Male and female Sprague-Dawley rats (135-195 g).

Dose Groups: Control (L-arginine, 18.7% aqueous); and 1500, 700, 950, 1100, and 1300 mg/kg drug in terms of activity 10 rats/sex/dose group

Postdose observation period: 14 days

Observations/Determinations: General health, mortality, morbidity (daily); body weights (days 0, 8, 15).

RESULTS

Within a couple of minutes after drug administration, overt toxicity including ataxia, decreased activity, difficult respiration, and tremors were observed at 950 mg/kg and higher dose levels. Prostration, ptosis, lacrimation and bluish discoloration of the extremities were frequently observed over the next several minutes. Deaths (950 mg/kg, 1/10; 1100, 1/10; 1300, 5/10; 1500, 9/10) generally occurred within 30 minutes after treatment and were frequently preceded by convulsions and/or Straub tail. Survivors recovered 20-153 minutes post treatment and no significant toxicity was observed thereafter. Median lethal doses were as follows: LD₅₀ (95% confidence limits)

<u>Sex</u>	<u>mg/kg</u> (range)
Males	1272
Females	1057

9. Cefepime Multiple-dose Intravenous and Subcutaneous Pilot Study in Rats (DAVI-TJ-20854; 1987).

Study was conducted by the sponsor.

STUDY DESIGN

Animals: Male Sprague-Dawley rats (197-228 g; 53 days old)

5 rats/dose group

<u>Group No.</u>	<u>Route</u>	<u>Daily Half-Dose*</u> mg/kg	<u>Conc. of Test Sol.*</u> mg/mL
I	I.V.	400	
II	I.V.	200	
III	SC	500	
IV	SC	500	
V	SC	250	

* In terms of BMY-28142 Zwitterion.

All doses were administered twice daily for 10 consecutive days.

OBSERVATIONS/DETERMINATIONS

Clinical signs of toxicity and body weights were recorded daily. Clinicopathologic determinations (serum chemistry, 11 parameters; hematology, 12; urinalysis, 7) were made at study termination, and then all rats were subjected to gross necropsy examinations. The liver and kidney tissues from rats administered i.v. doses of 800 mg/kg/day and s.c. doses of 1000 mg/kg/day (only 50 mg/mL concentration) were subjected to histopathologic examinations.

RESULTS/CONCLUSIONS

Except for minor irritation at the injection sites, no drug-related toxicity was observed in any dose group.

10. One-Month Subacute Intraperitoneal Toxicity Study in Rats (DAVI-TJ-20423; July 1986).

Study was conducted by the sponsor.

STUDY DESIGN

Animals: Eight-weeks old male (212-277 g) and female (177-220 g) Sprague-Dawley rats.

10 rats/sex/dose group

Dose Groups: 0, 500, 1000, or 1500 mg/kg/day.

All doses (aqueous) were administered daily for 28-30 consecutive days.

OBSERVATIONS/DETERMINATIONS

Clinical signs of toxicity: daily

Body weights: days 1, 4, 8, 11, 15, 18, 22, 24, and 27.

Daily food intake: days 1-8, 8-15, 15-22, and 22-27

Gross necropsy: at the end of the treatment period

Urinalyses (8 parameters): on days 25 or 28.

Hematology (12 tests) and serum chemistry (9 tests): days 25-31.

Histopathologic examinations (34 tissues/organs): all rats of the control and high dose groups.

RESULTS

No deaths occurred during the study. Mean body weight gain when compared to controls, was significantly less (25%, $p < 0.05$) in high-dose males. During the first 8 days, high dose males also consumed less food (12%, $p < 0.05$).

A brief extension of the hindlimbs occurred immediately after the administration of mid and high doses. Drug-related signs of irritation consisted of discoloration of the cutaneous and subcutaneous tissue over the injection sites and scrotal discoloration and swelling with subsequent formation of scabs in the mid and high dose groups. Reportedly, scrotal irritation was possibly due to drug passing from the peritoneum into the scrotum via the inguinal canal. Histopathologic examinations revealed focal areas of degeneration, ulceration, hyperplasia, fibrosis

and/or inflammation in these and other tissues as a result of local irritant-effects of the drug.

No significant drug-related changes in laboratory parameters were observed.

11. Cefepime: One-Month Subcutaneous Toxicity Study in Neonatal Rats (#91075; September-October 1991).

Study was conducted by the sponsor.

STUDY DESIGN

Animals: 7 days old male (15-25 g) and female (14-22 g) pups and their dams. All animals were of Sprague-Dawley (Cr1: CDBR VAF/Plus) strain.

10 pups/sex/treatment group.

<u>Dose Group</u>	<u>Test/Control Article</u>	<u>Daily Dose (mg/kg)</u>	<u>Concentration (mg/mL)</u>
I	Saline	-	
II	L-arginine	724*	
III	Cefepime	100	
IV	Cefepime	300	
V	Cefepime	1000	

* Daily dose equal to L-arginine dose for group No. V.

Procedures: Following dosing on study day 1, the pups were culled to either two male and three female or vice versa per dam. Pups were housed with dams until weaning (study day 15, approximately 21 days of age). On study day 22, pups were separately housed.

Aqueous solutions of test-substances were administered subcutaneously to pups in two equally divided daily doses approximately 6 hours apart.

Dams were sacrificed and discarded after weaning of the pups.

Amendment to the protocol: On day 12, three low-dose male pups accidentally received L-arginine solution instead of cefepime for the first daily half-dose on the same test day at the afternoon dosing, all low-dose pups accidentally received 10 times the specified dose volume. Reportedly, no adverse effects because of these dosing errors were observed.

OBSERVATIONS/MEASUREMENTS

Clinical observations: daily

Body weights: Prior to initiation of dosing (day 1) and twice a week for the study period (34-36 days)

Ophthalmic examinations: day 33

Food consumption: for 7 days (days 22 to 30).

Blood and 18-hour urine samples were collected from pups fasted for 18 hours for clinical pathology evaluation on tests days 27-29. All survivors were necropsied on test days 34-36. About 13 major organs were removed and weighed. A total of 42 organs/tissues obtained from groups I and V were subjected to histopathologic examinations. In addition, kidneys, injection sites, and other tissues with gross lesions from all other groups were also examined microscopically.

RESULTS

CLINICAL OBSERVATIONS/MORTALITY

On day one, one high-dose male died accidentally. No other deaths occurred during the study. In a majority of cefepime-treated pups, localized spots of alopecia, generally occurred over the dorsal posterior thoracic or anterior lumbar region and scab

formation on the injection sites. These lesions observed midway through the study period were not dose-dependent.

CLINICAL PATHOLOGY

Except for a slight but insignificant decrease in total protein and/or albumin in high dose animals, no other intergroup differences in hematology, serum chemistry or urinary parameters were observed.

ORGAN WEIGHTS

When compared to saline controls, the group mean absolute (16%) and relative (18%) kidney weights were significantly increased ($p < 0.05$) in the high-dose females. The mean relative kidney weight was also increased in the high-dose males. No other significant intergroup differences in organ weights were observed.

GROSS PATHOLOGY

Minute kidney changes (small cysts, dark foci, indentations) indicative of low grade spontaneous nephritis were more frequently observed in the cefepime-treated groups, however, none of the lesions were dose-dependent. As expected after the cephalosporin treatment, a low incidence of enlarged cecums was observed in the cefepime treated groups.

As expected after the cephalosporin treatment, a local incidence of enlarged cecums was observed in the cefepime treated groups.

HISTOPATHOLOGY

Microscopic lesions characteristic of background spontaneous nephritis (murine nephritis, nephrosis, nephropathy) were recorded in the kidney sections from most of the 100 rats in this study. However, these lesions were more pronounced in the mid- and high-dose groups. In addition, in these groups minimal or slight vacuolation and hypertrophy of one or more regenerative tubules within the nephritic lesions, were also observed.

A low incidence of large intestinal dilation and slightly increased local irritation in and near the injection sites, were observed at all dose levels.

GENOTOXICITY

12. Ames Microbial Mutagenicity Assay
(#87023, August, 1987).

MATERIALS AND METHODS

Salmonella typhimurium (histidine-) strains

TA98, TA100, TA1535, TA1537

Dose Levels Tested: 0.003, 0.01, 0.03, 0.1, and 0.3 ug/plate.

Initially, a dose-range finding study was conducted in strain TA100 at 11 concentrations ranging from _____ ug/plate.

All dose levels were tested in presence/absence of exogenous metabolic activation mix (S9).

Solvent control: water

Positive controls: 2-nitrofluorene

Na-azide

2-aminoanthracene

9-aminoacridine

DMSO was used as negative control as well as solvent for organic positive controls.

RESULTS/CONCLUSIONS

Moderate cytotoxicity (a reduction in histidine revertants) was observed at the highest dose level in all strain with/without S9 mix. However, there was no significant increase in histidine⁺ revertants in any drug treated cultures when compared to the negative control. Therefore, under the assay conditions, BMY-28142 was not mutagenic.

13. Cefepime Arginine: IV Bone Marrow Erythrocyte
Micronucleus Assay in Mice (YOTT-LP-21939, May-June 1991).

TESTING FACILITY:

MATERIALS AND METHODS

Animals: Nine to ten weeks old Swiss CD1 males and female mice.

Dose Levels: 800 and 1200 mg/kg

Solvent: Sterile water (control)

Positive control: 9,10-dimethyl-1,2-benzanthracene in DMSO

Procedures: Ten mice/sex/dose/sampling time received a single i.v. dose of the test article, and the survivors of each dose group were sampled at 24, 48 and 72 hours after treatment. Twelve mice (6M + 6F) received two intraperitoneal injections of positive control at 0 and 24 hours; survivors were sampled 48 hours after the treatment.

Bone marrow smears were analyzed for the formation of micronucleated polychromatic erythrocytes (PCEs).

RESULTS/CONCLUSIONS

Only one statistically significant increase in group mean micronucleated PCEs was recorded at 48 hour in low dose cefepime group. Reportedly, because of exceptionally low negative control micronucleus frequency, this single point increase was considered a statistical artifact. A 25% lethality was observed at the high cefepime dose level. Under the assay conditions, cefepime diHCl: arginine was not genotoxic.

LABELING

The proposed text of labeling should be modified to include the essential details as follows:

Carcinogenesis, Mutagenesis and Impairment of Fertility

No long-term animal carcinogenicity studies were conducted. A battery of in vivo and in vitro genotoxicity tests, including bacterial Forward and Reverse Mutations, CHO/HGPRT mammalian cell forward gene mutation, chromosomal aberration assay in human lymphocytes, CHO fibroblast clastogenesis, sister chromatid exchange, cytogenetic and micronucleus assays in mice, revealed no evidence for a mutagenic or clastogenic potential for the drug. No untoward effects on fertility or reproduction were observed in rats, mice and rabbits when subcutaneously administered at 1-4 times (mg/m²) the human dose.

(mg/m²)

NS



Pregnancy-Pregnancy Category B

Cefepime HCl was not teratogenic or embryocidal when administered during the period of organogenesis to rats at doses up to 1000 mg/kg/day (4 times the human dose in terms of mg/m²/day) or to mice at doses up to 1200 mg/kg/day (2 times human dose) or to rabbits at dose level of 100 mg/kg/day (approximately equal to daily human dose). There are, however, no adequate and well-controlled studies of cefepime HCl use in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

OVERDOSAGE

Intravenous overdose in rats within minutes caused ataxia, decreased activity, difficult respiration, and tremors. A large intravenous bolus dose in rats led to cardiovascular failure. Deaths in rabbits following the acute intravenous dose (2000 mg/kg) were attributed to acute colitis/typhlitis (enterotoxemia).

TOXICOLOGISTS' DISCUSSION & INTERPRETATION OF SAFETY DATA

The sponsor has presented a complete and elaborate toxicity profile for cefepime. A good number of studies were conducted with formulation containing instead of cefepime diHCl:arginine. Some of these studies did not follow the GLP guidelines. However, these deficiencies did not affect the final projection of a safety profile.

The patterns for metabolism and pharmacokinetics were very similar in animals and humans. In all species tested, the excretion of drug-related radioactivity was fairly rapid, and within 24 hours of administration more than 80% of intact drug was excreted in the urine. The $T_{1/2}$ of elimination in monkeys was 1.7 hours. The main catabolite, N-methylpyrrolidine was rapidly converted to the N-oxide in humans and all the animal species tested.

Following the intravenous administration in animals, cefepime exhibited a low order of acute toxicity. In dogs and monkeys, rapidly injected acute single doses produced only mild transient effects. In rats, rapid intravenous injection of cefepime resulted in significant but reversible cardiovascular effects; at high bolus doses, these effects caused deaths. However, no significant effects were observed in dogs or monkeys receiving similar intravenous bolus doses.

In the multiple dose studies with cefepime, the number of heterolysosomes in the epithelium of proximal tubules of kidneys increased in all animal species tested. Assumably, this change was related to the renal handling of the drug. An increase in the incidence and severity of age-associated nephropathy was observed in the 6-month study in rats. In a parallel dog study, within 5-6 weeks of dosing, severe hematotoxicity characterized by anemia, leukopenia, and thrombocytopenia, was observed. However, it must be mentioned that such effects have been observed with other cephalosporins.

In a battery of invitro and in vivo genotoxicity tests, cefepime was non-mutagenic and non-clastogenic. Drug was not teratogenic or embryocidal in rodents when tested at 1-4 times (mg/m²) of the proposed clinical dose. Several deaths in rabbit segment II study at 100 mg/kg (equivalent to about one times the human dose on mg/m² basis) were attributed to enterotoxemia thought to be the result of bactericidal activity of cefepime against Gram-positive bacteria and the subsequent changes in the intestinal flora.

RECOMMENDATIONS

1. From the preclinical point of view, cefepime has exhibited a fairly safe safety profile. Therefore, I have no objection to the approval of this new drug application.
2. The sponsor should be asked to expand the draft of labeling as suggested in this review.

Kumar D. Mainigi 01/26/93
Kumar D. Mainigi, Ph.D., DABT

Toxicologist

cc: Orig. NDA
HFD-82
HFD-502
HFD-520
HFD-520/Div. Dir./Lumpkin
HFD-520/Dep. Dir./Gavrilovich
HFD-520/M.O./Sherman
HFD-520/Micro/Dionne
HFD-520/Pharm./Mainigi
HFD-520/CSO/Debellas

REC 1/26/93
2/1/93

ADDENDUM

As pointed out on page 2, the following studies used to support this NDA were evaluated by other reviewers (Appendices I-VIII).

Reviewer: Gamil C. Debbas, Ph.D.

1. Acute toxicity studies in monkeys, mice, dogs and rats.
2. Acute toxicity studies in rabbits.
3. Pilot dose-range-finding studies (I.V.) in rat and monkey.
4. Subacute toxicity studies (I.V.) in rat and monkey.
5. CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay.
6. Hepatocyte Culture/DNA Repair Assay.
7. Rat-Comparative lethality-IV bolus vs. infusion.
8. Pharmacodynamic safety assessment of BMY-28142 (sodium chloride) in dogs and rats.
9. In Vivo and in Vitro cardiovascular evaluation of BMY in rats.
10. Safety pharmacology of BMY-28142-sulphate.
11. The possible role of serotonin in the acute (bolus) IV lethality in the rat.
12. Pharmacokinetics in cynomolgus monkeys and rats.

Reviewer: Almon W. Coulter, Ph.D.

1. Three-month toxicity study in rats (S.C.).
2. Three-month toxicity study in monkeys (I.V.).
3. Teratology and reproduction studies.
 - a. Segment I in rats-interim report.
 - b. Segment II in mice.
 - c. Segment II in rats.
 - d. Segment II in rabbits.
4. Acute toxicity studies in mice, rats and dogs.
5. Single-dose intramuscular irritation study in rabbits.
6. One-month subacute toxicity study (I.V.) in rats.
7. One-month subacute toxicity study (I.V.) in dogs.
8. Four-week intramuscular irritation (tolerability) study in dogs.
9. Teratology (Segment II) study in rats with Cefepime L-Arginine).
10. In vitro cytogenetic assay measuring chromosome aberration frequencies in human lymphocytes.

Reviewer: Kumar D. Mainigi, Ph.D., DABT

1. Six-month intravenous toxicity study in dogs.

Reviewer: Sandra L. Morseth. Ph.D.

1. A two-week subcutaneous toxicologic study in male neonatal rats.

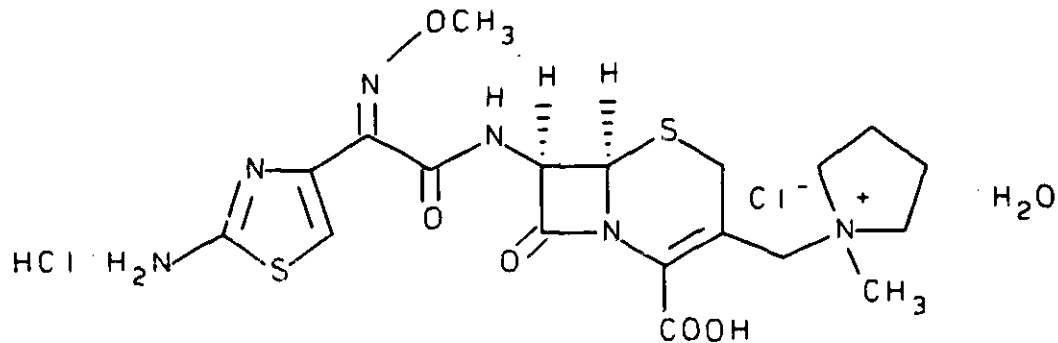
Reviewer: Charles A. Snipes, Ph.D.

1. Cefepime/Venopirin, intravenous multiple-dose safety study in beagle dogs.
2. Cefepime : A perinatal and postnatal study in rats.
3. In vivo cytogenetic assay in mice.

2.0 PHARMACOLOGIC CLASS, SCIENTIFIC RATIONALE, INTENDED USE AND POTENTIAL CLINICAL BENEFITS 000039

Pharmacologic Class

Cefepime is a semi-synthetic broad-spectrum cephalosporin antibiotic intended for parenteral administration. It has a methoxyimino-aminothiazole at the 7 side chain, and a 3' N-methyl pyrrolidine substituent. The structure and chemical name are presented below.



Pyrrolidinium, 1-[[7-[[[(2-Amino-4-thiazoyl)(methoxyimino) acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-, chloride, monohydrochloride, monohydrate, [6R-[6 α ,7 β (Z)]]-

Scientific Rationale

As with other cephalosporins and beta-lactam antibiotics, the mechanism of action of cefepime is interference with the binding of substrate to Penicillin Binding Proteins (PBP), which causes bactericidal changes in susceptible strains (reviewed by Waxman DJ and Strominger JL, "Beta-lactam antibiotics: Biochemical Modes of Action in Morin RB and Gorman M eds. Chemistry and Biology of Beta-lactam Antibiotics. 1982, Vol.3 pages 209-285. Academic Press, New York). Specific experimental data on the

02-000040

acylation of PBP by cefepime are documented in the Microbiology Section of this NDA. In particular, cefepime has very high affinity for *S. aureus* PBP1. In *E. coli* and *E. cloacae*, cefepime has greatest affinity for PBP3 and PBP2 and has lower affinity for PBP1a and PBP1b. The high affinity for PBP2 in these species is unique among advanced-generation cephalosporins and may explain the excellent activity of cefepime against *Enterobacter* spp and other gram-negative bacteria. The quaternary nitrogen in the N-methyl pyrrolidine moiety of the cefepime molecule appears to provide enhanced potency against *Pseudomonas*; the methoxyimino-aminothiazole moiety appears to aid cefepime's potency against gram-positive organisms.

Intended Use

The broad spectrum of activity, pharmacology, and clinical efficacy and safety data support the parenteral (both intravenous and intramuscular) use of cefepime in adults for the following types of infections: Pneumonia, Complicated and Uncomplicated Urinary Tract Infections, Skin and Skin-Structure Infections,

Potential Clinical Benefits

Cefepime offers, in a single agent, an excellent safety and efficacy profile with broad-spectrum activity against the principal bacterial pathogens causing the most important types of moderate, severe, and very severe, life-threatening infections in hospitalized patients. Cefepime displays better *in vitro* potency against *S. aureus* than ceftazidime, and better potency against *P. aeruginosa* than cefotaxime. Cefepime's potency against *Enterobacter*, an increasingly important nosocomial pathogen, is unique among currently available cephalosporins. In studies of the emergence of antibiotic-resistant strains, cefepime produces lower mutational frequencies *in vitro* than ceftazidime; in animal models cefepime produces much less frequent selection of resistant strains than do ceftriaxone or ceftazidime. Cefepime also provides pharmacologic and therapeutic advantages over other

cephalosporins. Cefepime displays linear kinetics (parameters unchanged by repeated dosing) with a half-life which permits BID dosing for all except very severe, life-threatening infections. When administered by the intramuscular route, cefepime is 100% bioavailable and better tolerated than ceftriaxone.

02 000041

Clinical
micro Rv

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Clinical Microbiological Review

NDA #: 50-679 REVIEW #: 2.1 REVIEW DATE: 07-21-94

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	30-06-92	07-07-92	15-07-92
AMENDMENT 25AC	22-12-92	23-12-92	26-12-92
AMENDMENT 26AC	30-12-92	31-12-92	07-01-93
AMENDMENT 56BL	04-06-93	07-06-93	08-06-93

NAME & ADDRESS OF APPLICANT: Bristol-Myers Squibb Company
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

DRUG PRODUCT NAME
Proprietary: MAXIPIME
Nonproprietary/USAN: Cefepime hydrochloride
Code Names/#'s: BMY-28142
Chemical Type/
Therapeutic Class: 1 S

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Antibacterial/
Antibiotic obtained by chemical synthesis

urinary tract infection;
skin and skin structure infections;

DOSAGE FORM: Sterile powder for
STRENGTHS: 500 mg, 1.0g, 2g / vial
ROUTE OF ADMINISTRATION: IM or IV
DISPENSED: XX Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT: C₁₅H₁₄N₄O₅S₂.Cl.Hcl.H₂O 571.5
Pyrrolidinium, 1((7-(((2-amino-4-thiazoyl)
(methoxyimino)acetyl)amino)-2-carboxy-8-oxo-5-thia-1-
azabicyclo(4.2.0)oct-2-en-3-yl)methyl-1-methyl-chloride,
monohydrochloride, monohydrate
CAS 123171-59-5 (Cefepime)

SUPPORTING DOCUMENTS:

IND
IND

REMARKS/COMMENTS:

The drug product presented in this NDA is a sterile homogenous blend of sterile cefepime hydrochloride and sterile L-arginine.

Review of this NDA is presented in two parts. Part 1.1 Review of Chemistry, Manufacturing, and Controls, entails review of the microbiological issues applicable to the manufacturing, processing and distribution of the drug substance (sterile cefepime hydrochloride) and the excipient (L-arginine) and the sterile drug product (blend of cefepime hydrochloride and L-arginine).

Part 2.1 Clinical Microbiological Review, covers the microbiological aspects related to the mechanism of action, in vitro spectrum of activity and efficacy of the new drug substance cefepime hydrochloride.

Chemistry and manufacturing controls applicable to manufacture and distribution of the drug substance and the drug product will be reviewed by HFD-520 Chemist.

CONCLUSIONS & RECOMMENDATIONS:

1. In vitro susceptibility of the clinical isolates is established by determining MIC levels and disk diffusion zone of inhibition. The test data provided in this NDA is satisfactory.
2. The antimicrobial spectrum of cefepime as determined by the 30 µg cefepime disk against aerobic bacteria is similar to that determined by MIC determinations. The test data provided in the NDA are satisfactory.
3. Effect of cefepime on the multi-resistant bacteria was investigated. Cefepime was often active against bacteria that were resistant to other cephalosporins. Development of in vitro resistance to cefepime in bacteria was investigated and the potential for selection of spontaneous, stable drug resistant mutant bacteria was low. These findings are supported by experimental data in the form of publications and reports.
4. Bactericidal activity was determined by time-kill kinetic analysis and by minimum bactericidal concentrations. In general the bactericidal activity was less than or twice that of the MIC.
5. Cefepime had no significant effect on opsonophagocytosis of either gram-positive or gram negative-bacteria. Post-antibiotic effect was dose-dependent and at peak concentrations ($\approx 65 \mu\text{g}/\text{Ml}$) PAE ranged between hours when tested against indicator strains. No PAE was noted against *P. aeruginosa*. Cefepime and aminoglycosides show slight synergistic effect against gram-negative bacteria and showed antagonism with imipenem or polymyxin B.
6. Data of pharmacokinetics and bioavailability studies in animal model and humans is provided. The sponsor states that cefepime is completely absorbed and within 24 hours of administration, >80% of the cefepime is excreted in the urine as unchanged drug. The levels of the drug in plasma exceed the MIC₉₀ of selected gram-positive and gram-negative pathogens and the drug levels in plasma were maintained higher than the MIC₉₀ for the period up to 8 hours. However, verification of these conclusions must await analysis of the data by the Division of Biopharmaceutics.

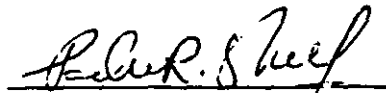
7. Development of drug resistance was determined in experiments conducted with animal models for selected bacterial infections and by *in vitro* test methods. Relative to all cephalosporins tested, cefepime selected less frequently resistant bacteria. These findings are supported by experimental data in the form of publications and reports.

8. The data provided to establish breakpoints resulted in the establishment of the following: zone diameters of ≥ 18 mm (MIC correlate, $\leq 8 \mu\text{g}/\text{mL}$) for susceptible, ≤ 14 mm (MIC correlate, $\geq 32 \mu\text{g}/\text{mL}$) for resistant and 15-17 mm (MIC correlate, $16 \mu\text{g}/\text{mL}$) for an intermediate range. Results of the MIC and disk diffusion quality control studies using standard cultures have been provided. The established breakpoints and quality control limits for the MIC and disk diffusion test were established by the FDA and are identical to those established by the NCCLS.

RECOMMENDATIONS:

The application is approvable from a manufacturing and controls microbiological perspective as provided under section 507 of the FD&C Act. All manufacturing facilities are currently in acceptable GMP compliance, however, the Review Chemist will be get an updated EER.

The indication section provided by the applicant will be modified by the Reviewing Medical Officer. The microbiological section of the original PI has been modified to reflect the recommendations of the "Points to Consider" document.



Pandu R. Soprey, Ph.D.
Review Microbiologist

cc: Orig. NDA 50-679
HFD-520/Division File
HFD-520/Micro/Soprey
HFD-520/Chem/Roy
HFD-520/MO/Sherman
HFD-520/Ph/Mainigi
HFD-520/CSO/DeBellas
HFD-520/SupMicro/Sheldon
R/D Init by: Sheldon: 3-5-93, 3-23-93, 6-2-94, 7/21/94
filename: N50679.r2.1 *TS 7/21/94*

cc 7/22/94

Chem

C 5
JAN 26 1991

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-679 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 1-25-93

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	6-30-92	7-2-92	8-2-92
AMENDMENT/AC	10-16-92	10-21-92	10-21-92
LETTER	12-3-92		
LETTER	12-14-92		
AMENDMENT/AC	12-22-92	12/23/92	12/24/92
AMENDMENT/BC	12-30-92	12/31/92	1/4/93
AMENDMENT/BC	1-6-93	1/7/93	1/11/93

NAME & ADDRESS OF APPLICANT: Bristol-Myers Squibb Company
5 Research Parkway
P. O. Box 5100
Wallingford, CT 06492-7660

DRUG PRODUCT NAME

Proprietary: To be decided
Nonproprietary/USAN: Cefepime hydrochloride
Code Names/#'s: BMY-28142
Chemical Type/
Therapeutic Class: 1 8

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:

Urinary tract
Infections; Skin and skin structure infections;

DOSAGE FORM:

Sterile Powder for Injection

STRENGTHS:

500mg ; 1.0g ; 2g /vial

ROUTE OF ADMINISTRATION:

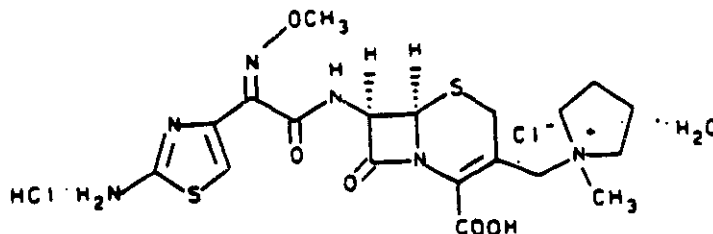
I.M or I.V

DISPENSED:

Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA.

MOL. WT: C₁₉H₂₂N₆O₅S₂.Cl.HCl. H₂O Mol. weight 571.5
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-methyl, chloride-pyrrolidinium hydroxide, inner salt, 7²-(Z)-(O-methyloxime), monohydrochloride, monohydrate



CAS 123171-59-5 (Cefepime)

NDA 50-679
Bristol-Myers
Cefepime hydrochloride

page 2

PATENT STATUS: U.S. Patents:
4,406,899 expires 9/27/2000
4,910,301 expires 9/27/2000
4,994,451 expires 2/19/2008
5,095,011 expires 3/10/2009

SUPPORTING DOCUMENTS:

IND
IND

DMF

RELATED DOCUMENTS (if applicable): None

CONSULTS:

Environmental Impact Assessment consult to Dr. Phillip Vincent, on 7/13/92. Consult is outstanding.

REMARKS/COMMENTS:

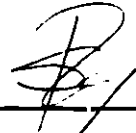
Environmental consult, methods validations and facilities inspections are outstanding.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 505 (or 507 for an antibiotic) of the Act.

NDA 50-679
Bristol-Myers
Cefepime hydrochloride

page 3



Suva B. Roy, Ph.D.
Review Chemist

cc: Orig. NDA 50-679
HFD-520/Division File
HFD-520/SBR/date
HFD-520/Sherman
HFD-520/Mainigi
HFD-520/Soprey
HFD-520/Debellas
HFD-520/SUPERVISOR *VA 1/14/94*
HFD-102/CKumkumian (#1 only)
R/D Init by: SUPERVISOR
filename:N50-679. R1 *1/24/94*

133

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-679 **CHEM. REVIEW #:** 2 **REVIEW DATE:** 3-16-93

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	6-30-92	7-2-92	8-2-92
AMENDMENT/AC	10-16-92	10-21-92	10-21-92
LETTER	12-3-92		
LETTER	12-14-92		
AMENDMENT/AC	12-22-92	12/23/92	12/24/92
AMENDMENT/BC	12-30-92	12/31/92	1/4/93
AMENDMENT/BC	1-6-93	1/7/93	1/11/93

NAME & ADDRESS OF APPLICANT: Bristol-Myers Squibb Company
5 Research Parkway
P. O. Box 5100
Wallingford, CT 06492-7660

DRUG PRODUCT NAME

<u>Proprietary:</u>	To be decided
<u>Nonproprietary/USAN:</u>	Cefepime hydrochloride
<u>Code Names/#'s:</u>	BMV-28142
<u>Chemical Type/</u>	
<u>Therapeutic Class:</u>	1 8

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:

Urinary tract
Infections; Skin and skin structure infections;

<u>DOSAGE FORM:</u>	Sterile Powder for Injection
<u>STRENGTHS:</u>	500mg ; 1.0g ; 2g /vial
<u>ROUTE OF ADMINISTRATION:</u>	I.M or I.V
<u>DISPENSED:</u>	<u> X </u> Rx <u> </u> OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL. WT: C₁₉H₂₄N₆O₅S₂.Cl.HCl. H₂O Mol. weight 571.5
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-methyl, chloride-pyrrolidinium hydroxide, inner salt, 7²-(Z)-(O-methyloxime), monohydrochloride, monohydrate

CAS 123171-59-5 (Cefepime)

PATENT STATUS: U.S. Patents:
4,406,899 expires 9/27/2000
4,910,301 expires 9/27/2000
4,994,451 expires 2/19/2008
5,095,011 expires 3/10/2009

NDA 50-679
Bristol-Myers
Cefepime hydrochloride

page 2

SUPPORTING DOCUMENTS:

IND
IND

DMF

RELATED DOCUMENTS (if applicable): None

CONSULTS:

Environmental Impact Assessment consult to Dr. Phillip Vincent, on 7/13/92. Consult is outstanding.

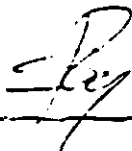
REMARKS/COMMENTS:

Environmental consult and facilities inspections are outstanding.

Methods validation report has been received. The methods have been validated.

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 507 of the Act.



Suva B. Roy, Ph.D.
Review Chemist

cc: Orig. NDA 50-679
HFD-520/Division File
HFD-520/SBR/date
HFD-520/Sherman
HFD-520/Mainigi
HFD-520/Soprey
HFD-520/Debellas
HFD-520/SUPERVISOR *11/17/97*
HFD-102/CKumkumian [#1 only] *1/20/98*
R/D Init by: SUPERVISOR
filename:N50-679. R2

10 16 93

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-679 **CHEM. REVIEW #:** 3 **REVIEW DATE:** 10-26-93

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	6-30-92	7-2-92	8-2-92
AMENDMENT/AC	10-16-92	10-21-92	10-21-92
LETTER	12-3-92		
LETTER	12-14-92		
AMENDMENT/AC	12-22-92	12-23-92	12-24-92
AMENDMENT/BC	12-30-92	12-31-92	1-4-93
AMENDMENT/BC	1-6-93	1-7-93	1-11-93
AMENDMENT/AC	8-4-93	8-9-93	8-11-93

* Responses to deficiencies from Review 1 and 2. Deficiency letter of 4/14/93

NAME & ADDRESS OF APPLICANT: Bristol-Myers Squibb Company
5 Research Parkway
P. O. Box 5100
Wallingford, CT 06492-7660

DRUG PRODUCT NAME

<u>Proprietary:</u>	To be decided
<u>Nonproprietary/USAN:</u>	Cefepime hydrochloride
<u>Code Names #'s:</u>	BMV-28142
<u>Chemical Type/</u>	
<u>Therapeutic Class:</u>	1 S

ANDA suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:

Urinary tract
Infections; Skin and skin structure infections;

DOSAGE FORM:

Sterile Powder for Injection

STRENGTHS:

500mg ; 1.0g ; 2g /vial

ROUTE OF ADMINISTRATION:

I.M or I.V

DISPENSED:

Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,

MOL.WT: C₁₉H₂₄N₆O₅S₇.Cl.HCl. H₂O Mol. weight 571.5
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-methyl, chloride-pyrrolidinium hydroxide, inner salt, 7²-(Z)-(O-methyloxime), monohydrochloride, monohydrate

CAS 123171-59-5 (Cefepime)

NDA 50-679
Bristol-Myers
Cefepime hydrochloride

page 2

PATENT STATUS: U.S. Patents:

4,406,899 expires 9/27/2000
4,910,301 expires 9/27/2000
4,994,451 expires 2/19/2008
5,095,011 expires 3/10/2009

SUPPORTING DOCUMENTS:

IND
IND

DMF

RELATED DOCUMENTS (if applicable): None

CONSULTS:

Environmental Impact Assessment consult to Dr. Phillip Vincent, on 7/13/92. Consult is outstanding.

REMARKS/COMMENTS:

Methods validation from the second laboratory and environmental Impact Assessment are outstanding. Facilities are acceptable

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 505 (or 507 for an antibiotic) of the Act.

NDA 50-679
Bristol-Myers
Cefepime hydrochloride

page 3

S. B. Roy

Suva B. Roy, Ph.D.
Review Chemist

cc: Orig. NDA 50-679
HFD-520/Division File
HFD-520/SBR/date
HFD-520/Sherman
HFD-520/Mainigi
HFD-520/Soprey
HFD-520/DeBellas
HFD-520/SUPERVISOR *1/14/94*
HFD-102/CKumkumian [#1 only]
R/D Init by: SUPERVISOR
filename:N50-679. R3

- DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
- Review of Chemistry, Manufacturing, and Controls

NDA #: 50-679 **CHEM.REVIEW #:** 4 **REVIEW DATE:** 2-28-94

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	6-30-92	7-2-92	8-2-92
AMENDMENT/AC LETTER	10-16-92	10-21-92	10-21-92
LETTER	12-3-92		
LETTER	12-14-92		
AMENDMENT/AC	12-22-92	12-23-92	12-24-92
AMENDMENT/BC	12-30-92	12-31-92	1-4-93
AMENDMENT/BC	1-6-93	1-7-93	1-11-93
AMENDMENT/AC*	8-4-93	8-9-93	8-11-93
AMENDMENT/AC**	2-15-94	2-16-94	2-23-94

- * Responses to deficiencies from Review 1 and 2. Deficiency letter of 4/14/93.
- ** Response to deficiencies from Review 3. Deficiency communication of 1/14/94.

NAME & ADDRESS OF APPLICANT: Bristol-Myers Squibb Company
5 Research Parkway
P. O. Box 5100
Wallingford, CT 06492-7660

DRUG PRODUCT NAME
Proprietary: MAXIPIME®
Nonproprietary/USAN: Cefepime hydrochloride
Code Names/#'s: BMY-28142
Chemical Type/
Therapeutic Class: 1 8

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Urinary tract
Infections; Skin and skin structure infections;

DOSAGE FORM: Sterile Powder for Injection
STRENGTHS: 500mg ; 1.0g ; 2g /vial
ROUTE OF ADMINISTRATION: I.M or I.V.
DISPENSED: RX OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT: C₁₉H₂₄N₄O₅S₂.Cl.HCl. H₂O Mol. weight 711.5
 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-methyl, chloride-pyrrolidinium hydroxide, inner salt, 7²-(Z)-(O-methyloxime), monohydrochloride, monohydrate

CAS 123171-59-5 (Cefepime)

NDA 50-679
Bristol-Myers
Cefepime hydrochloride

page 2

PATENT STATUS: U.S. Patents:

4,406,899 expires 9/27/2000
4,910,301 expires 9/27/2000
4,994,451 expires 2/19/2008
5,095,011 expires 3/10/2009

SUPPORTING DOCUMENTS:

IND
IND

DMF

RELATED DOCUMENTS (if applicable): None

CONSULTS:

Environmental Impact Assessment consult is complete.

REMARKS/COMMENTS:

Methods validation from Division of Research and Testing, FOB-8, is still outstanding. CFR Monograph is in draft. The outstanding methods validation from FOB-8 and CFR Monograph are not essential for the NDA approval from CMC standpoint.

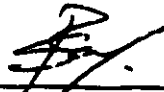
Environmental Assessment report and FONSI are attached (ATTACHMENT 1).

Final Update request has been made on 2/25/94, EER # 5978.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the manufacturing and controls standpoint.

DESCRIPTION and HOW SUPPLIED sections of package insert require editorial changes. The changes can be incorporated in the final labeling. A satisfactory Establishment Inspection Report is required for approval.


3/1/94
Suva B. Roy, Ph.D.
Review Chemist

NDA 50-679
Bristol-Myers
Cefepime hydrochloride

page 3

cc: Orig. NDA 50-679
HFD-520/Division File
HFD-520/SBR/date
HFD-520/Sherman
HFD-520/Mainigi
HFD-520/Soprey
HFD-520/Debellas
HFD-520/SUPERVISOR
HFD-102/CKumkumian [#1 only]
R/D Init by: SUPERVISOR
filename:N50-679. R4

W/S 2/2/94
-li 12/2/94

E. A. And
Fons:

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR

Cefepime for Injection

NDA 50-679

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

NDA 50-679

Cefepime for Injection

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Cefepime, Bristol-Myers Squibb has conducted a number of environmental studies and prepared an environmental assessment (21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental

release.

NOV - 5 1993

DATE



Phillip G. Vincent, Ph. D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

11/5/93

DATE



Charles S. Kumkumian, Ph. D.
Assistant Director (Chemistry)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: environmental assessment
MSDS

FINDING OF NO SIGNIFICANT IMPACT

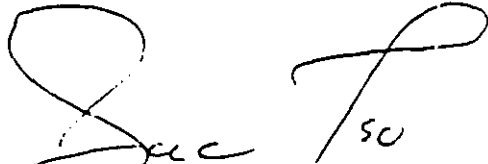
NDA 50-679

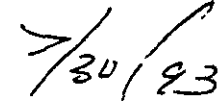
Bristol-Myers Squibb has submitted an environmental assessment to support a new drug application dated June 30, 1992. The application was submitted in pursuant to section 507 of the Food, Drug, and Cosmetic Act for Cefepime HCl (cefepime dihydrochloride. H2O/L-arginine) Sterile Powder/Injection, 500 mg, 1.0 g, and 2.0 g.

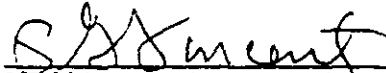
The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered all the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their application, the firm has prepared a environmental assessment according to 21 CFR 25.31a(a) which evaluates the environmental impacts of the manufacture and use of the drug products. The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects.

All manufacturing facilities are properly permitted. At manufacturing sites, air emission is controlled by high efficiency filters. Solvents are recovered. Solid wastes materials generated during manufacturing of the bulk drug substance are disposed in a licensed landfill. Aqueous wastes are treated either onsite or discharged into a public treatment plant before discharging into river. Precautions taken at the sites of manufacture of the finished products are expected to minimize occupational exposures and environmental release. Any residues of the drug substance and its major metabolites entering the environment as a result of administering the drug to humans are expected to be insignificant. In addition, no wetland areas, significant cultural resources or endangered species, air quality, fish and wildlife resources, environmentally significant habitats, and water quality would be significantly affected, and no significant land use changes would occur.


Prepared by Su C. Tso, Ph.D.


Date


Phillip G. Vincent, Ph.D
Environmental Assessment Officer

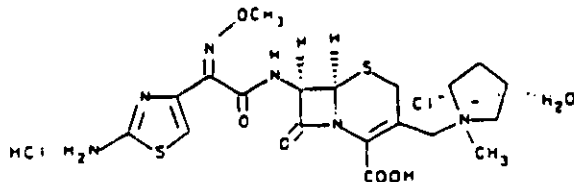

Date

cc: Original: NDA 50-679
HFD-362/Chao
HFD-520/SCTso, letter only
HFD-102/PVincent
HFD-520/WHDeCamp
HFD-102/CKumkumian
HFD-520/Debellas
FONSI file: NDA 50-679

NDA ENVIRONMENTAL ASSESSMENT REVIEW

CHEMIST'S REVIEW #1	1. ORGANIZATION DAIDP (HFD-520)	2. NDA NUMBER 50-679
3. NAME & ADDRESS OF APPLICANT		
Bristol-Myers Squibb Bio/Chem Division P. O. Box 4755 Syracuse, NY 13221-4755		
4. DATE OF SUBMISSION		
6/15/92		
5. DATE OF REPORT		
7/30/93		
6. DATE OF ASSIGNMENT		
5/27/93		
7. NAME OF DRUG	8. NONPROPRIETARY NAME	
Cefepime HCl	cefepime dihydrochloride. H2O/ L-arginine	
9. PHARMACOLOGICAL CATEGORY		
Anti-bacterial		
10. DOSAGE FORM(S)/ROUTE OF ADMINISTRATION		
Powder (sterile)/Injection		
11. STRENGTH		
500 mg, 1.0 g, and 2.0 g per vial		
12. CHEMICAL NAME AND STRUCTURE		

MOL. WT: C₁₉H₂₄N₆O₅S₂·Cl·HCl·H₂O Mol. weight 571.5
 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-methylchloride-pyrrolidinium hydroxide, inner salt, 7²-(2)-(O-methyloxime), monohydrochloride, monohydrate



CAS 123171-59-5 (Cefepime)

Stat

Statistical Review and Evaluation

APR 15 1994

NDA#: 50-679

Drug Class: 1 S

Applicant: Bristol-Myers Squibb Pharmaceutical Research Institute

Name of Drug: Maxipime* (Cefepime Hydrochloride) Injection

Documents Reviewed: Volumes 1.154 - 1.168 (15 volumes), 1.170 - 1.181 (12 volumes), 1.129-1.137 (9 volumes), 1.143-1.146 (4 volumes), 1.138-1.142 (5 volumes), 1.182 - 1.206 (25 volumes), 1.210 - 1.215 (6 volumes), 1.149 - 1.153 (5 volumes), 1.216 - 1.224 (9 volumes), 1.225 - 1.234 (10 volumes) , 1.237, 1.239 - 1.250 (12 volumes).
Amendment 21 dated Nov 19, 1992 (3 data diskettes),
Amendment 43 dated Apr 22, 1993 (16 data diskettes),
Amendment 50 dated May 11, 1992 (3 data diskettes),
Amendment 57 dated June 8, 1992 (6 data diskettes).

Medical Input: Dr. Linda Ann Sherman, HFD-520
Dr. William Erhardt, HFD-520

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A. INTRODUCTION

The sponsor submitted results to establish efficacy and safety profile of Maxipime™, Cefepime Hydrochloride for Injections. The indications submitted by the sponsor are :

- ii) Complicated Urinary Tract Infections including pyelonephritis)
- iii) Uncomplicated Urinary Tract Infections
- iv) Pneumonia (nosocomial and community-acquired)

- vi) Skin and Skin Structure Infections

The submission will be discussed with respect to efficacy of cefepime in individual indications. The safety issues were evaluated jointly with the reviewing Medical Officer (RMO) and are presented in the clinical review.

INTRODUCTION:

Reports of two controlled clinical studies were submitted by the sponsor, both conducted in U.S. Of these, Protocol A1411-119 is a Phase III open, randomized parallel study involving 207 patients at six centers in U.S. It is a 1:1 comparative study of Cefepime/Metronidazole and Gentamicin/Clindamycin in BID dosage regimen. Protocol A1411-120 is a Phase III open, randomized parallel study involving 241 patients at eleven centers in U.S. It is a 2:1 comparative study of Cefepime versus Gentamicin and Mezlocillin in BID dosage regimen.

B. EVALUATION

I. Baseline consistency:

For the evaluable patients in Protocol A1411-119, there is no obvious baseline disparity over treatment groups with respect to age or gender of the enrolled patients. However, patient enrollment among centers is not uniform over the trial as shown in Table -1. The database is as per the RMO.

Table 1. Baseline Consistency in number of Strictly Evaluable patients

	Cefepime / Metronidazole	Gentamycin / Clindamycin
Total enrolled	89	66
Total evaluable	20	29
Dr. Berne (% of total evaluable)	19 (95%)	23 (79%)

In the test drug treatment arm, 19 of the 20 evaluable patients come from a single center. There is also a disproportionately large enrollment of Hispanic patients in this center, which causes an imbalance in baseline ($p = 0.02$). The results of this study are evaluated as if it is a single center trial. It is believed race has no bearing on success rates of either drug, therefore racial imbalance is ignored. There were some randomization errors where patients assigned to the control arm actually received the test drug. This resulted in an imbalance in patient enrollment over the treatment arms (Volume 239, pp 08-53798-53800). This may have biased outcomes since we could not determine the extent or genesis of these errors.

In Protocol AI 411-120, there was no baseline imbalances noticed with regard to gender, race or age.

Efficacy Analyses:

The primary efficacy variables are clinical and bacteriologic cure rates. A clinical response is said to be satisfactory if all pre-treatment signs and symptoms of the infection are improved or resolved and no new signs and symptoms of the infection are present at the post-treatment followup visit. A patient is called strictly evaluable if he/she is clinically and bacteriologically evaluable.

A summary of cure rates from two efficacy studies is presented in Table 2. The database submitted by the sponsor was modified and verified by the RMU and the cure rates reported here are as per her determination.

The purpose of Protocol AI 411-119 is to show therapeutic equivalence of Cefepime/Metronidazole concurrent medication regimen to Gentamycin/Clindamycin and of AI 411-120 on Cefepime monotherapy to Gentamycin/Mezlocillin concurrent therapy in treatment of

Table 2 : Summary of Clinical Response (Protocol AI 411-119)

Cure Rates	Treatment Profile		Confidence Interval n_t, n_c (95% C.I.) p_t, p_c
	CEF/MET	CLI/GEN	
Clinical Cure for all evaluable population	34	43	34, 43 (-.0016, .3491) 94, 76
Clinical Cure for strictly evaluable population	20	29	20, 29 (-.2003, .3141) 85, 79
Clinical Cure with Reviewer's Evaluable pool	26	33	26, 33 (-.1479, .2808) 88, 81

The 95% confidence intervals are reported as : n_t = number of subjects in the treatment arm, n_c = number of subjects in the control arm, p_t = cure rate in the treatment arm, p_c = cure rate in the control arm. A continuity correction factor has been applied to the confidence intervals.

Several points are worth noting here. In the "all evaluable patients" case, Cefepime/Metranidazole concurrent therapy is therapeutically equivalent to Gentamycin/Clindamycin. For strictly evaluable population, the 95% CI exceeds the required $\pm 15\%$ delta required to show therapeutic equivalency. Further, confidence limits on medical reviewer's "evaluable pool", are barely within $\pm 15\%$ stipulated limits to be considered equivalent. If one ignores the randomization problems, these three combined confidence intervals provide rather weak statistical support for the claim that the two drug regimens are equally efficacious.

Clinical response in Protocol AI 411-120 is discussed in table -3.

Table -3 : Summary of Clinical Response (Protocol AI 411-120)

Cure Rates	Treatment Profile		Confidence Interval n_1, n_2 (95% C.I.) p_1, p_2
	CEFEPIME	GENTA /MEZLO	
Clinical Cure for evaluable population	30	13	30.13 (-.1700, .2571) 96 92
Clinical Cure for strictly evaluable population	14	2	14.2 (-.4920, .3491) 92 10
Clinical Cure for clinically evaluable only	23	5	23.5 (-.3771, .6038) 91 80

Several points are to be mentioned. In all cases, Cefepime monotherapy fails to establish therapeutic equivalence with Gentamycin/Mezlocillin concurrent regimen and is seen to be statistically inferior to it. Moreover, there is an imbalance in the number of patients over the two treatment arms, with the number of evaluable subjects in the comparator arm being unacceptably low. This renders interpretations of the confidence intervals virtually meaningless.

Microbiological Eradication Analysis:

In bacteriologic response, the causative pathogen is said to be "eradicated" if it is not present in the post-treatment culture or if there is no suitable specimen source. The microbiological cure rates reported here are calculated on the database developed by the Medical Officer. Continuity correction factors have not been attached to the confidence intervals.

Table -4: Microbiological Cure Rates

Protocol	Over All Microbiologic Eradication
Protocol AI 411-119	80.58 (-.1497, -.1244) 88% 87%
Protocol AI 411-120	27.2 (-.108, .0342) 98% 100%

It is seen that the confidence interval for overall microbiologic eradication in Protocol AI 411-119 is barely inside the stipulated $\pm 15\%$ limit. For Protocol AI 411-120, even though the confidence interval satisfies the criteria for therapeutic equivalence, the number of evaluable subjects is too low to make any practically meaningful inferences. There is also a serious imbalance in sample size between the treatment arms in this case.

Cure Rates based on Specific Causative Organisms:

The reviewing M.O. expressed concern regarding cure rates on two specific causative organisms -- E. Coli and P. Aeruginosa. A summary of the analysis of these two pathogens is presented in Table IABD-5:

Table -5: Cure Rates Based on Specific Causative Organisms

Causative Organism	Protocol AI 411-119	Protocol AI 411-120
E. Coli	18.23 (-.2738, .2883) 83% 87%	n = 7.0; Cures = 6.0; confidence interval meaningless
P. Aeruginosa	8.5 (-.6482, .3148) 83% 100%	n = 1.0; Cures = 1.0; confidence interval meaningless

The evaluation problems noted before are present here. Confidence intervals or any statistical evaluations under such sample size constraints are essentially worthless. However, for E.Coli in Protocol AI 411-119, there is a significant difference between the treatment arms in terms of eradication, in favor of the active control therapy.

Safety Analysis:

Two pivotal studies (Protocol AI 411-119 and AI 411-120) provide safety profile of the test drug.

Adverse Clinical Events:

In Protocol AI 411-119, a total of 29 adverse clinical events are reported in the test arm, none of which are probably related to the drug. On the other hand, of the 26 reported on the active control arm, 4 are probably related to the drug. A confidence interval for the difference in means is obtained to be 29.26 (-.3290, 0.02131) 0% 15% which shows the test drug to have a better safety profile than the active control. Digestive system was the most commonly affected body system. A Mantel-Haenszel p-value between the treatment arms is 0.823, which does not show any significant difference between the treatments.

In Protocol AI 411-120, a total of 80 adverse clinical events are reported in the test arm, 7 of which are probably related to the drug. On the other hand, of the 46 reported on the active control arm, 5 are probably related to the drug. A confidence interval for the difference in means is obtained to be $80.46 (-.130, 0.088)$ 8% 10% which shows two treatment arms to have equivalent safety profiles. Digestive system was the most commonly affected body system. A Mantel-Haenszel p-value between the treatment arms is 0.045, which shows a marginally significant difference between the treatments.

Adverse Laboratory Experiences:

According to the reviewing Medical Officer, abnormal liver functions, as indicated by elevated alkaline phosphatase, SGOT, SGPT and total bilirubin may be noticed with test drug therapy and are of clinical relevance. They are summarized below.

Table 6. Summary of adverse laboratory events

Adverse Laboratory Event	Confidence Interval for AI 411-119	Confidence Interval for AI 411-120
Alkaline Phosphatase	59.57 (-.4578, -.1131) 13% 42%	106.54 (-.1674, .1828) 41% 40%
AST (SGOT)	74.63 (-.2934, .0695) 45% 57%	100.51 (-.1237, .2425) 53% 47%
AST (SGPT)	64.57 (-.5430, -.1812) 23% 59%	55.28 (-.2327, .2561) 85% 64%
Total Bilirubin	59.52 (-.1977, -.0640) 6% 13%	153.28 (-.2736, -.0397) 7% 22%

The comparator for cefepime/metronidazole in protocol AI 411-119 was gentamicin/clindamycin, while cefepime monotherapy was compared with gentamicin/mezlocillin in protocol AI 411-120.

In Protocol AI 411-119, Cefepime/Metronidazole therapy has better safety profile than the active control in all alkaline phosphatase, SGPT and total bilirubin. It fails to establish statistical equivalency with the active control in incidents related to SGOT. In Protocol AI 411-120, Cefepime monotherapy was statistically equivalent in adverse event rates to its the active control in alkaline phosphatase and SGOT, but fails to establish equivalency in SGPT. It has a better safety profile than gentamicin/mezlocillin in total bilirubin related adverse events.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

These analyses fail to demonstrate therapeutic equivalence of Cefepime in monotherapy or in Cefepime/Metronidazole concurrent therapy in treatment of

through -5). (tables -1

Indication: Complicated Urinary Tract Infections (including pyelonephritis)

A. INTRODUCTION

Reports of four comparative clinical studies conducted in north America were submitted by the sponsor to establish efficacy and safety of Cefepime in treatment of complicated urinary tract infections, including pyelonephritis. Two north American non-comparative trials were presented to provide corroboration for the cure rates obtained in the comparative trials. The European studies, both comparative and non-comparative will not be discussed in the efficacy analysis, but will be considered as a part of the safety database.

Comparative trials:

Protocol AI411-071 was a Phase III open, randomized, parallel, 2:1 comparative study of Cefepime and Cefepime at 250 mg BID dosage regimen. It specifically sought to enroll patients with complicated UTI, but several patients with complicated UTI were enrolled.

Protocol AI411-083 was an open, randomized (2:1 Cefepime : Ceftazidime) clinical trial which tried to enroll patients with complicated UTI, including pyelocystitis, pyelonephritis and pyelitis. Dose regimen of 500 mg every twelve hours for Cefepime and Ceftazidime administered by intravenous infusion or intramuscularly were compared.

Protocol AI411-108 was a randomized (1:1 Cefepime : Ceftazidime) clinical trial performed in U.S. which also tried to enroll patients with greater severity of disease than protocol AI411-071. Dose regimen of 1 gram Cefepime every twelve hours was compared against Ceftazidime.

Protocol 411-097 was a randomized (1:1 Cefepime:Ceftazidime), comparative clinical study at multiple centers in North America. At the majority of the centers, the investigation was conducted in an open fashion, however, at three centers, the investigation was conducted in a double-blind manner. It allowed inclusion of patients with suspected bacteremia without a source of infection, patients with serious and/or patients with serious SSTI.

Non-comparative trials:

The non-comparative trials, AI 411-061 and AI 411-140, were essentially the same design to the comparative ones but with a different dosage regimen. Protocol AI 411-061 administered cefepime at 1 gram every 12 hours, while in protocol AI 411-140, cefepime was administered at 2 grams every 12 hours.

B. EVALUATION

I. Baseline consistency:

For the evaluable patients, there is no obvious baseline disparity over treatment groups with respect to gender (p-value = 0.894), ethnicity (p-value = 0.842) or age (p-value = 1.0).

It was indicated by the Medical Officer that the duration of therapy may be different in two treatment arms in protocol AI 411-097 at 2 gms BID. Patients received a mean of 8.3 days on Cefepime but 9.6 days of Ceftazidime. Any disparity resulting from it could not be verified due to inadequate information.

Efficacy Analyses:

The primary efficacy variables are clinical and bacteriologic cure rates. A clinical response is said to be satisfactory if all pre-treatment signs and symptoms of the infection are improved or resolved and no new signs and symptoms of the infection are present at the post-treatment followup visit. A patient is called "fully evaluable" if he/she is clinically and bacteriologically evaluable.

Clinical efficacy at 5-9 days post-therapy is presented Table CUTI-1.

Table CUTI-1 : Summary of Clinical Response at 5-9 days post-therapy

Protocol	dose regimen	Cures		C.I. for clinically evaluable patients
		CEFFPIME	CEFTAZIDIME	
AI 411-071	0.25 gms BID	9/12	5/5	12.5(-.6367,.1367)75% 100%
AI 411-083	0.50 gms BID	74/103	35/55	103.85(-.0858,.2500)71% 63%
AI 411-108	0.50 gms BID	11/21	7/13	21.13(-.4219,.3926)52% 53%
AI 411-097	2 gms BID	48/58	44/58	58.98(-.0951,.2331)82% 71%

The 95% confidence intervals are reported as : n_t = number of subjects in the test arm, n_c = number of subjects in the control arm, p_t = cure rate in the test arm, p_c = cure rate in the control arm. A continuity correction factor has been applied to the confidence intervals.

Several points are to be noted here. At 0.25 gms BID, cefepime fails to establish therapeutic equivalency to Ceftazidime. This may be due to low sample size in this protocol or low dosage. At 0.5 gms BID, it is therapeutically equivalent to Ceftazidime in protocol AI 411-083, but does not meet the criteria for equivalence in protocol AI

411-108. At the highest dose, i.e. 2 gms BID, cefepime is equivalent to Ceftazidime in clinical efficacy.

It was investigated if two north american comparative trials at 0.5 gms BID can be combined to obtain a consolidated confidence interval via meta-analysis. A p-value of 0.6158 was obtained, showing these two studies are combinable. A combined 95% confidence interval of (-0.0745, 0.2066) was obtained which meets the criteria for equivalence of cefepime with its control.

In the non-comparative trials, 75% success rate was noted for evaluable population at 1 gm BID dose, whereas 71% was noted at 2gm BID. This shows a lower cure rate in the non-comparative trials at 2gms BID. This was not analyzed further due to paucity of data.

Microbiological Eradication Analysis:

A summary of bacteriologic efficacy at the 5-9 days post-therapy for patients diagnosed with complicated UTI, including pyelonephritis is presented in Table CUTI-2. The database submitted by the sponsor was modified and verified by the reviewing M.O and the cure rates reported here are as per his determination.

Table CUTI-2 : Summary of Bacteriologic efficacy at 5-9 days post-therapy evaluation

Protocol	Number of cures		Confidence Interval n,n. (95% C.I.) p,p.
	CEF	CEFTAZ	
AI 411-071 (0.25 gms BID)	8/12	5/5	12.5 (-.7417, .0751) 67 10
AI 411-083 (0.5 gms BID)	88/109	41/55	108.55 (-.0886, .2124) 81 75
AI 411-108 (0.5 gms BID)	18/22	10/13	22.13 (-.2923, .3902) 81 76
AI 411-097 (2 gms BID)	53/67	52/62	67.62 (-.1968, .1015) 79 83

Several points are to be noted here. At 0.25 gms BID, cefepime fails to establish therapeutic equivalency to Ceftazidime. This may be due to low sample size in this protocol. At 0.5 gms BID, it is therapeutically equivalent to Ceftazidime in protocol AI 411-083, but does not meet the criteria for equivalence in protocol AI 411-108. At the highest dose, i.e. 2 gms BID, cefepime fails to establish equivalency to Ceftazidime in bacteriologic efficacy.

It was investigated if two north american comparative trials at 0.5 gms BID can be combined to obtain a consolidated confidence interval via meta-analysis. A p-value of 0.9351 was obtained, showing these two studies are combinable. A combined 95% confidence interval of (-0.0635, 0.1823) was obtained which meets the criteria for equivalence of cefepime with its control.

Two studies, AI 411-083 and AI 411-108 had intramuscular as well as intravenous route of administration. A summary of the cure rates obtained at days 5-9 post-therapy is presented in Table CUTI-3. Breslow-Day test summarizes homogeneity of odds-ratio, which is an indicator of equivalence of success rates.

Table CUTI-3 : Summary of Bacteriologic efficacy by route of administration

Protocol	Intravenous		Intramuscular		Breslow-Day p-value for homogeneity of odds-ratio
	CEFEPIME	CEFTAZIDIME	CEFEPIME	CEFTAZIDIME	
AI 411-083	54/72 (75%)	30/41 (73%)	34/37 (92%)	11/14 (79%)	p-value = 0.2901
AI 411-108	14/18 (78%)	8/10 (80%)	4/4 (100%)	2/3 (67%)	p-value undefined

Cefepime establishes therapeutic equivalence with Ceftazidime in bacteriologic efficacy with respect to route of administration. For protocol AI 411-108, sample sizes were too small to calculate the p-value.

Cure Rates based on Specific Causative Organisms:

The confidence interval for bacteriologic response by specific causative organisms are presented in Table CUTI-4.

Table CUTI-4. Bacteriologic response by infecting pathogens

Pathogen	Number of cures		Confidence Interval n,n. (95% C.I.) p,p.
	CEFEPIME	CEFTAZ	
500 mg BID or TID			
All organisms	115/146	62/81	146.81 (-.1010, .1454) 78.76
E.Coli	68/83	27/41	83.41 (-.0245, .3461) 81.65
P. Aeruginosa	11/17	10/11	17.11 (-.6205, .0965) 84.90
P. Mirabilis	10/12	5/5	12.5 (-.5192, .1858) 83.10
2 gms BID			
All organisms	64/82	65	82.81 (-.1589, .1149) 78.80
E.Coli	36/39	41/46	39.44 (-.1147, .1782) 82.89

It is noted that cefepime is equivalent to Ceftazidime in overall eradication rate when all infecting pathogens or E.Coli isolates are considered. It fails to establish microbiologic equivalence when the infecting pathogens were P.Aeruginosa or P.Mirabilis. Sample sizes were too small to construct confidence intervals for any other organism.

Safety Analysis:

The safety issues will be addressed in the Medical Officer's review as a joint clinical-statistical review.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

Cefepime is equivalent to Ceftazidime in clinical efficacy at both 0.5 gms BID and at 2 gms BID. It fails to establish therapeutic equivalence at 0.25 gms BID (table CUTI-1). This is reflected in microbiologic eradication rates at 0.5 gms and 2 gms BID respectively also (table CUTI-2). Eradication with respect to causative pathogen is equivalent when all organisms are considered and with E.Coli in particular (table CUTI-4).

Indication: Uncomplicated Urinary Tract Infections

A. INTRODUCTION

Reports of four comparative clinical studies conducted in north America were submitted by the sponsor to establish efficacy and safety of Cefepime in treatment of uncomplicated urinary tract infections. Two north American non-comparative trials were presented to provide corroboration for the cure rates obtained in the comparative trials. The European studies, both comparative and non-comparative will not be discussed in the efficacy analysis but will be considered as a part of the safety database.

Comparative trials:

Protocol AI411-071 was a Phase III open, randomized, parallel, 2:1 comparative study of Cefepime and Ceftazidime at 250 mg BID dosage regimen. It specifically sought to enroll patients with uncomplicated UTI, but several patients with complicated UTI were enrolled.

Protocol AI411-083 was an open, randomized (2:1 Cefepime : Ceftazidime) clinical trial which tried to enroll patients with complicated UTI, including pyelocystitis, pyelonephritis and pyelitis. Dose regimen of 500 mg gram every twelve hours for Cefepime and Ceftazidime administered by intravenous infusion or intramuscularly were compared.

Protocol AI411-108 was a randomized (1:1 Cefepime : Ceftazidime) clinical trial performed in U.S. which also tried to enroll patients with greater severity of disease than protocol AI411-071. Dose regimen of 1 gram every twelve hours for Cefepime was compared against Ceftazidime.

Protocol 411-097 was a randomized (1:1 Cefepime:Ceftazidime), comparative clinical study at multiple centers in North America. At the majority of the centers, the investigation was conducted in an open fashion, however, at three centers, the investigation was conducted in a double-blind manner. It allowed inclusion of patients with suspected bacteremia without a source of infection, patients with serious SSTI.

Non-comparative trials:

The non-comparative trials, AI 411-061 and AI 411-140, were essentially similar in design to the comparative ones but with a different dosage regimen. Protocol AI 411-061 administered cefepime at 1 gram every 12 hours, while in protocol AI 411-140, cefepime was administered at 2 grams every 12 hours.

B. EVALUATION

I. Baseline consistency:

For the evaluable patients, there is no obvious baseline disparity over treatment groups with respect to gender, ethnicity or age.

Efficacy Analyses:

The primary efficacy variables are clinical and bacteriologic cure rates. A clinical response is said to be satisfactory if all pre-treatment signs and symptoms of the infection are improved or resolved and no new signs and symptoms of the infection are present at the post-treatment followup visit.

Clinical efficacy at 5-9 days post-therapy is presented Table UUTI-1.

Table UUTI-1 : Summary of Clinical Response at 5-9 days post-therapy

Protocol	dose regimen	Cures		C.I. for clinically evaluable patients
		CEFEPIME	CEFTAZIDIME	
AI 411-071	0.25 gms BID	8/9	6/6	inadequate sample size
AI 411-083	0.50 gms BID	10/18	9/9	inadequate sample size
AI 411-108	0.50 gms BID	6/8	6/6	inadequate sample size
AI 411-097	2 gms BID	9/9	8/11	inadequate sample size

The sample sizes are too small to construct confidence intervals.

It was investigated if two north american comparative trials at 0.5 gms BID can be combined to obtain a consolidated confidence interval via meta-analysis. A p-value of 0.3131 was obtained, showing these two studies are combinable. A combined 95% confidence interval of (-0.5563, -0.1881) was obtained, indicating that cefepime is statistically inferior in clinical efficacy to Cefotaxime in treatment of uncomplicated UTI.

In the non-comparative trials, 75% success rate was noted for evaluable population at 1 gm BID dose, whereas 100% was noted at 2gm BID. This shows an lower cure rate in the non-comparative trials at 2gms BID. This was not analyzed further due to paucity of data.

Microbiological Eradication Analysis:

A summary of bacteriologic efficacy at the 5-9 days post-therapy for patients diagnosed with complicated UTI, including pyelonephritis is presented in Table UUTI-2. The database submitted by the sponsor was modified and verified by the reviewing M.O and the cure rates reported here are as per his determination.

Table UUTI-2 : Summary of Bacteriologic efficacy at 5-9 days post-therapy evaluation

Protocol	dosage	Number of cures		Confidence Interval n,n. (95% C.I.) p,p.
		CEF	CEFTAZ	
AI 411-071	0.25 gms BID	7/9	7/7	inadequate sample size
AI 411-083	0.5 gms BID	17/19	8/9	inadequate sample size
AI 411-108	0.5 gms BID	7/8	5/6	inadequate sample size
AI 411-097	2 gms BID	8/9	11/13	inadequate sample size

The sample sizes are too small to construct confidence intervals.

It was investigated if two north american comparative trials at 0.5 gms BID can be combined to obtain a consolidated confidence interval via meta-analysis. A p-value of 0.876 was obtained, showing these two studies are combinable. A combined 95% confidence interval of (-0.1900, 0.2233) was obtained which meets the criteria for equivalence of cefepime with its control.

It was indicated by the Medical Officer that several demographic considerations may cause differential cure rates over two treatment arms. A summary of the cure rates obtained at days 5-9 post-therapy is presented in Table UUTI-3. Breslow-Day test summarizes homogeneity of odds-ratio, which is an indicator of equivalence of success rates.

Table UUTI-3 : Summary of Bacteriologic efficacy by demographic criteria

Criteria		Efficacy rates		Breslow-Day p-value for homogeneity of odds-ratio
		CEFEPIME	CEFTAZIDIME	
Location	N. America	39/45 (87%)	31/35 (89%)	p-value = 0.8313
	Europe	8/10 (80%)	11/14 (79%)	
Gender	males	8/11 (73%)	1/2 (50%)	p-value = 0.6127
	females	39/44 (88%)	41/47 (87%)	
Age	> 65 years	26/31 (84%)	20/22 (91%)	insufficient data
Ethnicity	white	38/45 (84%)	30/37 (81%)	p-value = 0.2552
	black	6/6 (100%)	8/8 (100%)	
	other	3/4 (75%)	4/4 (100%)	

Cefepime establishes therapeutic equivalence with Ceftazidime in bacteriologic efficacy with location, gender and ethnicity. For the age group over 65, sample sizes were too small to calculate the p-value.

Cure Rates based on Specific Causative Organisms:

The confidence interval for bacteriologic response by specific causative organisms are presented in Table UUTI-4.

Table UUTI-4. Bacteriologic response by infecting pathogens

Pathogen	Number of cures		Confidence Interval n, n. (95% C.I.) p, p.
	CEFEPIME	CEFTAZIDIME	
500 mg BID or TID			
All organisms	30/34	21/24	34.24 (-.1991, .2138) 88, 87
E.Coli	24/28	15/17	28.17 (-.2731, .2227) 85, 88
2 gms BID			
All organisms	10/12	14/18	12.18 (-.2991, .4102) 83, 78
E.Coli	7/9	8/11	9.11 (-.4287, .5297) 78, 72

It is noted that cefepime is equivalent to Ceftazidims in overall eradication rate when all infecting pathogens are considered at 500 mg, BID dosage. It fails to establish microbiologic equivalence when all infecting pathogens are considered at 2 gms BID or when the isolate is an E.Coli. Sample sizes were too small to construct confidence intervals for any other organism.

Safety Analysis:

The safety issues will be addressed in the Medical Officer's review as a joint clinical-statistical review.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

There were insufficient sample sizes to draw any inferences on clinical or microbiologic efficacy of cefepime in treatment of patients with uncomplicated UTI. (Tables UUTI-1 and UUTI-2). Eradication with respect to causative pathogen is equivalent when all organisms are considered at 500 mg BID dosage level. These trials fail to establish therapeutic equivalence of cefepime with Ceftazidime when all isolates are considered at 2 gms BID or E.Coli is the causative pathogen (table UUTI-4).

Overall, sample sizes in these trials are too small to support the sponsor's claims of therapeutic equivalency.

Indication: Pneumonia

A. INTRODUCTION

Reports of two comparative clinical studies conducted in north America were submitted by the sponsor to establish efficacy and safety of Cefepime in treatment of pneumonia. Four north American non-comparative trials were presented to provide corroboration for the cure rates obtained in the comparative trials. The European studies, both comparative and non-comparative will not be discussed in the efficacy analysis, but will be considered as a part of the safety database.

Comparative trials:

Protocol AI411-070 was a Phase III open, randomized, parallel, 2:1 comparative study of Cefepime and Ceftazidime in thirty centers in US and nine centers in Europe. Three of the US centers conducted blinded studies. The dosage used was 1gm Q12h for mild to moderate infections and 2 gms Q12h for severe infections.

Protocol AI411-097 was an open, randomized clinical trial comparing cefepime with Ceftazidime which enrolled patients having pneumonia, other infections. Of forty-two centers participating, three conducted the studies in a blinded fashion. The dosage used was 1gm Q12h for mild to moderate infections and 2 gms Q12h for severe infections.

Non-comparative trials:

The non-comparative trials, were similar in design to the comparative ones but with a different dosage regimens. Protocol AI 411-061 administered cefepime at 1 gram every 12 hours, while in protocol AI 411-115 and AI 411-140, cefepime was administered at 2 grams every 12 hours. Protocol AI 411-067 had a low dose of 1 gm BID for mild to severe infections and 2 gm BID for severe cases.

B. EVALUATION

I. Baseline consistency:

For the clinically evaluable patients, there is no obvious baseline disparity over treatment groups with respect to gender (p-value = 0.410), ethnicity (p-value = 0.553) or age (p-value = 0.951). For the strictly evaluable patients also, there is no obvious baseline disparity over treatment groups with respect to gender (p-value = 0.715), ethnicity (p-value = 0.769) or age (p-value = 0.596).

Efficacy Analyses:

The primary efficacy variables are clinical and bacteriologic cure rates.

A patient is called clinically evaluable if clinical response for that patient can be equivocally determined. A clinical response is said to be satisfactory if all pre-treatment signs and symptoms of the infection are improved or resolved and no new signs and symptoms of the infection are present at the post-treatment followup visit. A patient is called "strictly evaluable" if he/she is clinically evaluable and has satisfactory gram stains and blood culture to be microbiologically evaluable.

The etiology of pneumonia can be either and would have been ideally analyzed as such. However, there was insufficient data to analyze according to etiology. In this review, the overall clinical and microbiological rates are considered as per the Medical Officer's database, disregarding the etiology.

The reviewing Medical Officer was concerned about the effect of underlying respiratory status of the patients on the clinical efficacy. A summary of the clinical efficacy for the clinically evaluable population is presented in Table PNEU-1.

Table PNEU-1 : A Summary of the Clinical Efficacy for the clinically evaluable population

Criteria	CE Cures		C.I. for clinically evaluable patients
	CEFEPIME	CONTROL	
All U.S. studies	133/213	68/100	213/100(-.175,.064)62% 68%
All studies combined	245/379	111/163	379/163(-.125,.056)64% 68%
Underlying respiratory status			
smokers	41/59	22/35	59.35(-.155,.287)69% 62%
non-smokers	54/83	21/32	83.32(-.221,.210)65% 65%

Key: CE = clinically evaluable

The 95% confidence intervals are reported as : n_t = number of subjects in the treatment arm, n_c = number of subjects in the control arm, p_t = cure rate in the treatment arm, p_c = cure rate in the control arm. A continuity correction factor has been applied to the confidence intervals.

Cefepime is seen to be therapeutically equivalent to its control on all trials conducted in U.S. for the clinically evaluable patient population. Clinical efficacy of cefepime is equivalent to its control in clinical efficacy for the patient sub-population that are smokers. This is not reflected in the non-smoking population.

If we consider the overall cure rates between smokers and non-smokers, the 95% confidence interval is obtained as $94.115 (-.12, .10)$ 67%, 65% which shows that there is no statistically significant difference relative to response/cure between smokers and non-smokers. There is almost an indication that smokers do better than non-smokers. If we consider the response within drug type, the confidence interval for cefepime is $59.83 (-.13, .22)$ 70%, 65% and that for the control is $35.32 (-.29, .23)$ 63%, 66%. These confirm that there is no statistically significant difference between smokers and non-smokers within drug type also.

A summary of clinical efficacy for the strictly evaluable population is presented in table PNEU-2.

Table PNEU-2 : A Summary of the Clinical Efficacy for the strictly evaluable population

Criteria	SE Cures		C.I. for strictly evaluable patients
	CEFEPIME	CONTROL	
All U.S studies	30/45	22/26	$45.26 (-.405, .046)$ 66% 64%
All studies combined	39/56	28/35	$56.35 (-.306, .099)$ 70% 60%
Underlying respiratory status			
smokers	8/10	5/6	insufficient sample size
non-smokers	5/9	5/8	insufficient sample size

Key: SE = strictly evaluable

It is noted that cefepime fails to establish clinical efficacy with its control in clinical efficacy for the strictly evaluable population. There are insufficient sample sizes to draw any inferences on the effect of smoking habits in strictly evaluable population, even though higher cure rates are seen in smokers compared to the non-smokers.

It was investigated if the North American and European comparative trials can be combined to obtain an overall confidence interval via meta-analysis. A p-value of 0.7707 was obtained, showing these two studies are combinable. A combined 95% confidence interval of $592.263 (-0.1107, 0.0260)$ 63%, 68% was obtained which meets the criteria for equivalence of cefepime with its control.

In the non-comparative trials, 58% success rate was noted for the clinically evaluable population, whereas 52% was noted for the strictly evaluable patient group. This shows a lower cure rate than the comparative protocols, which was not analyzed further due to paucity of data.

Microbiological Eradication Analysis:

A summary of bacteriologic efficacy for patients diagnosed with pneumonia is presented in Table PNEU-3. The database submitted by the sponsor was modified and verified by the reviewing M.O and the cure rates reported here are as per her determination.

Table PNEU-3 : Summary of Bacteriologic efficacy at post-therapy evaluation

Criteria	Number of cures		95% Confidence Intervals n,n (95% C.I.) p,p
	CEFEPIME	CONTROL	
Overall response	45/67	31/40	67.40 (-.2947, .0880) 67 77
2 gm BID dose	16/21	6/14	21.44 (-.0430, .7096) 76 42
respirator pathogens	42/57	27/36	57.36 (-.2176, .1913) 73 75

Several points are to be noted here. On an overall microbiologic response, cefepime fails to establish therapeutic equivalency to its control. At 2 gms BID dosage regimen, it is therapeutically equivalent to its control in microbiologic eradication. With respect to respirator pathogens, cefepime fails to establish equivalency to its control in bacteriologic efficacy.

Cure Rates based on Specific Causative Organisms:

The sample sizes obtained on each causative pathogen is insufficient to make any inferences on it.

Safety Analysis:

The safety issues will be addressed in the Medical Officer's review as a joint clinical-statistical review.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

Cefepime is therapeutically equivalent to its control in all trials conducted in U.S. for the clinically evaluable patient population (table PNEU-1). However, cefepime fails to demonstrate clinical efficacy with its control in clinical efficacy for the strictly evaluable population (table PNEU-2). Clinical efficacy of cefepime is equivalent to its control in clinical efficacy for the patient sub-population that are smokers. This is not reflected in the no-smoking population (table PNEU-1). There were insufficient sample sizes to draw any inferences on the strictly evaluable population.

With respect to the overall microbiologic eradication rates, cefepime fails to

demonstrate therapeutic equivalency to its control. At 2 gms BID dosage regimen, it is therapeutically equivalent to its control in microbiologic eradication. With respect to respirator pathogens, cefepime fails to demonstrate equivalency to its control in bacteriologic efficacy (table PNEU-3). Eradication with respect to causative pathogen was not analyzed due to insufficient sample size.

Pages 25-28

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Indication: Skin and Soft Tissue Infections

A. INTRODUCTION

Reports of three comparative clinical studies were submitted by the sponsor, all conducted in North America to establish efficacy and safety of Cefepime in treatment of skin and soft tissue infections. Two non-comparative trials in North America were presented to provide corroboration for the cure rates obtained in the comparative trials. The European studies, both comparative and non-comparative will not be discussed in the efficacy analysis, but will be considered as a part of the safety database.

Comparative trials:

Protocol AI411-075 was a Phase III open, randomized parallel study involving 154 patients in five centers. It was a 2:1 comparative study of Cefepime and Ceftazidime at 500 mg BID dosage regimen.

Protocol AI411-081 was an open, randomized (2:1 Cefepime : Ceftazidime) clinical trial performed in U.S. and Puerto Rico which tried to enroll patients with greater severity of disease than protocol AI411-075. A dose regimen of 1 gram every twelve hours for Cefepime was compared against 1 gm every 8 hours for Ceftazidime.

Protocol AI411-081 was a randomized (1:1 Cefepime : Ceftazidime) clinical trial performed in U.S. which also tried to enroll patients with greater severity of disease than protocol AI411-075. Three study centers were blinded while the rest were conducted in an open manner. A dose regimen of 2 gram every twelve hours for Cefepime was compared against 1 gm every 8 hours for Ceftazidime.

Non-comparative trials:

The non-comparative trials, AI 411-061 and AI 411-140, were essentially similar in design to the comparative ones but with a different dosage regimen. Protocol AI 411-061 administered cefepime at 1 gram every 12 hours, with more severe patients receiving 2 grams BID. Protocol AI 411-140 administered cefepime at 2 grams every 12 hours with more severe patients receiving 2 grams TID.

B. EVALUATION

I. Baseline consistency:

For the evaluable patients in Protocol AI 411-075, there is no obvious baseline disparity over treatment groups with respect to gender (p-value = 0.660), ethnicity (p-value = 0.5) or age (p-value = 1.0) of the clinically evaluable patients. For

patients who are clinically as well as bacteriologically evaluable, denoted as "fully evaluable" patients by the Medical Officer, no baseline disparity was noted with respect to gender (p-value = 0.813), ethnicity (p-value = 0.312) and age (p-value = 0.890). It was indicated by the Medical Officer that mean was significantly different in two treatment arms but it could not be verified due to inadequate information. However, patient enrollment among centers is not uniform over the trial with one center supplying 70% of the enrolled patients. The number of evaluable patients is extremely small, resulting in inadequate power for the statistical tests.

In Protocol AI 411-081, there is no obvious baseline disparity over treatment groups with respect to gender (p-value = 0.473), ethnicity (p-value = 0.773) or age (p-value = .851) of the clinically evaluable patients. For "fully evaluable" patients, no baseline disparity was noted with respect to gender (p-value = 0.293), ethnicity (p-value = 0.990) and age (p-value = 0.205). Center 001 enrolled majority of the patients that may cause an imbalance over two treatment arms.

In Protocol AI 411-097, majority of the patients were enrolled in 6 of the 33 participating centers. No baseline disparity over treatment groups was noted with respect to gender (p-value = 0.320), ethnicity (p-value = 0.088) or age (p-value = .832) of the clinically evaluable patients. For "fully evaluable" patients, no baseline disparity was noted with respect to gender (p-value = 0.319), ethnicity (p-value = 0.419) and age (p-value = 0.469).

Efficacy Analyses:

The primary efficacy variables are clinical and bacteriologic cure rates. A clinical response is said to be satisfactory if all pre-treatment signs and symptoms of the infection are improved or resolved and no new signs and symptoms of the infection are present at the post-treatment followup visit. A patient is called "fully evaluable" if he/she is clinically and bacteriologically evaluable.

A summary of cure rates from the Protocol AI 411-075 is presented in Table SSTI-1 for the fully evaluable population. The database submitted by the sponsor was modified and verified by the reviewing M.O and the cure rates reported here are as per his determination.

Table SSTI-1 : Summary of Clinical Response (Protocol AI 411-075)

Cure Criteria	Number of cures		Confidence Interval n_t, n_c (95% C.I.) p_t, p_c
	CEF	CEFTAZ	
Overall Cure	22	15	37.20 (-.2349, .1187) 89 95
Cellulitis	8	9	12.9 (-.6972, .0306) 67 10
Abscess	7	5	$n = 7, 5$; sample size small
Wound Infection	6	1	$n = 7, 5$; sample size small
Infected Ulcers	2	0	$n = 2, 0$; sample size small

The 95% confidence intervals are reported as : n_t = number of subjects in the treatment arm, n_c = number of subjects in the control arm, p_t = cure rate in the treatment arm, p_c = cure rate in the control arm. A continuity correction factor has been applied to the confidence intervals.

Several points are to be noted here. With respect to overall cure, Cefepime fails to establish therapeutic equivalency to Ceftazidime. For individual clinical responses such as cellulitis, abscess, wound infection and infected ulcers, the sample sizes were too small to warrant confidence interval calculation.

As stated earlier, there was a significant difference in weight of the enrolled patients in two treatment arms. Therefore, an attempt was made to further analyze the effect of weight by the Breslow-Day test in Statxact. Patients were classified as < 73.5 kg and those less than 84.4 kgs respectively. In the Cefepime arm, cure rates of 70% and 68% were noted for these two classes, while 100% cure was noted in both classes in Ceftazidime arm. This indicates a patient weight by treatment interaction. However, due to extreme values and small sample size, the statistical tests were not sensitive enough to be of any further information.

An attempt was made to note the effect of Center 001 on the clinical outcome, as it enrolled 70% of the patient population. In the Cefepime arm, cure rates of 73% in center 001 and 77% for all other centers were noted, while 100% cure was noted in both cases in Ceftazidime arm. Center by treatment interaction was attempted to be analyzed by Breslow-Day test in Statxact. Owing to small sample sizes and extreme values encountered, the test was not sensitive enough to be of any further information.

Clinical response in Protocol AI 411-081 is presented in Table SSTI-2.

Table SSTI-2 : Summary of Clinical Response (Protocol AI 411-081)

Criteria	Clinically evaluable cures		Fully evaluable cures		C.I. for clinically evaluable patients	C.I. for fully evaluable patients
	CEF	CEFTAZ	CEF	CEFTAZ		
Overall	76	31	53	21	100.36(-.2606,.0583) _{76% 86%}	85.22(-.2979,.0196) _{81% 95%}
Cellulitis	49	19	35	16	63.21(-.3209,.0669) _{77% 90%}	42.16(-.3225,-.0108) _{83% 100%}
Abscess	11	5	10	3	n = 15,6; C.I not meaningful	n = 13,4; C.I not meaningful
Furuncle Carbuncle	2	0	2	0	n = 2,0; C.I not meaningful	n = 2,0; C.I not meaningful
Wound Infection	6	0	5	0	n = 7,0; C.I not meaningful	n = 6,0; C.I not meaningful
Infected ulcers	8	7	1	2	n = 13,9; C.I not meaningful	n = 2,2; C.I not meaningful

Cefepime fails to establish therapeutic equivalence with Ceftazidime in overall cure rates and with respect to underlying physical conditions. For abscess, furuncle, carbuncle, wound infection and infected ulcers, sample sizes were too small to calculate confidence intervals.

As in Protocol AI411-075, center 001 enrolled majority of the patients. In the Cefepime arm, cure rates of 90% in center 001 and 66% for all other centers were noted, while 94% and 78% cure rates were noted in the Ceftazidime arm. It is of interest to see if there is a center by outcome interaction. To investigate this, cures were combined across treatment arm and overall rates for the centers obtained. In center 001, the cure rate is 91%, while it is 68% for other centers. The confidence interval on the difference in cure rates is $_{60, 76} (0.09180, .37312)$ _{91% 68%}, which indicates that there center 001 may indeed have a higher success rate. Breslow-Day test in Statxact yielded a p-value of .9824, while Zelen exact test yielded p-value = 1.0, which were not sensitive enough to detect a statistically significant difference in the cure rates.

According to the Medical Officer, another possible reason for differential cure rates can be inclusion of patients with infected decubitus ulcers in center 005 only. In the Cefepime arm, cure rates of 62% in center 001 and 78% for all other centers were noted, while 67% and 90% cure rates were noted in the Ceftazidime arm. To investigate a center by outcome interaction, it was noted that in center 001, the cure rate is 63%, while it is 81% for other centers. The confidence interval on the difference in cure rates is $_{15, 117} (-0.4391, .0783)$ _{63% 81%}, which indicates that there center 005 may indeed have a much lower success rate. Breslow-Day test in Statxact

yielded a p-value of .5671, while Zelen exact test yielded p-value = 1.0, which fail to detect a statistically significant difference in cure rates due to inclusion of patients with infected decubitus ulcers.

Clinical response in Protocol AI 411-097 is discussed in Table SSTI-3.

Table SSTI-3 : Summary of Clinical Response (Protocol AI 411-097)

Criteria	Clinically evaluable cures		Fully evaluable cures		C.I. for clinically evaluable patients	C.I. for fully evaluable patients
	CEF	CEFTAZ	CEF	CEFTAZ		
Overall	64	65	39	44	79.79(-.1096,.1253) _{89% 88%}	47.48(-.2408,.0670) _{82% 81%}
Cellulitis	31	29	19	21	34.35(-.1029,.2692) _{91% 82%}	21.22(-.2490,.1495) _{90% 95%}
Abscess	16	24	12	17	19.26(-.3198,.1579) _{84% 92%}	13.19(-.2365,.2931) _{92% 89%}
Wound Infection	14	8	7	5	21.91(-.5893,.1449) _{86% 88%}	n = 12,5; C.I not meaningful
Otitis externa	0	1	0	1	n = 0,2; C.I not meaningful	n = 0,2; C.I not meaningful
Infected ulcers	3	2	1	0	n = 5,6; C.I not meaningful	n = 1,0; C.I not meaningful
Infected burns	0	1	0	0	n = 0,1; C.I not meaningful	n = 0,0; C.I not meaningful

This shows that Cefepime is therapeutically equivalent to Ceftazidime in clinically evaluable patients, but fails to establish equivalence in fully evaluable population. For patients with cellulitis, abscess and wound infection, Cefepime cannot be taken to be clinically equivalent to Ceftazidime. The sample sizes are too small to infer on the patient population having otitis externa, infected ulcers or infected burns.

It was noted earlier that three centers conducted the trial in a double-blinded fashion. It is of interest, then, to note if there is a difference in the cure rates from the open centers. For clinically evaluable patients, the confidence interval for difference in cure rates is 15.21(-.3375,.1660)_{86% 95%}, which is similar to the overall results obtained in Table SSTI-3. However, Cefepime fails to establish therapeutic equivalence to Ceftazidime in the blinded centers. The sample sizes were too small to establish confidence interval in the fully evaluable population.

Protocol AI 411-097 attempts to enroll patients with severe skin infections. It is of interest to note the efficacy of Cefepime in the "difficult to treat" patients having wound infections, infected burns and infected ulcers as underlying conditions. For clinically evaluable population, the confidence interval for difference in cure rates is 26.16(-.3757,.3084)_{65% 68%}, which is much lower than the overall cure rates. It is noted that Cefepime is not therapeutically equivalent to Ceftazidime for this population.

In the non-comparative trials, 50% success rate was noted for both clinically and fully

evaluable population at 1 gm BID dose, whereas 88% and 85% respectively were noted at 2gm BID. This shows an overall lower cure rate in the non-comparative trials at the lower dose, indicating the higher dose should be the preferred one. This was not analyzed further due to paucity of data.

Microbiological Eradication Analysis:

In bacteriologic response, the causative pathogen is said to be "eradicated" if it is not present in the post-treatment culture or if there is no suitable specimen source. The microbiological cure rates reported here are calculated on the database developed by the Medical Officer.

Table SSTI-4: Microbiological Cure Rates

Protocol	Cefepime dosage	Overall Microbiologic Eradication
Protocol AI 411-075	1 gram every 12 hours	27.15 (-.3340, .0377) 85% 100%
Protocol AI 411-081	1 gram every 12 hours	65.22 (-.1703, .1074) 92% 95%
Protocol AI 411-097	2 grams every 12 hours	47.48 (-.1732, .1262) 87% 89%

It is seen that Cefepime fails to establish equivalence in eradication rates with Ceftazidime for all protocols.

In the non-comparative trials, 77% success rate was noted for patients on 1 gm BID dose, whereas 90% was noted at 2gm BID. This is similar to the results obtained from the comparative trials and indicates that the 2 gm BID should be the preferred dose.

Cure Rates based on Specific Causative Organisms:

In Protocol AI411-075, the confidence interval for combined S.aureus cases isolated from abscess, cellulitis and wound infections was .17.10(-0.4371, .0841) 82%, 100%. This fails to establish that Cefepime is equivalent to Ceftazidime in eradication of S. aureus pathogen. The sample sizes were too small to construct confidence intervals for any other organism.

In Protocol AI411-081, the confidence interval for S. aureus cases isolated from patients having cellulitis was .30.10(-0.2740, .0740) 90%, 100%. This fails to establish that Cefepime is equivalent to Ceftazidime in eradication of S. aureus pathogen. In cellulitis patients having isolates of Strep. (beta hemolytic), the confidence interval was .15.8(-0.0958, .0958) 100%, 100%, which meets the stipulation for equivalence in eradication rates just barely. Sample sizes were too small to construct confidence

intervals for any other organism.

In Protocol AI 411-097, the sample sizes were too small to construct confidence intervals for individual pathogens. However, since it fails to support the equivalency claim based on all pathogens, it is highly unlikely that it would support any more restrictive claim.

Safety Analysis:

The safety issues will be addressed in the Medical Officer's review as a joint clinical-statistical review.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

Protocol AI 411-075 does not support the efficacy of Cefepime in treatment of skin and soft tissue infections at a dose of 0.5 grams q8h (see tables SSTI-1 and SSTI-4). This concurs with the sponsor's results.

Protocol AI 411-081 fails to establish equivalent efficacy profile of Cefepime 1 gm q12h with Ceftazidime at 1 gm q8h regimen (see tables SSTI-2 and SSTI-4).

Protocol AI 411-097 supports the sponsor's claim of clinical efficacy of Cefepime at dose of 2 gms every 12 hours for patients with moderate to severe skin and soft tissue infection. However, it fails to establish microbiologic equivalency with Ceftazidime (tables SSTI-3 and SSTI-4).

Pages 36-44

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D. OVERALL CONCLUSIONS (Which May be Conveyed to the Sponsor)

Complicated Urinary Tract Infections:

Cefepime is equivalent to Ceftazidime in clinical efficacy at both 0.5 gms BID and at 2 gms BID. It fails to establish therapeutic equivalence at 0.25 gms BID (table CUTI-1). This is reflected in microbiologic eradication rates at 0.5 gms and 2 gms BID respectively also (table CUTI-2). Eradication with respect to causative pathogen is equivalent when all organisms are considered and with E.Coli in particular (table CUTI-4).

Uncomplicated Urinary Tract Infections:

There were insufficient sample sizes to draw any inferences on clinical or microbiologic efficacy of cefepime in treatment of patients with uncomplicated UTI. (Tables UUTI-1 and UUTI-2). Eradication with respect to causative pathogen is equivalent when all organisms are considered at 500 mg BID dosage level. These trials fail to establish therapeutic equivalence of cefepime with Ceftazidime when all isolates are considered at 2 gms BID or E.Coli is the causative pathogen (table UUTI-4).

Overall, sample sizes in these trials are too small to support the sponsor's claims of therapeutic equivalency.

Pneumonia

Cefepime is therapeutically equivalent to its control in all trials conducted in U.S. for the clinically evaluable patient population (table PNEU-1). However, cefepime fails to demonstrate clinical efficacy with its control in clinical efficacy for the strictly evaluable population (table PNEU-2). Clinical efficacy of cefepime is equivalent to its control in clinical efficacy for the patient sub-population that are smokers. This is not reflected in the no-smoking population (table PNEU-1). There were insufficient sample sizes to draw any inferences on the strictly evaluable population.

With respect to the overall microbiologic eradication rates, cefepime fails to demonstrate therapeutic equivalency to its control. At 2 gms BID dosage

regimen, it is therapeutically equivalent to its control in microbiologic eradication. With respect to respirator pathogens, cefepime fails to demonstrate equivalency to its control in bacteriologic efficacy (table PNEU-3). Eradication with respect to causative pathogen is was not analyzed due to insufficient sample size.

Skin and Soft Tissue Infections:

Protocol AI 411-075 does not support the efficacy of Cefepime in treatment of skin and soft tissue infections at a dose of 0.5 grams q8h (see tables SSTI-1 and SSTI-4). This concur with the sponsor's results.

Protocol AI 411-081 fails to establish equivalent efficacy profile of Cefepime 1 gm q12h with Ceftazidime at 1 gm q8h regimen (see tables SSTI-2 and SSTI-4).

Protocol AI 411-097 supports the sponsor's claim of clinical efficacy of Cefepime at dose of 2 gms every 12 hours for patients with moderate to severe skin and soft tissue infection. However, it fails to establish microbiologic equivalency with Ceftazidime (tables SSTI-3 and SSTI-4).

Alaka Chakravarty
4-12-94

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Orig. NDA-50-679

HFD-520

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HFD-713/Dr. R. Harkins

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HFD-344/Dr. A. Lisook

Chron.

This review contains 47 pages.

Statistical Review and Evaluation
(Addendum)

MAY 12 1994

NDA#: 50-679

Drug Class: 1 S

Applicant: Bristol-Myers Squibb Pharmaceutical Research Institute

Name of Drug: Maxipime* (Cefepime Hydrochloride) Injection

Documents Reviewed: Amendment 57 dated June 8, 1992 (6 data diskettes).

Medical Input: Dr. Linda Ann Sherman, HFD-520
Dr. William Erhardt, HFD-520

A. INTRODUCTION

The Reviewing Medical Officers (RMOs) requested additional safety analyses to be performed. The purpose of this addendum is to answer the following queries:

- 1) Based on the entire patient safety database, how many patients in comparative U.S. trials had normal platelet counts at baseline and had clinically relevant deviation in platelet counts at endpoint?
- 2) What is the demographic profile of patients having such deviations?

Analyses were performed on the database provided by the sponsor on all patients having platelet count data during or after the therapy. Subset analyses were performed with gender, age, duration of therapy and dosage regimen as strata. In this report, only the overview of the analysis is presented, details based on the strata information are going to be incorporated as a part of the clinical review.

B. EVALUATION

A patient is said to have normal platelet count at baseline if his/her counts lie within the lower and upper limits for the test laboratory. Each patient had at least three observations for platelet counts -- the baseline value, the worst value during treatment and the worst value after the dosage regimen. Endpoint is defined as the last available value. This is the most conservative worst-case scenario. To define what is considered a clinically relevant deviation in platelet count, two definitions are considered:

- a) **One sided definition:** The platelet count for the patient is $\leq 50,000$.
- b) **Two-sided definition:** The platelet count for the patient is $\leq 50,000$ or $\geq 800,000$.

Patients were classified on the route of administration of the drug -- intravenously or intramuscularly.

Table 1 summarizes patients who had clinically relevant deviation in platelet counts (in thousands) according to two-sided definition.

Table 1: Summary of platelet count deviations in patients receiving intravenous administration of the drug (two-sided definition)

TREATMENT GROUP	DEVIATION CATEGORY				Total
	Frequency	1	2	3	
CEFEPIME	738 63.40	79 6.79	332 28.52	15 1.29	1164
CEFTAZID	509 60.31	50 5.92	269 31.87	16 1.90	844
Total	1247	129	601	31	2008

Legend for deviation category : 1 = lower limit - upper limit (normal)
 2 = (101 - lower limit) or (upper limit - 400)
 3 = (51 - 100) or (401- 800)
 4 = ≤ 50 or ≥ 800 (clinically relevant)

It is seen that 1.5% of the patients who had normal counts at baseline show clinically relevant change in platelet count at endpoint. Of them, 1.2% of the cefepime patients and 1.9% of the ceftazidime patients experience clinically relevant change.

Table 2 lists demographic and patient details of all subjects showing clinically relevant shifts in platelet count.

Table 2: List of patients having clinically relevant platelet count shift at endpoint (IV patients, two-sided definition)

OBS	SUBJ	INV	SEX	DRUG	DURCAT	DRUGREG	AGECAT	DEVIATION
1		411070012	F	CEFEPIME	2	.	1	4
2		411070015	F	CEFEPIME	1	2	1	4
3		411070019	M	CEFEPIME	2	2	1	4
4		411070045	M	CEFEPIME	2	2	1	4
5		411081015	M	CEFTAZID	2	3	.	4
6		411081032	M	CEFEPIME	1	2	1	4
7		411083004	M	CEFEPIME	2	1	2	4
8		411083004	M	CEFEPIME	2	6	1	4
9		411083004	M	CEFEPIME	2	1	2	4
10		411083014	F	CEFTAZID	2	1	1	4
11		411083030	F	CEFTAZID	1	1	2	4
12		411097001	M	CEFTAZID	1	5	1	4
13		411097001	M	CEFTAZID	2	5	2	4
14		411097004	M	CEFTAZID	2	5	1	4
15		411097008	F	CEFTAZID	1	5	1	4
16		411097012	M	CEFTAZID	2	5	1	4
17		411097013	.	CEFEPIME	1	4	1	4
18		411097013	.	CEFTAZID	1	4	2	4
19		411097014	M	CEFEPIME	2	4	2	4
20		411097015	M	CEFEPIME	2	4	1	4
21		411097020	F	CEFTAZID	2	5	2	4
22		411097025	F	CEFEPIME	1	4	2	4
23		411097026	M	CEFTAZID	2	8	2	4
24		411097028	F	CEFTAZID	2	5	2	4
25		411097033	F	CEFTAZID	1	5	1	4
26		411097037	M	CEFEPIME	2	2	1	4
27		411097042	M	CEFTAZID	2	3	1	4
28		411097042	F	CEFTAZID	2	3	1	4
29		411097043	F	CEFEPIME	2	4	2	4
30		411097053	F	CEFTAZID	2	5	2	4
31		411131001	F	CEFEPIME	2	5	1	4

Legend:

DURCAT = Duration of therapy

- 1= < 5 days
- 2= 5-18 days
- 3= > 18 days

DRUGREG = Dosage regimen

- 1= 500 mg BID
- 2= 1000 mg BID
- 3= 1000 mg TID
- 4= 2000 mg BID
- 5= 2000 mg TID
- 6= 500 mg QD
- 7= 500 mg TID
- 8= 1000 mg QD
- 9= 2000 mg QD

AGECAT = Age category

- 1= <= 65 years
- 2= > 65 years

DEVIATION = Platelet count shift (see legend in table 1 for details)

INV = Investigator

SUBJ = Patient identification

Table 3 summarizes the shifts if platelet count of $\leq 50,00$ is considered to be the only clinically relevant category.

Table 3: Summary of platelet count deviations in patients receiving intravenous administration of the drug (one-sided definition)

TREATMENT GROUP	DEVIATION CATEGORY				Total
	Frequency	1	2	3	
CEFEPIIME	748 64.26	79 6.70	332 28.52	5 0.43	1164
CEFTAZID	525 62.20	50 5.92	269 31.87	0 0.00	844
Total	1273	129	601	5	2008

Legend: vide table 1.

Only 0.4% of the cefepime patients show clinically relevant shifts while none experience it in the ceftazidime arm.

Table 4: List of patients having clinically relevant platelet count shift (in thousand) at endpoint (IV patients, one-sided definition)

OBS	SUBJ	INV	SEX	DRUG	DURCAT	DRUGREG	AGECAT	DEVIATION
1		411083004	M	CEFEPIIME	2	1	2	4
2		411097014	M	CEFEPIIME	2	4	2	4
3		411097025	F	CEFEPIIME	1	4	2	4
4		411097043	F	CEFEPIIME	2	4	2	4
5		411131001	F	CEFEPIIME	2	5	1	4

Legend: vide table 2

Table 5 summarizes patients who had clinically relevant deviation in platelet counts (in thousands) according to two-sided definition when the drug was administered intramuscularly.

Table 5: Summary of platelet count deviations in patients receiving intramuscular administration of the drug (two-sided definition)

TREATMENT GROUP	DEVIATION CATEGORY				Total
	Frequency	1	2	3	
CEFEPIIME	48 76.19	1 1.59	13 20.63	1 1.59	63
CEFTAZID	33 84.62	2 5.13	4 10.26	0 0.00	39
Total	81	3	17	1	102

Legend: vide table 1

Only 1 (1.5%) patient on cefepime experiences clinically relevant shift in platelet count, while none are reported on ceftazidime arm. Details on the patient profile is provided in table 6.

Table 6: Patient having clinically relevant platelet count shift (in thousand) at endpoint (IM patient, two-sided definition)

OBS	SUBJ	INV	SEX	DRUG	DURCAT	DRUGREG	AGECAT	DEVIATION
1		411081032	M	CEFEPIME	1	2	1	4

No patient reported a clinically shift in platelet count when one-sided definition was applied.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

Analyses were performed on the database provided by the sponsor on all patients having platelet count data during or after the therapy. Subset analyses were performed with gender, age, duration of therapy and dosage regimen as strata. In this report, only the overview of the analysis is presented, details based on the strata information are incorporated as a part of the clinical review.

To define what is considered a clinically relevant deviation in platelet count, two definitions are considered:

- a) **One sided definition:** The platelet count for the patient is $\leq 50,000$.
- b) **Two-sided definition:** The platelet count for the patient is $\leq 50,000$ or $\geq 800,000$.

If two-sided definition is used for patients receiving intravenous administration of the drug, it is seen that 1.5% of the patients who had normal counts at baseline show clinically relevant change in platelet count at endpoint. Of them, 1.2% of the cefepime patients and 1.9% of the ceftazidime patients experience clinically relevant change (table 1). Only 0.4% of the cefepime patients show clinically relevant shifts while none experience it in the ceftazidime arm if one-sided definition is used (table 3).

For patients who received intramuscular administration of the drug, only one patient in the cefepime arm showed clinically relevant shift in platelet count when two-sided definition is used, while none reported on the ceftazidime arm (table 5). No patient had clinically relevant shift when one-sided definition is used.

Based on the analyses performed, there is no statistically detectable difference

between treatments in percent of patients reporting clinically relevant elevation in platelet count. This is reflected in the overall results, as well as on subsets based on age, gender, duration of therapy or dosage regimen.

Alaka Chakravarty
05/10/94

Alaka G. Chakravarty, Ph.D.
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Ralph Harkins, Ph.D., 5/11/94

Concur: Ralph Harkins, Ph.D.

Satya D. Dubey, Ph.D., 5-12-94

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Orig. NDA-50-679

HFD-520

HFD-520/Dr. L. Gavrilovich

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HFD-344/Dr. A. Lisook

Chron.

This review contains 6 pages.

Statistical Review and Evaluation
(Amendment II)

NDA#: 50-679

Drug Class: 1 S

Applicant: Bristol-Myers Squibb Pharmaceutical Research Institute

Name of Drug: Maxipime® (Cefepime Hydrochloride) Injection

Medical Input: Dr. Renata Albrecht, HFD-520
Dr. Murray Lumpkin, HFD-520

A. INTRODUCTION

Following the completion of the statistical review, several questions and concerns arose at the management review. The purpose of this amendment is address these issues and provide clarification for any inconsistencies.

It is to be noted that only the domestic (US) pivotal comparative studies are considered to be a part of the statistical efficacy analysis. Foreign studies are not subjected to statistical review and are considered supportive, unless specified by the reviewing Medical Officer (RMO). It was decided that in this submission, no foreign study needed a statistical review. Non-comparative studies, domestic and foreign, were deemed supportive only by the RMO and needed no statistical input. All studies contributed to the safety database.

Table -1 has been updated to make it more comprehensive.

Table -1. Baseline Consistency in number of Strictly Evaluable patients

Criteria	Cefepime / Metronidazole	Gentamicin / Clindamycin
Total enrolled in the trial	114	93
Total enrolled by Dr. Berne	89	66
Total evaluable in the trial	20	29
Total evaluable in Dr. Berne's center (% of total evaluable)	19 (95%)	23 (79%)

This bears out the fact that Study 411-119 was essentially a single center study.

Efficacy Analyses:

Concern was expressed on correctness of the confidence interval for clinical cure with reviewer's evaluable pool. It is to be noted that the statistical reviewer constructed the confidence interval based on the data on MOR page 22, while the one that was quoted in the correction is based on the data on MOR pg 23.

Table -2 : Summary of Clinical Response (Protocol AI 411-119)

Cure Rates	Treatment Profile		Confidence Interval n_t, n_c (95% C.I.) p_t, p_c
	CEF/MET	CLI/GEN	
Clinical Cure with Reviewer's evaluable pool (MOR pg 22)	26	33	26, 33 (-.1479, .2808) .88, .81
Clinical Cure with Reviewer's Evaluable pool (MOR pg 23)	25	35	25, 35 (-.1143, .3314) .88, .77

The 95% confidence intervals are reported as : n_t = number of subjects in the treatment arm, n_c = number of subjects in the control arm, p_t = cure rate in the treatment arm, p_c = cure rate in the control arm. A continuity correction factor has been applied to the confidence intervals.

Following this correction, the Cefepime/Metronidazole concurrent therapy is therapeutically equivalent to Gentamycin/Clindamycin for patients who are clinically evaluable only.

Concern was expressed over correctness of confidence interval for clinical response in Protocol AI 411-120, as discussed in table -3.

Table -3 : Summary of Clinical Response (Protocol AI 411-120)

Cure Rates	Treatment Profile		Confidence Interval n_t, n_c (95% C.I.) p_t, p_c
	CEFEPIME	GENTA /MEZLO	
Clinical Cure for clinically evaluable only	23	5	23, 5 (-.3771, .6038) .91, .80

The total number of patients on Genta/Mezlo arm was changed to 6. According to MOR available to the statistical reviewer (page 20), this number is 5. If it changed in a later version, the revised numbers were not communicated to the statistical reviewer. A copy of the page is enclosed.

Please note that the clinical cure rate on cefepime for patients who were strictly evaluable is 92.8%.

The confidence interval for overall microbiologic eradication for protocol AI 411-119 (Table 4) should read 60.58(-0.1497, 0.1244) 86%. 87%. Statistical interpretation on it remain unchanged.

Table -5: Cure Rates Based on Specific Causative Organisms

Causative Organism	Protocol AI 411-119	Protocol AI 411-120
E. Coli	18.23 (-.2738, .2883) 83% 82%	n = 7,0; Cures = 6,0; confidence interval meaningless
P. Aeruginosa	6.5 (-.6472, .3148) 83% 100%	n = 1,0; Cures = 1,0; confidence interval meaningless

There was a comment saying the interpretations of the confidence intervals in 5 are not understandable. The interpretations on them are reiterated here:

There is insufficient sample size in Protocol AI 411-120 to construct confidence intervals. In Protocol AI 411-119, the sample size is adequate to make inferences to E.Coli only; Cefepime fails to establish microbiologic equivalency with its control in this comparison.

C. CONCLUSIONS (Which May be Conveyed to the Sponsor)

These analyses fail to clearly demonstrate statistically the therapeutic equivalence of Cefepime in monotherapy or in Cefepime/Metronidazole concurrent therapy in treatment of infections (tables 1 through -5).

Indication: Complicated Urinary Tract Infections (including pyelonephritis)

Efficacy Analyses:

It is to be noted that in the MOR, patients diagnosed with pyelonephritis were pooled and analyzed with the patients having complicated urinary tract infection (CUTI).

Clinical efficacy at 5-9 days post-therapy is presented Table CUTI-1.

Table CUTI-1 : Summary of Clinical Response at 5-9 days post-therapy

Protocol	dose regimen	Cures		C.I. for clinically evaluable patients
		CEFEPIME	CEFTAZIDIME	
AI 411-071	0.25 gms BID	9/12	5/5	12.5 (-.6367, .1367) 85%, 100%
AI 411-083	0.50 gms BID	74/103	35/55	103.5 (-.0858, .2500) 71%, 63%
AI 411-108	0.50 gms BID	11/21	7/13	21.1 (-.4219, .3926) 52%, 53%
AI 411-097	2 gms BID	48/58	44/58	58.5 (-.0951, .2331) 82%, 77%

There was a comment saying the numbers are not updated. These numbers are per the database given by the RMO for patients with CUTI and pyelonephritis. The handwritten corrected numbers are for the total evaluable patients, which include patients with CUTI and uncomplicated UTI.

Cure Rates based on Specific Causative Organisms:

Based on the numbers presented by the RMO, the confidence interval for bacteriologic responses by specific causative organisms are presented in Table CUTI-4.

Table CUTI-4. Bacteriologic response by infecting pathogens

Pathogen	Number of cures		Confidence interval n, n. (95% C.I.) p, p.
	CEFEPIME	CEFTAZ	
500 mg BID or TID			
All organisms	115/146	62/81	146.81 (-.1010, .1454) 78, 76
E.Coli	68/83	27/41	83.41 (-.0245, .3461) 81, 85
P. Aeruginosa	11/17	10/11	17.11 (-.6205, .0965) 64, 90
P. Mirabilis	10/12	5/5	12.5 (-.5192, .1858) 82, 100
2 gms BID			
All organisms	64/82	65/81	82.81 (-.1589, .1149) 78, 80
E.Coli	36/39	41/46	39.46 (-.1147, .1782) 92, 89

Concern was expressed that the column heading "500 mg BID or TID" is misleading. It means that Cefepime was administered 500 mg BID while the ceftazidime was administered 500 mg TID. The comment "#s wrong" can be explained by the fact that

the table is based on the efficacy summary data submitted by the RMO on 3/4/94. The complete review on UTI (complicated and uncomplicated) had been submitted via the CSO on 11/29/93. In a verbal communication, the RMO specified that the tables should be generated on the more recent efficacy summary data. A copy of the page is enclosed.

Indication: Pneumonia

In table PNEU-1, Cefepime is seen to be therapeutically equivalent to its control on all trials conducted in U.S. for the clinically evaluable patient population. Clinical efficacy of cefepime is equivalent to its control in clinical efficacy for the patient sub-population that are smokers. This is not reflected in the non-smoking population. This may be more due to small sample size than due to a lack of clinical significance.

Indication: Skin and Soft Tissue Infections

On statistical review, page 29, third paragraph under "Comparative trial", it should read as protocol AI 411-097.

In table SSTI-1, the confidence interval for overall cure in the fully evaluable patients should read as : 27.15 (-.3835, .0131) .81, .10 . The interpretation on it remain unchanged.

In table SSTI-3, the confidence interval for overall cure in the clinically evaluable patients should read as : 79.79 (-.1460, .1207) .81, .82 . The interpretation on it remain unchanged.

In first paragraph of "Conclusions", 0.5 grams q8h should read 0.5 grams BID.

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7/22/94
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NDA 58679

12 OF 13

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NDA: 50,679

MARCH 21, 1994

CEFEPIME HCL

5 Research Parkway
P.O. Box 5100
Wallingford
CT 06492-7660

REVIEWER: Ene Ette, Ph.D.

TYPE OF SUBMISSION: AMENDMENT No. 92
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BACKGROUND:

Cefepime is a new injectable cephalosporin antibiotic with a broad spectrum of antimicrobial activity. It is eliminated from the body primarily by glomerular filtration.

SYNOPSIS:

This is an amendment to NDA 50-679 on an open study undertaken to evaluate the pharmacokinetics of cefepime and ceftazidime after the administration of multiple intravenous doses to patients with serious bacterial infections. Patients were randomly assigned to either treatment. Each patient treated for a maximum of 14 days received a 2 g dose of cefepime or ceftazidime q12h or q8h, respectively, infused over 30 min. Male and female patients participated in the study. The mean (SD) age of cefepime treated patients was 68 (15) yr with a range of 26 to 78 yr; only one patient was 26 yr old while the rest were >= 60 yr old. The mean (SD) age of ceftazidime patients was 59 (20) yr. After 3 days of therapy at a minimum, serial blood and urine samples were collected to evaluate pharmacokinetic profiles. The mean +/- SD Cmax, AUC0-7, t1/2, total clearance (CLT), and Vss were
ug*/h/ml, h, ml/min, L for cefepime, and
ug*/ml, h, ml/min, and
L for ceftazidime. The t1/2 of cefepime in this study is consistent with what has been reported for the elderly population, a consequent of a decline in renal function with age. Renal function is the only determinant of cefepime clearance. Except for t1/2, the results suggest that the PK of cefepime and ceftazidime are not significantly altered in patients treated for serious bacterial infections.

COMMENT:

The findings of this study are supportive of what is known about the pharmacokinetics of cefepime.

RECOMMENDATION:

The Division of Biopharmaceutics recommends that the study is acceptable.

STUDY SUMMARY:

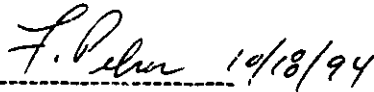
This was an open study (AI411-111-003) to evaluate the pharmacokinetics of cefepime and ceftazidime in patients with serious bacterial infections. Patients were randomly assigned to either treatment. Each patient treated for a maximum of 14 days received a 2 g dose of cefepime or ceftazidime q12h or q8h, respectively, infused over 30 min. Male and female patients participated in the study. The mean (SD) age of cefepime treated patients was 68 (15) yr with a range of 26 to 78 yr; only one patient was 26 yr old while the rest were ≥ 60 yr old. The mean (SD) age of ceftazidime patients was 59 (20) yr with a range of 20 to 81 yr; one patient was 20 yr old while the rest were ≥ 50 yr old. After 3 days of therapy at a minimum, serial blood and urine samples were collected to evaluate pharmacokinetic profiles. The results are summarized in Table 1. The $t_{1/2}$ of cefepime in this study is consistent with what has been reported for the elderly population, a consequent of a decline in renal function with age. Renal function is the primary determinant of cefepime clearance. Except for $t_{1/2}$, the results suggest that the PK of cefepime and ceftazidime are not significantly altered in patients treated for serious bacterial infections.



10/18/94

Ene Ette, Ph.D.

Pharmacokinetic Evaluation Branch II



RD/FT initialed by F. Pelsor, Pharm.D.

cc: NDA 50-679, HFD-520 (Clinical Division), HFD-427 (E. Ette, F. Pelsor, M. L. Chen), HFD-426 (N. Fleischer), HFD-340 (Vishwanathan), HFD-19(FOI), Chron, Drug, Reviewer's file.

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NDA: 50-679

SUBMISSION DATE: JUNE 30, 1992

CEFEPIME HYDROCHLORIDE:

**500 mg, 1 g, 2 g vials, and 1 g, 2 g piggyback
(100 ml) bottles**

BRAND NAME:

Maxicef, Cefmax, or Maxcef proposed

**Bristol-Myers Squibb Company
Pharmaceutical Research Institute
5 Research Parkway - P.O. Box 5100
Wallingford, CT 06492-7660**

REVIEWER: ENE ETTE, Ph.D.

TYPE OF SUBMISSION:

Original NME

CODE: 1 S

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SYNOPSIS: NDA 50-679 was filed on June 30, 1992 for cefepime (BMY-28142) hydrochloride injection, a drug for the treatment of urinary tract infections, skin and skin structure infections, and cefepime hydrochloride (to be marketed formulation) were used for pharmacokinetic studies. The Sponsor has carried out bioavailability, bioequivalence and pharmacokinetic (PK) studies (single and multiple dose studies) in healthy volunteers and patients. Pharmacokinetic studies have been done with doses ranging from 250 mg to 4000 mg, and absolute bioavailability of cefepime administered intramuscularly has been determined. Bioequivalence study was done with the product as reference using a dose of 2000 mg given as a 30 min infusion. Studies were also done in special populations (elderly, lactating women, cystic fibrosis, hepatic, and renal impaired patients). Also, tissue penetration and drug interaction studies were carried out. In most of the studies cefepime was administered by intravenous (IV) infusion. A summary of assay methodology and validation was provided.

RECOMMENDATION: The Division of Biopharmaceutics has reviewed NDA 50-679 submitted on June 6, 1992 for Cefepime. The data submitted in support of this submission are acceptable toward adequately characterizing the pharmacokinetics of the drug.

Please convey the above "Recommendation" and "Labelling Comments" 1 through 3 (pages 20 and 21) to the Sponsor.

ORGANIZATION OF REVIEW: A description of the drug formulations will be followed by a summary of dose proportionality, bioavailability / bioequivalence / PK studies, population pharmacokinetic analyses, and labelling comments.

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BACKGROUND: Cefepime-HCl, a pyrrolidinium, is a semi-synthetic broad spectrum cephalosporin antibiotic for the treatment of infections of urinary and skin and skin structure. It has a methoxyimino-aminothiazole at 7 side chain, and 3' N-methyl pyrrolidine substituent (Fig. 1). It is highly resistant to hydrolysis by most beta-lactamases, and has low affinity for chromosomally-encoded beta-lactamases. The drug rapidly penetrates into gram-negative (G⁻) bacterial cells. Comparable with other cephalosporins, cefepime binds to a group of proteins on the cell surface of bacteria that are called penicillin binding proteins (PBP). The essential PBP are acylated, inactivating the enzyme with the resultant prevention of peptidoglycan (bacterial cell wall) synthesis. As with other broad spectrum cephalosporins, cefepime has the greatest affinity for PBP3, but its affinity for PBP2 is greater than that of the other cephalosporins, such as ceftazidime. Bacterial cell walls contain few PBP2 so that a few molecules of cefepime can saturate these sites and thereby interfering with cell wall synthesis. The high affinity of cefepime for PBP2 accounts, in part, for the effectiveness of the drug against certain members of *Enterobacteriaceae*, such as *E. coli* and *E. cloacae*.

Cefepime-HCl is manufactured by

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DRUG FORMULATION: Two cefepime formulations and hydrochloride with arginine (ARG)) were used for clinical and PK studies (see Tables 1 - 2). Most of the PK studies were done with cefepime hydrochloride, the dosage form to be marketed. Cefepime is a lyophilized-product consisting of cefepime and sodium chloride. This formulation included three strengths: 0.25 g, 0.5 g, and 1.0 g (Table 1). Formulations of cefepime sodium chloride drug product had 15% overage, but during the course of clinical trials the overage of the 1.0 g strength was reduced to 8%.

Cefepime hydrochloride for injection is also produced in three strengths: 0.5, 1.0, and 2.0 g. The ratio of sterile cefepime hydrochloride to sterile L-arginine is w/w (L-arginine to cefepime hydrochloride) in all three strengths. Table 2 summarizes the quantitative compositions of the three strengths of the new product for the IM and IV preparations.

Table 1. Composition of Cefepime and Sodium Chloride Formulation

Product Identification (PI) Number	Cefepime Activity	Sodium Chloride
28142-P250-02	mg	mg
28142-P500-03	mg	mg
28142-P1X0-04	g	mg

Table 2. Composition of Cefepime Hydrochloride for Injection

Vial Presentation	Ingredients	mg per vial
0.5 g ^a	Sterile cefepime HCl Sterile L-arginine	615 ^b 446 ^c
1.0 g ^a	Sterile cefepime HCl Sterile L-arginine	1140 ^d 826 ^e
2.0 g ^f	Sterile cefepime HCl Sterile L-arginine	2100 ^e 1522 ^e
1.0 g Piggyback ^f	Sterile cefepime HCl Sterile L-arginine	1050 ^e 761 ^e
2.0 g Piggyback ^f	Sterile cefepime HCl Sterile L-arginine	2100 ^e 1522 ^e

a To deliver for intramuscular (IM) or (IV) use.

b Indicates mg cefepime and includes 18% overfill and 5% overage.

- c Exact amount was determined during laboratory studies and initial plant trials by
This ratio
has been confirmed to be 0.6: 1.0 w/w L-arginine to cefepime hydrochloride.
- d Indicates mg cefepime and includes 9% overfill and 5% overage.
- e Indicates mg cefepime and includes 5% overage.
- f To deliver for IV use.

SUMMARY OF BIOAVAILABILITY AND PHARMACOKINETIC STUDIES

1. ASSAY METHODS: Sensitive, specific, precise, and accurate HPLC/UV, HPLC/Radiometric, and GC assay methods were used for the quantification of cefepime in body fluids.

2. SINGLE AND MULTIPLE DOSE, DOSE PROPORTIONALITY PHARMACOKINETIC AND BIOAVAILABILITY STUDIES

2.1. SINGLE AND REPEATED IV INFUSIONS OF 250, 500, AND 1000 MG: Study 411-058-001 was carried out to determine the pharmacokinetics of cefepime after single and repeated IV infusions of 250, 500, and 1000 mg doses to normal, healthy male, volunteers.

47 healthy, normal, male volunteers aged 19 to 45 years, in six treatment groups participated, with informed consent, in the study (Table 3). This was originally a parallel study, but later modified into a placebo controlled double blind study. All dosing entailed IV infusion of either cefepime or saline, at constant rate, over min interval.

The original design entailed the administration of cefepime to eight normal subjects in 3 groups, I, II, III, corresponding to treatments of 250 mg t.i.d, 500 mg t.i.d, and 1000 mg b.i.d, respectively. The first dose for each Group I subject was followed by a 24 h collection interval to obtain single-dose kinetic data. On treatment day 2, beginning with the morning dose (0600 h), each subject received 250 mg t.i.d, with the final, 29th dose on the morning of treatment day 11. Serial blood samples, and the total urine output of each subject were collected after the 0600 h dose on treatment days 1, 6, and 8. This procedure was repeated for Group II, but due to supply considerations a different drug lot (20757) was used. Treatment of this group was discontinued on day 6 due to adverse experiences.

Subsequent progression of the study ultimately entailed incorporation of ancillary groups IIA, IIC, and IIB into the study. Control subjects in each group received only saline, and a double-blind dosing scheme was introduced. The specific lot of drug was presumed to be an experimental parameter. Also, the original treatment design for Group III was revised to include placebo treatment and blinded dosing.

Group IIA subjects received 29 infusions of either saline or 500 mg cefepime of the lot (S85K013) used in Group I. The successive groups, IIC, IIB, and III, entailed administration of

250, 500, and 1000 mg cefepime lot 20759, respectively. Blood and urine collections were essentially similar to those described above, except that a complete collection of urine was included on day 4, and the schedule for Group III reflected the b.i.d. dosing schedule. Sampling for Group IIC, which preceded Group IIB for reasons of safety evaluation, was restricted to a few blood (peak and trough) samples for verification of exposure (Table 4).

The evaluation of urinary recovery was suspended, because it became evident that urine samples were prepared incorrectly.

Statistical moments analysis methods were used to estimate PK parameters. ANOVA procedures were utilized to evaluate C_{max} , AUC, $t_{1/2}$, MRT(IV), and V_d following single and multiple IV doses of cefepime. Analyses were performed to assess differences among parameter values with respect to dose (250, 500, and 1000 mg) and time (Days 1, 6, and 11). Additional evaluations were carried out to determine the significance of differences among three 500 mg dose groups corresponding to three different cefepime lots.

A one-way ANOVA was used to evaluate differences among dose groups on day 1 with respect to dose-normalized C_{max} , AUC_{0-24} , $t_{1/2}$, MRT(IV), and V_d . Differences in dose groups on day 1 with respect to each of these parameters (except V_d), were also evaluated. Tukey-Kramer multiple comparison procedure was used to compare mean parameter values among dose-groups. ANOVA was also used to compare means for the three 500 mg groups on day 1.

Key pharmacokinetic parameters are compiled and summarized in Tables 5 - 8 and Fig. 2 - 6). Evaluation of the plasma data indicated minor differences among pharmacokinetic parameter values for one of the three distinct 500 mg dose groups and the 250 mg and 1000 mg groups. Although these differences preclude definitive characterization, the data are indicative of linear pharmacokinetics. Overall mean (S.D.) parameter values, averaged across all treatment groups for day 1, and normalized to a 1000 mg dose are $C_{max} = 68$ (10) ug/ml, and $AUC_{0-24} = 128$ (20) ug*h/ml. Overall means for dose-independent parameters are: MRT = 2.2 (0.3) h; $t_{1/2} = 2.1$ (0.6) h; CLT = 134 (22) ml/min; and $V_d = 17.6$ (2.0) L. These values are essentially the same as those reported for other studies below. No significant change in parameter values was observed as a result of multiple dosing.

These results for single and repeated administration of cefepime are indicative of linear pharmacokinetics that are invariant with respect to duration of treatment. There were no significant differences in dose-normalized C_{max} and AUC values for Gps I, II, and III.

2.2. THE USE OF SHORTER INFUSION TIMES: Study 411-056-001 was carried out to determine the safety and tolerability of single 2000 mg IV infusions of cefepime administered over progressively shorter intervals until infusion over 3 min period was accomplished to healthy male volunteers.

16 healthy volunteers aged 21 to 38 years (weight: 67.7 to 100.9 kg) participated, with informed consent, in the study. The subjects were divided into 4 treatment groups of 4 subjects each. It was a double-blind study with ceftazidime as the control drug. Each of the 4 subjects in each treatment group was to receive a single dose of both antibiotics, according a cross-over design, with a wash-out period of at least 48 h between treatments. However, 2 subjects received only cefepime, and 1 only ceftazidime. The 2 cephalosporins were administered as either 15, 10, 5, or 3 min constant-rate infusions, depending on treatment group. Serial plasma samples were collected after every treatment.

Statistical moments analysis methods were used for most of the analysis. A 2 compartment open model was used to fit the data for the estimation of C_{max} . Data from the three subjects who took only cefepime or ceftazidime were excluded in analyses. Analyses were carried out to assess differences in parameters with respect to infusion time (TAU) and drug. An overall test of TAU differences was carried out at the 5% level, using the between-group error term.

The following parameters for cefepime were invariant with respect to TAU, and thus indicative of linear pharmacokinetics. Mean (S.D.) values for all individuals were: MRT = 2.3 (0.2) h; $t_{1/2}$ = 1.9 (0.2) h; AUC_{inf} = 239 (32) ug*h/ml; CLT = 142 (18) ml/min; and V_d = 19 (2) L. These values were consistent with previous studies, and comparable to results for ceftazidime (Tables 9 - 11), although some statistically significant differences between values for the 2 cephalosporins were observed.

C_{max} was not coincident with the end of infusion, for many subjects. This anomalous kinetic behavior appeared reproducible, since results for cefepime in a given individual were similar to those of ceftazidime. The lag in C_{max} precluded a rigorous evaluation of this parameter with respect to TAU. Actual C_{max} values for cefepime were compared to reference values obtained by extrapolation of data for subjects of study 411-058-001, who received 30 min infusions. Actual C_{max} values were not significantly different from the reference values.

The results of this study are indicative of the similarity of the PK of cefepime and ceftazidime, and vary with infusion rate in a predictable manner.

2.3. SINGLE AND MULTIPLE DOSE STUDIES WITH 500, 1000 AND 2000 MG DOSES:

Study 411-063-001 (subsequently referenced as -063) was conducted to assess safety / tolerance, and to characterize pharmacokinetics for single and multiple dosing of 1000 and 2000 mg cefepime to normal, healthy male, volunteers.

Study 411-064-001 (subsequently referenced as -064) was conducted to assess the safety of two different lots of cefepime when administered to healthy male volunteers on a 500 mg tid treatment regimen.

With informed consent, 20 subjects divided equally into 2 groups (age: 20 - 45 years, weight: 66.2 - 98.9 kg) participated in Study -063, and 9 subjects (age: 21 - 43 years, weight: 60.8 - 82.7 kg) participated in Study -064.

Study -064 was a placebo controlled double-blind study. 3 subjects received 500 mg cefepime, lot 20757, 3 subjects received 500 mg cefepime, lot 20759, and 3 control subjects received saline only. The first dose for each subject was followed by a 24 h hiatus period. Beginning with the morning dose on treatment day 2, each subject received IV injections on a tid schedule, with the final, 29th injection given on the morning of treatment day 11. 2 or 3 plasma samples were collected from each subject on treatment days 1, 4, 6, 8, and 11 to monitor plasma cefepime concentrations.

Study -063 was a parallel study conducted in a double-blind manner. Each dosing entailed IV infusion of 50 ml cefepime solution or saline, at a constant rate, over a 30 min interval. A vitamin concentrate was added to the saline solution at the 2000 mg dose level to match the color of the cefepime dosing in each dosing solution. The two groups of ten subjects each

corresponded to 1000 mg tid and 2000 mg tid regimens. In each group, 7 subjects received cefepime, and 3 control subjects received the placebo infusions. The first dose for each subject was followed by a 24 h collection interval to obtain single-dose data. Beginning with the morning dose on treatment day 2, each subject received either 1000 mg tid or 2000 mg tid. The final, 29th dose was given on the morning of treatment day 11. Serial blood samples, and the total urine output of all twenty study subjects were collected after the morning doses on treatment days 1, 6 and 11.

ANOVA procedures were utilized to evaluate C_{max} , AUC, $t_{1/2}$, MRT(IV), and V_{ss} following the tid regimen of cefepime. Analyses were performed to assess differences among parameter values with respect to dose (250, 500, and 1000 mg from Study 411-058-001) and in the case of the 1000 and 2000 mg tid groups, days 1, 6, and 11. A one-way ANOVA was used to evaluate differences among dose groups on day 1 with respect to dose-normalized C_{max} , AUC_{inf} , $t_{1/2}$, MRT(IV), and V_{ss} . Linear regression was used to assess dose proportionality.

The summarized results are in Tables 12 to 14 and Fig. 7 to 13. The PK of cefepime is linear over the dose range of 250 to 2000 mg. Overall mean (SD) parameter values (normalized to 1000 mg dose level), based on results for 46 healthy male subjects receiving either 250, 500, 1000 or 2000 mg cefepime, are: $C_{max} = 68(10)$ ug/ml, and $AUC_{inf} = 128(20)$ ug.h/ml. Overall means for dose-independent parameters: MRT = 2.3 (0.3) h; $t_{1/2} = 2.1(9.6)$ h; CLT = 133 (21) ml/min; and $V_{ss} = 17.9(2.3)$ L. Overall mean (SD) UR at 500, 1000, and 2000 mg dose levels is 80 (8) % dose. Parameter values for treatment days 6 and 11 are essentially equivalent to corresponding values for the initial dose. Thus, cefepime pharmacokinetics are invariant with respect to treatment duration.

2.4. SINGLE AND MULTIPLE ADMINISTRATION OF 2000 MG CEFEPIME ARG.: Study 411-090-001 was executed to characterize the pharmacokinetics of single and multiple administration of 2000 mg cefepime hydrochloride/arginine.

10 healthy male volunteers (age: 31 - 45 years; weight: 68 - 73 kg) participated in the study after giving informed consent. The study design and sampling schedule was similar to that used in Study -063 with 2000 mg dose given q8h.

Accumulation was calculated using standard formulae. In evaluating the effects of multiple dosing, paired t-tests were used to compare day 1 (single dose) data to the day 11 (multiple dose) data. The parameters: C_{max} , $t_{1/2}$, MRT (IV), CLT, and V_{ss} were included in the assessment.

The results are summarized in Tables 15 and 16, and Fig. 14 - 16. Parameter values for treatment days 1 and 11 were equivalent to corresponding values for the initial dose. Cefepime PK were invariant with respect to treatment duration. The degree of accumulation expected for cefepime was estimated from a theoretical factor, R_s (i.e. $1/(1-e^{-k\tau})$), which for tid dosing and $t_{1/2}$ of 2 h, indicates steady state concentrations about 13% above single-dose levels. However, estimates of actual accumulation factor, based on inspection of C_{max} and C_{min} and AUC, suggest no accumulation on multiple dosing (Table 16). These results are consistent with those obtained for the formulation.

2.5. SINGLE AND MULTIPLE ADMINISTRATION OF 4000 MG CEFEPIME ARG.: Study 411-130-001 was designed to characterize the pharmacokinetics of single and multiple

administration of 4000 mg cefepime hydrochloride/arginine. 12 healthy male volunteers (age: 18 - 43 years; weight: 60.8 - 84.4 kg) participated in the study after giving informed consent. 7 subjects were administered cefepime, while 3 were administered placebo (multivitamin parenteral solution). 2 subjects in the cefepime treated group had skin rash and were replaced.

The study design and sampling schedule was similar to that used in Study -063 with 4000 mg dose given q8h.

Pharmacokinetic analysis was by statistical moments methods. Plasma and urine data were evaluated to determine key PK parameters on days 1 and 11. The effect of study day on selected pharmacokinetic parameters was evaluated by a randomized block ANOVA with subjects as blocks.

Results are summarized in Tables 16b and 17, and Fig. 17 and 18. Days 6 and 11 C_{max} were significantly greater than day 1 C_{max} ; the best estimate of the mean accumulation factor was 17%. Day 11 CLT was significantly lower than Day 1 CLT (magnitude of difference: 8.8%, not likely to be clinically significant). Furthermore, there were no statistically significant differences between days 1 and 11 in other pharmacokinetic parameters (e.g. CLR which accounts for at least 90% of cefepime eliminated, MRT(IV) and V_{ss} (by definition $CLT = V_{ss}/MRT(IV)$)).

2.6. SAFETY, TOLERANCE, DOSE PROPORTIONALITY AND BIOAVAILABILITY

: Study 411-096-001 was conducted to evaluate safety, tolerance and pharmacokinetics (dose proportionality, absolute bioavailability, and steady state pharmacokinetics) of cefepime HCl (ARG) after IM administration. Single IM doses of 250, 500, 1000, and 2000 mg, multiple doses (q12h) of 1000 mg (for 10 days) and single IV doses of 2000 mg were administered to healthy male volunteers subdivided into 4 dose-groups. Subjects in groups I - III participated in a parallel study to determine tolerance and dose proportionality in cefepime pharmacokinetics, while group IV subjects were involved in a randomized crossover study to determine the absolute bioavailability of cefepime HCL given IM. Pain at IM injection site was scored using a visual analog scale. Serial blood samples and total urine output were collected at specified times. One way ANOVA was used in the comparison of PK parameters obtained from the single dose study sessions, while 90% confidence interval (CI) based on the two one sided test approach was used for evaluating the bioavailability of the IM formulation.

Cefepime was well tolerated after IM administration. Most subjects experienced none to mild pain and minimum discomfort at the site of injection. Cefepime was rapidly absorbed on IM injection with T_{max} ranging between h. Pharmacokinetics of cefepime was linear (Fig. 19 & 20) with no evidence of accumulation during the multiple-dose phase of the study (1000 mg q 12 h) (Fig. 21 & 22) at the dose levels studied. The total body clearance (CLT) varied between ml/min. The AUC and C_{max} increased in a dose-proportional manner. 100% bioavailability was observed with IM administration of the drug as observed from the AUC and urinary recovery data (Tables 18 & 19).

2.7. SAFETY AND SINGLE-DOSE PROPORTIONALITY STUDY: Study 411-155-001

assessed cefepime PK at single 250, 500, 1000, and 2000 mg IV doses (ARG formulation) according to a balanced incomplete block crossover design. Each of 12 normal adult male volunteers received 3 of 4 dose levels, in randomized order, with a 3 day washout between

successive doses. Plasma levels were collected over 0 - 24 h after each dose and assayed for cefepime. Urine samples were also collected. However due to errors in urine sample collection or processing, urine data were excluded from the PK analysis.

Table 20. A Summary of Pharmacokinetic Parameters

Dose (mg)	C _{max} (ug/ml)	MRT(IV) (h)	t _{1/2} (h)	AUC _{0-∞} (h*ug/ml)	CLT (ml/min)	V _d (L)
250	20.2 (3.2)	2.27 (0.41)	2.12 (0.73)	36.2 (5.20)	117.0 (19.0)	15.8 (2.6)
500	39.1 (3.5)	2.22 (0.29)	1.87 (0.34)	70.8 (6.7)	119.0 (12.0)	15.7 (1.3)
1000	81.7 (5.1)	2.23 (0.30)	2.04 (0.39)	148.5 (15.1)	113.0 (10.0)	15.0 (1.2)
2000	163.9 (25.3)	2.14 (0.32)	2.94 (2.08)	284.8 (30.6)	118.0 (13.0)	15.1 (2.3)

The PK parameters are summarized in the Table 20 above and Fig. 23 to 25. These parameters are in agreement with previous results for equivalent cefepime doses to normal subjects. By linear regression analysis, C_{max} and AUC_{0-∞} are dose-proportional. There were no significant differences by dose level among the remaining parameters. Cefepime PK are linear, and the drug was well tolerated by volunteers.

3. BIOEQUIVALENCE: A randomized cross over study (Study 411-086-001) using the split plot design was carried out to determine the bioequivalence of cefepime HCl/arginine (ARG) formulation when compared with cefepime NaCl lyophil formulation as the reference. 2000 mg dose of each of the two formulations was administered as 30 min infusions with approximately 48 h between infusions to each of 12 healthy male volunteers (aged 22 to 45, and weight 66.7 to 92.1 kg). Subjects were not permitted to use any medication 1 week prior to the beginning of the study and during the study period. They also abstained from alcohol and caffeine during the study period with the exception of one dose of (650 mg) of acetaminophen if required for headache. Subjects were confined to the test facility for the duration of the studies, and were fasted from 2200 h preceding each dosing, until a standardized lunch was served approximately 3 h after infusion. 200 ml of water or juice about 1, 2 and 3 h after the initiation of dosing was taken by each subject to ensure diuresis.

Each 1 g vial of was reconstituted with 3.5 ml sterile water for injection, resulting in a clear solution containing 250 mg/ml cefepime activity. Each vial of the dihydrochloride/arginine blend containing 1 g cefepime activity was reconstituted with 208 ml of sterile water for injection, resulting in 250 mg/ml cefepime activity. After reconstitution, the 250 mg/ml reconstituted solution was diluted with sterile normal saline to

prepare infusion solution containing 40 mg/ml cefepime activity. Heparinized serial blood samples were collected predose and at specified time intervals over a 16 h period after the commencement of infusion. The total urine output of each of subject was collected after each dose over specified time intervals after the beginning of infusion.

The data was evaluated using statistical moments methods. ANOVA of log-transformed C_{max} , $t_{1/2}$, V_d , AUC_{inf} , and UR was done. The results are summarized in Tables 21 and 22. For T_{max} , the Wilcoxon signed rank test was used. The Wilcoxon statistic was not significant. No significant differences between mean C_{max} , $t_{1/2}$, V_d , AUC_{inf} , and UR values for ARG and formulations were found. The final characterization of each parameter, for each formulation, was based on evaluation of the ratio (ARG mean / mean) relative to the 90% confidence interval ratio. For every parameter tested, the 90% confidence interval for the mean ratio was within 20% of reference mean value (Fig 26). The two formulations are bioequivalent. ✓

4. STUDIES IN SPECIAL POPULATION GROUPS

4.1. AGE AND GENDER PHARMACOKINETICS STUDY (411-109-001) IN HEALTHY VOLUNTEERS: The effect of age and gender on the PK of cefepime (ARG formulation) was investigated in 48 subjects divided into 4 groups: (I) young males, (II) young females, (III) elderly males, and (IV) elderly females. Each subject was administered a single 1000 mg dose of the drug by a 30 min IV infusion. Serial blood samples and total urine output were collected predose and at specified time intervals during and after infusion for the determination of cefepime.

The C_{max} was: (I) 75.1 ± 9.7 , (II) 90.1 ± 17.8 , (III) 74.1 ± 11.9 , and (IV) 83.5 ± 20.0 ug/ml; $t_{1/2}$ was : (I) 2.26 ± 0.51 , (II) 2.15 ± 0.33 , (III) 3.05 ± 0.50 , and (IV) 2.92 ± 0.38 h; CLT was: (I) 114 ± 16 , (II) 98 ± 13 , (III) 86 ± 12 and (IV) 78 ± 11 ml/min; CLR was: (I) 106 ± 16 , (II) 87 ± 12 , (III) 80 ± 13 , and (IV) 63 ± 11 ml/min; and CLCR was: (I) 113 ± 17.6 , (II) 88.4 ± 9.1 , (III) 75.5 ± 15.1 , and (IV) 73.5 ± 15.8 ml/min; and V_d was: (I) 15.8 ± 2.6 , (II) 13.1 ± 2.4 , (III) 17.8 ± 2.0 , and (IV) 15.4 ± 4.4 L. There was a linear relationship between CLT and CLCR ($r = 0.72$, $p < 0.0001$). The disposition of cefepime was independent of age and gender in the presence of CLCR.

4.2. STUDIES IN CYSTIC FIBROSIS (CF) PATIENTS:-

4.2.1 PEDIATRIC STUDY (411-129-004):

The PK of cefepime (ARG) was assessed in "pediatric" cystic fibrosis (CF) patients with bronchopulmonary infections after single and multiple IV doses.

12 patients (7 females, 5 males), aged 5 to 41 years with weight ranging from kg were treated with a 50 mg/kg (2000 mg maximum) dose of cefepime every 8 h as a min infusion, for up to 14 days. Serial blood, sputum and urine samples were collected after the first and last dose. Attainment of steady state was assessed by monitoring the trough concentration (C_{min}) of the drug in plasma samples collected periodically during the study. PK parameters were estimated using statistical moments analytical methods. The results are summarized in Tables

23 to 25.

There were no significant differences between PK parameters obtained after the first and last doses of the drug (Table 23). The average C_{min} on days 3, 6, 9, and 12 ranged from $\mu\text{g/ml}$, and there were no significant differences among days (Table 24). In the first dosing interval average sputum concentration of cefepime ranged from $\mu\text{g/ml}$. After the last dose the average value ranged from $\mu\text{g/ml}$ (Table 25).

The PK of cefepime in cystic fibrosis patients were not sufficiently different from those in normal volunteers, and would not warrant dose adjustment.

COMMENT:

This was not a truly a pediatric study. Of the 12 patients, 3 were ≤ 12 years old, 5 were under 18 years old, while the remaining 4 were between 26 and 41 years old. Thus, data from this study and the one described immediately below were pooled for a population analysis to characterize the PK of cefepime in the cystic fibrosis patients.

4.2.2 ADULT STUDY (411-163-004):

The study was designed to compare cefepime pharmacokinetics in normal subjects with those in stable CF patients after a single 2000 mg dose of cefepime (ARG) given by a 30 min IV infusion.

12 normal volunteers (with equal number of both sexes) and 11 CF patients (5 males, 6 females), were enrolled for the study. CF patients did not have active respiratory infection at the time of the study. Serial blood samples and total urine output were collected for up to 24 h after dosing. Sputum samples were collected from CF patients at specified times. PK parameters were estimated using statistical moments analytical methods. The results are summarized in Tables 26 to 28.

Cefepime was detectable in 15 out of a total of 68 sputum samples that were collected after dosing (Table 26). The average peak concentration, equivalent to 3.4 mg/ml, was measured at 4 h after dosing. The drug was not quantifiable in sputum 6 h after dosing. Cefepime penetration into sputum of CF patients without active respiratory infection was minimal. Of the PK parameters, CLT and renal clearance (CLR) values normalized for body weight in CF patients were significantly greater than the corresponding values in normal subjects (Table 27 & 28). However, the magnitude of the difference did not exceed 23% for either parameter. Dosage adjustment is not necessary for CF patients. There was no gender effect.

4.3. STUDIES IN PATIENTS WITH VARYING RENAL FUNCTION: Two single dose studies (STUDY 07A1A-001-001) with $\mu\text{g/ml}$ formulation and STUDY-411-117-081 with ARG formulation) involving 48 volunteers (10 normal volunteers, and 38 patients with varying degrees of renal impairment) were done to examine the PK of cefepime in varying renal status. The dose, 1 g IV, of cefepime was infused for 30 and 5 min for the $\mu\text{g/ml}$ and ARG formulations, respectively. 10 patients had end stage renal disease (ESRD) and were on hemodialysis. 1 g dose of the drug was given by IV infusion to each subject. Serial blood and urine samples were taken in subjects with CRCL above 90 ml/min for up to 12 h and for up to 24 to 48 h in others after

infusion, depending on the degree of renal impairment.

The results of the two studies were similar (Tables 29 & 30, Tables 31 & 32, ARG). The mean peak plasma concentrations of cefepime at the end of a 30 min infusion ranged from 1000 ug/ml, and were not affected by renal impairment. The $t_{1/2}$ in normal renal function was 2.2 h in those with normal kidney function, and increased to 13 h in patients with ESRD (CRCL < 10 ml/min). There was a linear relationship between CLT and CLCR (CLT = 10.92 + 0.96 CLCR (r = 0.95) for ARG) and between CLR and CRCL (CLR = 0.33 + 0.88 CRCL (r = 0.93) for ARG), and between CLR and GFR (CLR = 0.87 GFR - 6.1 (r = 0.989) for ARG). The mean V_d in healthy subjects was 20.5 ± 4.84 L in healthy volunteers, and was not significantly different in those with renal insufficiency. The cumulative urinary recovery of cefepime in healthy volunteers was 80.2 - 82.9% of the administered dose in normal volunteers, but this was significantly decreased in those with CLCR less than 30 ml/min (57.2%). During hemodialysis the average plasma flow was 431 ml/min, hemodialysis clearance was 161 ml/min, and the $t_{1/2}$ fell to 2.3 h from 13.5 h during the predialysis period. After dialysis the elimination rate returned to the predialysis period. A dialysis period of 3 h would remove 68% of the drug. Cefepime dosage should be adjusted in proportion to renal function.

4.4. STUDY 411-093-001:- PATIENTS UNDERGOING CONTINUOUS AMBULATORY PERITONEAL DIALYSIS: 10 ambulatory patients undergoing continuous ambulatory peritoneal dialysis (CAPD) were studied. 5 patients received a single 1000 mg dose and 5 a single 2000 mg dose, all as 30 min infusions. Plasma, urine and peritoneal dialysate concentrations of cefepime were measured over 72 h.

The increases in C_{max} (62.9 ± 15.8 ug/ml for 1000 mg, and 124.0 ± 14.0 ug/ml for 2000 mg) and AUC (1106.0 ± 356.0 ug*h/ml for 1000 mg, and 2405.0 ± 213.0 ug*h/ml for 2000 mg) were dose proportional. There were no significant differences among dose levels for other PK parameters (Table 33). 26% of the dose was excreted intact into the peritoneal dialysis fluid over the 72 h sampling period. As a route of elimination of systemically administered cefepime, CAPD is a less efficient than hemodialysis (dialysis clearance (CL_D) of cefepime in CAPD is ca. 9% of that reported for hemodialysis) but CAPD is applied continuously. Over at least a 48 h period after the 2000 mg dose, mean dialysate cefepime concentrations at the end of each dialysis interval exceeded the MIC_{90} values of bacteria (including *Pseudomonas sp.*) which commonly cause CAPD peritonitis.

4.5. METABOLISM AND DISPOSITION OF ^{14}C -CEFEPIME IN NORMAL AND RENAL IMPAIRED PATIENTS: Study 411-077-001 was carried out in 4 healthy and 4 renally impaired male volunteers after an IV infusion of a single 1000 mg dose (100 μ Ci) of ^{14}C -labelled cefepime (product No. 28412-PIX0-10) prepared as an aqueous solution in NaCl (1:1 mole ratio). The ^{14}C -label was located in the methyl group of the N-methylpyrrolidine (NMP) moiety at the 3' position of cefepime. Serial blood and total urine output were collected at specified intervals. The samples were assayed for intact cefepime (HPLC/UV assay), NMP and NMP-N-oxide (HPLC/Radiometric assay) and total radioactivity.

Cefepime accounted for $\approx$ 95% and over 76% of the plasma radioactivity in normal volunteers and renal impaired subjects, respectively. The elimination $t_{1/2}$ of cefepime was $\approx$ 2 h in normal volunteers and increased from 3.96 h in a subject with renal impairment to 12.3 h in a subject with severe renal impairment. The V_d was $\approx$ 18 L, and not significantly affected by the degree of renal impairment. The urinary recovery of intact cefepime was $>$ 85% of the administered dose in normal subjects (Tables 34 & 35). The urinary recovery of unchanged drug decreased as the severity of renal impairment increased. Almost all the administered radioactivity was recovered in the urine of normal volunteers and subjects with mild to moderate impairment. Most of the total radioactivity of radiolabelled cefepime was recovered as cefepime. 87.9, 6.8, 2.5 and $<$ 1% of cefepime, NMP-N-oxide, 7-epimer of cefepime and NMP, respectively, were recovered after the administration of the radiolabelled drug to healthy volunteers. As the severity of renal impairment increased, the proportion of ^{14}C recovered as cefepime decreased and that of NMP-N-oxide increased (Fig 27).

4.6. COMPARISON OF CEFEPIME PK IN NORMAL AND HEPATICALLY IMPAIRED MALE SUBJECTS: In Study 411-112-001 11 each of normal and cirrhotic subjects, matched for age and weight received single 1000 mg cefepime dihydrochloride/arginine doses as 30 min IV infusions. Serial blood samples and total urine output were collected from each subject over a 12 to 36 h depending on the degree of hepatic impairment.

All PK parameter values for both groups were within ranges for cefepime PK parameters in normal subjects (Table 36). Cefepime dosage adjustment is unnecessary in cirrhotic patients.

5. TISSUE PENETRATION STUDIES

5.1. Penetration into Human Breast Milk (Study 411-151-001): 9 healthy lactating women received single 1000 mg IV doses of cefepime dihydrochloride/arginine as 30 min infusions. Serial plasma, urine, and breast milk samples were collected for 24 h dosing and were assayed for cefepime by validated HPLC/UV methods.

The PK of cefepime in lactating women - $C_{max} = 78.5 \pm 13.7$ ug/ml, $t_{1/2} = 2.08 \pm 0.34$ h, $CLT = 112 \pm 14$ ml/min, $CLR = 94 \pm 14$ ml/min, $V_d = 15 \pm 2$ L, UR (urinary recovery as % of dose) = 83.9 ± 6.0 , milk recovery (% of dose) = 0.0095 ± 0.0060 - were similar to those in non-lactating young women (Tables 37 & 38). Breast milk excretion of the drug is negligible. The excretion of the drug in breast milk remained at a relatively constant rate of 0.48 ug of cefepime per ml of breast milk produced until 8 h after dosing. After 8 h this rate decreased in association with a decrease in milk formation rate. Thus, if the concentration of cefepime in milk remains constant at 0.5 ug/ml, the peak value observed in any subject, an infant ingesting 1000 ml of milk per day will be exposed to approximately 0.5 mg/day of cefepime. This is equivalent to 0.02% of the daily dose if the lactating mother receives 1000 mg cefepime IV t.i.d.

5.2. Penetration into Appendix Tissue and Peritoneal Fluid (Study 411-119-001): The penetration of cefepime (ARG) into appendix tissue (AP) and peritoneal fluid (PF) collected from

patients requiring surgery to treat intra-abdominal sepsis was evaluated. Patients received multiple 2000 mg IV doses of cefepime q12h, in combination with metronidazole (500 mg q6h). Surgery was performed within 72 h of institution of antibiotic therapy. A piece of appendix tissue and a sample of peritoneal fluid were collected during surgery, including blood samples.

Cefepime penetrated rapidly into the peritoneal fluid and AP of patients with maximal concentrations in PF and AP being achieved within 2 h of a 2000 mg IV dose, and detectable levels were present for up to 10 h after dosing (Tables 39 & 40). The rate of elimination of the drug from PF paralleled the rate observed in plasma. The PF/plasma ratio was between 0.64 - 1.0 for samples taken between 0.95 and 10 h. AP/plasma ratios increased as the time post-dose increased: 0.24 (0 - 2 h sampling range) to 0.82 (8 - 10 h sampling range), suggesting slower elimination from this tissue. Tissue concentrations > MIC₉₀ values for critical pathogens such as *E. coli* (MIC = 0.2 ug/ml) and *Enterobacter cloacae* (MIC = 0.4 ug/ml) were maintained for up to 10 h after dosing. For *P. aeruginosa*, the concentration of cefepime in the appendix tissue exceeded the MIC₉₀ value (7 ug/ml) for ≈ 3.5 h post dose.

5.3. Penetration of Blister Fluid (Study 411-127-001): The blister fluid penetration of cefepime (ARG), ceftazidime and cefoperazone were evaluated in 6 male volunteers after the administration of single 2 g IV doses in a crossover study. 3 days was allowed to elapse between successive treatments. Concentrations of each antibiotic was determined in serum and blister fluid. Bactericidal and inhibitory activity in both matrices were evaluated using single isolates of *Enterobacter cloacae*, *P. aeruginosa*, and *Staphylococcus aureus*.

Cefepime penetrated blister fluid, achieving an area under the curve that was equivalent to 68% of the area under the serum concentration - time curve. Corresponding penetration values for ceftazidime and cefoperazone were 1.21 and 0.38, respectively (Tables 41 & 42). Bactericidal activity in serum and blister fluid was demonstrated for all three antibiotics against the 3 evaluated organisms. Based on serum bactericidal and inhibitory area under the curve data, cefepime appears to be more active against *E. cloacae* than ceftazidime and cefoperazone. On the other hand, ceftazidime is more active against *P. aeruginosa* and cefoperazone against *S. aureus* than cefepime when comparing serum bactericidal titer (BT) and inhibitory titer (IT) data. These relationships appeared to be the same for blister fluid BT and IT values, although the evaluable data were more limited.

5.4. Prostate Penetration (Study 411-153-001): Prostate tissue penetration of cefepime (ARG) at various times after a single 2000 mg IV dose was evaluated in 5 male patients undergoing elective prostatectomy.

There was considerable variability in the serum and prostate concentration values and penetration ratios at many of the sampling times, and samples were collected at 1, 3, 6, 9, 12, and 18 h. The concentration of cefepime was maximal at 1 h after dosing with a prostate / serum ratio of 0.51 ± 0.07 (Table 43), but the greatest penetration ratio was observed at 18 h (i.e. prostate / serum ratio of 1.38). However, this was associated with a large variability (S.D. = 1.35). The concentration of cefepime in prostate tissue generally decreased as the time after dosing increased.

5.5. Penetration of Gall Bladder and Bile (Study 411-120-016): Tissue penetration of cefepime was studied in patients requiring therapy for

Patients were randomly assigned to receive cefepime (2000 mg q12h IV) or gentamicin (1.5 mg/kg q8h IV) / mezlocillin (3000 mg q4h IV). Patient underwent surgery within 72 h of the initiation of antibiotic therapy. Peripheral blood, peritoneal fluid, bile, and/ or gall bladder tissue were collected during surgery for the determination of cefepime. Tissue penetration data were available from 55 cefepime-treated patients.

Cefepime penetrated the peritoneal fluid, bile and gall bladder tissue of patients. Tissue / plasma ratios were: 1.6 ± 2.07 (N = 24) for peritoneal fluid (collection time: 9.8 ± 4.6 h), 14.9 ± 29.7 (N = 26) for bile (collection time: 9.4 ± 4.7 h), 3.46 ± 11.8 (N = 38) for gall bladder (collection time: 8.9 ± 4.6 h) (Table 44). Concentrations of cefepime greater than the MIC₉₀ values for pathogens such as *E. coli* and *E. cloacae* were maintained in the fluids / tissues during a 12 dosing interval.

5.6. Penetration of Bronchial Mucosa (Study 411-085-001): 20 patients undergoing diagnostic fiberoptic bronchoscopy were administered single 2 g doses of cefepime (30 min IV infusion), and drug concentrations in the bronchial mucosa were measured. The concentrations were compared with simultaneous serum concentrations.

The mean bronchial mucosal concentration was 24.1 ± 17.8 mg/kg, while the mean serum concentration was 40.4 ± 28.1 mg/L (Table 45). The mean percentage penetration was $59.8 \pm 12.5\%$. The MIC₉₀ of cefepime for *Streptococcus pneumoniae* is 0.5 ug/ml, for *Klebsiella pneumoniae* 0.06 ug/ml, for *Haemophilus influenzae* 0.06 ug/ml, for *P. aeruginosa* 7.0 ug/ml, and for *Staph. aureus* 2 ug/ml. The concentrations of cefepime in these subjects exceeded these MIC's at most of the sampling times.

6. DRUG INTERACTION STUDY: CEFEPIME AND AMIKACIN (Study 411-154-001):

The pharmacokinetic interaction, at steady state, between co-administration of cefepime (ARG) and amikacin was investigated. 16 healthy adult male volunteers were randomly assigned to 2 groups (A and B). Group A received a first course of 2000 mg cefepime, followed by a second course of cefepime + 300 mg amikacin, and a third course of 2000 mg cefepime. Group B received a first course of 300 mg amikacin, a second course of 2000 mg cefepime + 300 mg amikacin, and a third course of 300 mg. Each course consisted of 4 consecutive doses q8h as 30 min infusions. Serial plasma and urine samples, collected after the fourth dose of each course, were assayed for cefepime and / or amikacin.

There were no significant differences among any parameters, for either cefepime or amikacin, in any courses. Cefepime and amikacin may be co-administered to patients with normal renal function without any need to adjust dosage regimens (Fig. 28 to 31).

7. OTHER STUDIES: PK IN PATIENTS WITH SERIOUS BACTERIAL INFECTIONS (STUDY 411-111-003): This study was designed to evaluate the PK of cefepime and ceftazidime in patients with serious bacterial infections after the administration of multiple doses. 2000 mg dose of cefepime or ceftazidime was administered every 12 or 8 h, respectively. Serial blood and urine samples were collected after a minimum of 3 days treatment. Data was available from 10 patients (equal number of both sexes; age: 26 to 78 yr, all but one patient were > 60 years old) randomized to receive cefepime therapy.

The PK parameters of cefepime are summarized below:

Day	N	C _{max} (ug/ml)	AUC _{0-τ} (ug*h/ml)	t _{1/2} (h)	CLT (ml/min)	V _d (L)
5	10	91.8 (22.4)	273.0 (110.0)	3.02 (0.83)	142.0 (60.0)	27.0 (6.4)

A modest prolongation in t_{1/2}, 3.02 h in the present study versus an average value of approximately 2.1 h in normal young volunteers, is consistent with data obtained in healthy subjects of comparable age. C_{max}, AUC and CLT values were more variable than those observed in previous studies and are probably reflective of the clinical conditions under which these data were collected. The PK of cefepime was not altered to a clinically significant degree in patients treated for serious bacterial infections.

8. POPULATION PHARMACOKINETIC ANALYSES

8.1. POPULATION PHARMACOKINETICS OF CEFEPIME: The Reviewer took an advantage of the richness of the data set (2307 plasma and urine concentrations from 139 subjects (patients) in 6 studies) to determine the population PK parameters of cefepime and their distribution in the population using the NONMEM-PREDPP program. Data were pooled from studies involving healthy subjects (age and gender study), cystic fibrosis patients (2 studies), renal impaired patients (2 studies), and patients with liver impairment (1 study). The 2 compartment open model with input and output to and from the central compartment characterized the data better than the 1 compartment open model (the difference in objective function between the models, LLD, was 1621). The analysis was done in the stepwise manner (see Appendix VI).

The importance of renal function (CRCL) as a predictor of cefepime CL was apparent (Fig. 32). It is approximately 90% renally cleared. The estimated t_{1/2} is 2 h. Dosage adjustment for renal impairment should be based on the following nomogram:

$$CL \text{ (L/h)} = \text{CRCL}$$

The numbers in parentheses represent the standard errors of the estimates. For a given maintenance dose (say, 2 g q8h) in healthy subjects, patients with CRCL < 4.1 L/h (60 ml/min) but > 2.3 L/h (30 ml/min) can be dosed every approximately 12 h; and those with CRCL < 2.3 L/h (<30 ml/min) but > 0.6 L/h (10 ml/min) can be dosed every 24 h. A simulation of steady state levels for average 70 kg patients with different CRCL's based on the above dosage

recommendation is shown in Fig. 33. Other simulated dosage regimens are shown in Fig. 34 and 35.

Weight was a predictor of the volume of the central compartment (Fig. 36), intercompartmental clearance, Q (Fig. 37), and volume of the peripheral compartment, V2 (Fig. 38). The dose may be based on body weight. The equation for the estimation of V1 is:

$$V1 (L) = \dots * WT$$

The equations for the estimations of Q and V2, respectively, are:

$$Q (L/h) = \dots WT$$

$$V2 (L) = \dots * WT$$

The variability associated with these parameters are summarized in Table 46 below.

Table 46. InterSubject Variability

Parameter	Variability	95% CI
CL	29.82%	24.02 - 34.66%
V1	33.02%	25.50 - 39.12%
Q	57.62%	19.49 - 79.12%
V2	29.34%	21.56 - 35.45%

The intrasubject residual error from plasma data was 59.4% at 2 ug/ml and < 13.8% at concentrations greater than 20 ug/ml. The intrasubject residual error from urine data was 75% at 50 ug/ml and < 73.% at concentrations greater than 100 ug/ml.

8.2. PHARMACOKINETICS IN PATIENTS WITH VARYING RENAL FUNCTION: Data from 46 in two renal studies (Study 07A1A-001-001 and Study-411-117-081) were pooled and analysed using the NONMEM approach to characterize the PK of cefepime in subjects with various degrees of renal function. The 46 subjects supplied 719 plasma and 92 urine concentrations of cefepime. The 2 compartment open model with input and output to and from the central compartment, respectively, characterized the data better than the 1 compartment open model (Fig. 39). The analysis was done in the stepwise (see Appendix VI).

CRCL was found to be a predictor of CL (Fig. 40), while weight was significant in the modeling of V1. CL and V1 were described by the following equations:

$$CL (L/h) = \dots CRCL_{(L/h)}$$

$$V1 (L) = \dots * WT$$

The typical population values of Q and V2 were (L), respectively. The numbers in parentheses are the standard errors of the estimates. The regression equation obtained using the population method is not very different from that obtained in individual

studies. The intersubject variability associated with these parameters are given in Table 47 below:

Table 47. InterSubject Variability

Parameter	Variability	95% CI
CL	26.1%	21.75 - 29.75%
V1	32.2%	21.21 - 40.37%
Q	61.9%	21.67 - 84.79%
V2	38.0%	24.90 - 47.75%

The intrasubject residual error was 17.69% at plasma concentrations of 2 ug/ml and $\leq$ 8.92% at concentrations greater than 20 ug/ml. The intrasubject residual error from urine data was 61.16% at 50 ug/ml and $\leq$ 30.78% at concentration $\geq$ 100 ug/ml.

8.3. PHARMACOKINETICS IN CF PATIENTS: Data from the two CF studies were pooled and analysed using the NONMEM approach to characterize the PK of cefepime in the CF patient population. 23 subjects supplied 339 plasma concentrations of cefepime. The 2 compartment open model with input and output to and from the central compartment, respectively, characterized the data better than the 1 compartment open model. The analysis was done in the stepwise (see Appendix VI).

CRCL (renal function) was found to be a predictor of CL (Fig. 41), while weight was significant in the modeling of V1 (Fig. 42). CL and V1 were described by the following equations:

$$\begin{aligned} \text{CL (L/h)} &= \dots \cdot \text{CRCL} \\ \text{V1 (L)} &= \dots \cdot \text{WT} \end{aligned}$$

The estimates of Q, and V2 were ... (L), respectively. The intersubject variability associated with the PK parameters were 19% (95% CI: 11.0 - 25.0%) for CL, 20% (95% CI: 16.0 - 33.0%) for V1, 26% (25.0 - 67.0%) for Q. The variability in V2 was infinitesimal and had to be removed. The intrasubject residual error was 39%.

For the average subject with CRCL of 120 ml/min, the value of CL (7.1 L/h) is not different from that of the typical population value obtained in Section 8.1 above. Consequently, dosage adjustment is not required for this group of patients.

LABELLING COMMENTS:

The Division of Biopharmaceutics has the following comments on the labelling:

1. Clinical Pharmacology: The statements on total body clearance, average renal clearance, and volume of distribution at steady state do not describe the variability of these values within the population, and should be replaced by the following sentences.

The typical population total body clearance ($CL_{ml/min}$) of cefepime is given by:

$$9.1 + 0.852 * \text{Creatinine Clearance}_{(ml/min)}$$

and renal clearance accounts for = 90% of this. The typical population volume of the central compartment ($V1_L$) is given by:

$$WT$$

The typical population value for the volume of the peripheral compartment ($V2_L$) is 6.3 L for the average 70 kg patient, while the typical population value for intercompartmental clearance, Q , is approximately ml/min. The intersubject variability in CL , $V1$, Q and $V2$ are 30, 33, 58, and 29%, respectively. For an average 70 kg patient the volume of distribution at steady state is 17 L. The estimated half-life of the drug is 2 h in the average patient with normal renal function.

2. There is no mention of the metabolism of cefepime in this section. In paragraph 2, the statement on urinary recovery should be rephrased and a statement on metabolism should be added thus:

Urinary recovery of unchanged cefepime accounts for = 87.9% of dose, resulting in high concentrations in the urine. Cefepime is metabolized to N-methylpyrrolidine (NMP) which is rapidly converted to the N-oxide (NMP-N-oxide). Less than 1% of the administered dose is recovered as NMP, 6.8% as NMP-N-oxide, and 2.5% as the epimer of cefepime.

These sentences should be inserted before the statement on protein binding, and the statement on average volume of distribution at steady state deleted, given comment #1.

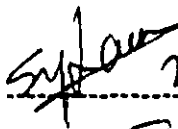
3. Recommended Maintenance Schedule in Patients with Renal Impairment: There is need for dosage adjustment for subjects with creatinine clearance between 30 and 60 ml/min. Thus, Table 6 of the Label should be replaced with the Table below which includes dosage guidelines for subjects with CRCL between 30 and 60 ml/min.



Eric I. Ette, Ph. D.
Pharmacokinetic Evaluation Branch

Biopharm Day (12/22/92, J. Collins, T. Ludden, H. Malinowski, N. Fleischer, P. Hepp, S. Lam)

RD initialed by S. Lam, Ph. D.



2/9/93

FT initialed by N. Fleischer, Ph.D.



7/6/93

cc: NDA 50-679, HFD-520 (Clinical Division), HFD-426 (E. I. Ette, N. Fleischer), Chron. Drug. Reviewer's Files, DI, A, G, RI. HFD-340 (Viswanathan)

57A

Recommended Maintenance Schedule in Patients with Renal Impairment

Creatinine Clearance (ml/min)	Normal Recommended Dosing Schedule		
	2 g q8h	2 g q12h	1 g q12h
30 - 60	2 g q12h	2 g q24h	1 g q24h
11 - 30	1 g q12h	1 g q24h	500 mg q24h
≤ 10	1 g q24h	500 mg q24h	250 mg q24h

Table 3 Demographic data for clinical study 411-058-001.

Subject No	Treatment Group	Age (yr)	Sex	Height (cm)	Weight (kg)	BSA (m ²)
I		22	M	175.0	77.3	1.93
I		34	M	168.0	67.2	1.74
I		38	M	169.0	65.5	1.75
I		30	M	179.0	58.5	1.74
I		41	M	163.0	83.7	1.89
I		30	M	180.0	71.7	1.91
I		32	M	181.0	68.3	1.87
I		24	M	171.0	81.5	1.94
II		28	M	177.5	75.9	1.93
II		33	M	173.0	69.9	1.83
II		36	M	167.0	69.2	1.78
II		22	M	173.0	69.2	1.82
II		23	M	177.0	66.9	1.83
II		32	M	177.8	72.2	1.89
II		23	M	176.0	76.0	1.92
II		45	M	165.0	64.3	1.71
IIA		21	M	175.0	74.4	1.90
IIA		43	M	164.0	73.4	1.80
IIA		37	M	170.5	67.2	1.78
IIA		24	M	176.0	63.3	1.78
IIA		26	M	183.0	76.3	1.98
IIA		36	M	169.0	58.6	1.67
IIIC		21	M	173.0	69.3	1.82
IIIC		34	M	172.0	78.2	1.91
IIIC		19	M	175.0	65.0	1.79
IIIC		22	M	177.0	69.3	1.86
IIIC		37	M	167.0	53.8	1.60
IIIC		22	M	168.0	74.0	1.84
IIIB		30	M	172.0	70.1	1.83
IIIB		25	M	174.0	70.2	1.84
IIIB		27	M	177.5	83.0	2.01
IIIB		25	M	165.1	51.8	1.56
IIIB		34	M	183.0	72.7	1.94
IIIB		28	M	176.0	84.5	2.01
IIIB		37	M	178.0	66.5	1.83
IIIB		32	M	174.0	75.5	1.90
IIIB		37	M	195.0	80.6	2.12
IIII		35	M	187.0	84.7	2.10
IIII		40	M	167.0	69.4	1.78
IIII		35	M	.	63.0	.
IIII		36	M	179.0	80.6	1.99
IIII		36	M	170.0	67.0	1.78
IIII		41	M	167.0	69.0	1.78
IIII		41	M	180.0	78.1	1.98
IIII		30	M	165.0	61.7	1.68
IIII		37	M	179.0	66.2	1.83
IIII		23	M	162.0	54.0	1.59
Mean		31		173.7	70.4	1.84
SD		7		6.7	7.9	0.12

*Placebo group.

Table 4 Key organizational details for cefepime multiple-dose study
411-058-001. Dose groups listed in order of completion.

DOSE GROUP	TREATMENT (LOT NO.)	SUBJECT NUMBER		PHARMACOKINETIC SAMPLING	
		TREATED	CONTROL	PLASMA	URINE
I	250 mg tid (S85K013)	1-8	none	A	B
II	500 mg tid (20757)	9-16	none	C	C
IIA	500 mg tid (S85K013)	201,204 206	202,203 205	A	D
IIC	250 mg tid (20759)	302,304 306	301,303 305	E	E
IIB	500 mg tid (20759)	207,208 211-214	209,210 215	A	D
III	1000 mg bid (20759)	18,19,21 22,24,25 26	17,20,23	F	G

- A: Serial blood sampling on day (dose 1), day 6 (dose 14) and day 11 (dose 29), with peak and trough sampling on day 4 (dose 3) and day 8 (dose 20).
- B: Total urine output collected after doses 1, 14, and 29.
- C: Same as A and B, except sampling ended prior to day 4; treatment terminated on day 6.
- D: Same as B, with total urine collection on day 4 (dose 8) also.
- E: Peak and trough blood sampling on days 1, 4, 6, 8 and 11 for verification of exposure. No urine collections.
- F: Serial blood sampling on day 1 (dose 1), day 6 (dose 10) and day 11 (dose 20). Peak and trough sampling on day 4 (dose 6) and day 8 (dose 14).
- G: Total urine output collected after doses 1, 6, 10, 14 and 20.

Table 5 Summary of pharmacokinetics for treatment Group 1 (250 mg) of Study 411-058-001.

INDIVIDUAL PHARMACOKINETIC DATA
 CEPEPINE (BNY-28142) STUDY 411-058-001 (PC8475)

TREATMENT = GROUP 1 250 MG (lot 885K013)

 PHARMACOKINETIC PARAMETER VALUES

SUBJ NO.	C _{MAX} (ug/ml)	T _{MAX} (hr)	T _{1/2} (IV) (hr)	T _{1/2} P (hr)	AUC(INF) (ug.hr/ml)	AUC(0-T) (ug.hr/ml)	CLT (ml/min)	VSS (L)

ANALYSIS INTERVAL = DAY 1 (DOSE 1)

MEAN	17.9	0.51	2.18	2.00	33.1	32.0	128	16.6
SD	2.4	0.02	0.21	0.38	4.3	4.3	16	2.5

ANALYSIS INTERVAL = DAY 6 (DOSE 14)

MEAN	18.4	0.53	.	1.76	37.2	35.4	.	.
SD	3.5	0.03	.	0.16	6.4	6.0	.	.

ANALYSIS INTERVAL = DAY 11 (DOSE 29)

MEAN	17.5	0.52	2.30	2.09	35.1	33.9	.	.
SD	2.3	0.03	0.34	0.32	4.9	4.3	.	.

BETWEEN-DAY MD NA MD MD 6 11 1 NA NA
 COMPARISONS

Means ordered from highest to lowest. Means connected by a common underline are not significantly different ($\alpha = 0.05$; Tukey multiple comparison procedure). MD, no significant differences. NA, not analyzed. AUC(INF) for day 11 compared to AUC(0-T) for days 6 and 11.

** Subject 1 received only 225 mg. Values normalized to 250 mg level.

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Table 6. Summary of pharmacokinetics for treatment Group II (500 mg) of study 411-058-001.

INDIVIDUAL PHARMACOKINETIC DATA
 CEPEPINE (BNY-20142) STUDY 411-058-001 (PKS475)

TREATMENT = GROUP II 500 MG (lot 20757)

PHARMACOKINETIC PARAMETER VALUES								
SUBJ NO.	C _{MAX} (ug/ml)	T _{MAX} (hr)	W _{IT(IV)} (hr)	T _{1/2F} (hr)	AUC(INF) (ug.hr/ml)	AUC(O-T) (ug.hr/ml)	CLT (ml/min)	VSS (L)
ANALYSIS INTERVAL = DAY 1 (DOSE 1)								
MEAN	36.4	0.91	2.32	2.47	65.3	61.9	130	17.9
SD	4.4	0.02	0.30	0.73	9.2	7.6	17	1.8

Table 7 Summary of pharmacokinetics for treatment Group 118 (500 mg) of study 411-038-001.

INDIVIDUAL PHARMACOKINETIC DATA
 CEFEPIME (BNY-28142) STUDY 411-038-001 (P25335)

YTREATMENT = Group 118 500 MG (Loc 20759)

 PHARMACOKINETIC PARAMETER VALUES

SUBJ NO.	C _{MAX} (ug/ml)	T _{MAX} (hr)	MRT(IV) (hr)	T _{HAL} (hr)	AUC(INF) (ug.hr/ml)	AUC(0-T) (ug.hr/ml)	CLT (ml/min)	VES (L)

 ANALYSIS INTERVAL = DAY 1 (DOSE 1)

MEAN	28.7	0.51	1.97	1.86	51.3	50.0	165	19.3
SD	4.0	0.02	0.17	0.26	6.4	5.7	20	1.4

 ANALYSIS INTERVAL = DAY 6 (DOSE 14)

MEAN	30.3	0.51	.	1.79	61.7	59.0	.	.
SD	4.2	0.02	.	0.26	10.8	9.5	.	.

 ANALYSIS INTERVAL = DAY 11 (DOSE 29)

MEAN	30.4	0.52	2.11	1.88	59.2	57.6	.	.
SD	2.7	0.03	0.20	0.21	7.0	6.1	.	.

 BETWEEN-DAY COMPARISONS MD NA MD MD 6 11 1 NA

Means ordered from highest to lowest. Means connected by a common underline are not significantly different (α = 0.05; Tukey multiple comparison procedure). MD, no significant differences. NA, not analyzed. AUC(INF) for day 1 compared to AUC(0-T) for days 6 and 11.

TABLE 7b. Summary of pharmacokinetics for treatment Group IIA (500 mg) of study 411-058-001.

INDIVIDUAL PHARMACOKINETIC DATA
 CEFEPIME (BNY-28142) STUDY 411-058-001 (PK5535)

TREATMENT = GROUP IIA 500 MG (lot 885K013)

PHARMACOKINETIC PARAMETER VALUES

SUBJ NO.	C _{MAX} (ug/ml)	T _{MAX} (hr)	MRT(IV) (hr)	T _{1/2} F (hr)	AUC(INF) (ug.hr/ml)	AUC(0-T) (ug.hr/ml)	CLT (ml/min)	VSS (L)

ANALYSIS INTERVAL = DAY 1 (DOSE 1)

MEAN	38.1	0.50	2.20	2.31	67.2	64.0	127	16.3
SD	3.9	0.00	0.49	1.12	12.9	10.0	26	0.7

ANALYSIS INTERVAL = DAY 6 (DOSE 14)

MEAN	35.7	0.52	.	1.88	66.2	63.2	.	.
SD	3.0	0.03	.	0.11	7.8	7.0	.	.

ANALYSIS INTERVAL = DAY 11 (DOSE 29)

MEAN	32.9	0.52	2.19	2.35	63.5	60.5	.	.
SD	2.8	0.03	0.45	1.02	10.6	8.5	.	.

BETWEEN-DAY COMPARISONS 1 6 11 NA ND ND --- ND --- NA NA

Means ordered from highest to lowest. Means connected by a common underline are not significantly different ($\alpha = 0.05$; Tukey multiple comparison procedure). ND, no significant difference; NA, not analyzed. AUC(INF) for day 1 compared to AUC(0-T) for days 6 and 11.

Table 8 Summary of pharmacokinetics for treatment Group III (1000 mg) of study 411-058-001.

INDIVIDUAL PHARMACOKINETIC DATA
 CEPEPINE (BNY-28142) STUDY 411-058-001 (PK5553)

TREATMENT = Group III 1000 MG (lot 20759)

.....
 PHARMACOKINETIC PARAMETER VALUES

SUBJ NO.	C _{MAX} (ug/ml)	T _{MAX} (hr)	MRT(IV) (hr)	T _{HALF} (hr)	AUC(INF) (ug.hr/ml)	AUC(0-T) (ug.hr/ml)	CLT (ml/min)	VSS (L)

.....
 ANALYSIS INTERVAL = DAY 1 (DOSE 1)

MEAN	70.6	0.51	2.41	1.99	139.9	138.0	121	17.3
SD	8.0	0.02	0.16	0.21	9.3	9.0	8	1.2

.....
 ANALYSIS INTERVAL = DAY 6 (DOSE 10)

MEAN	70.8	0.51	.	2.21	144.9	142.1	.	.
SD	7.5	0.02	.	0.45	14.7	14.5	.	.

.....
 ANALYSIS INTERVAL = DAY 11 (DOSE 20)

MEAN	66.3	0.51	2.51	2.04	142.6	140.3	.	.
SD	7.7	0.02	0.24	0.23	11.4	11.3	.	.

BETWEEN-DAY COMPARISONS ND MA ND ND --- ND --- MA N/

Means ordered from highest to lowest. Means connected by a common underline are not significantly different ($\alpha = 0.05$; Tukey multiple comparison procedure). ND, no significant differences. MA, not analyzed. AUC(INF) for day 1 compared to AUC(0-T) for days 6 and 11.

Table 9 Summary of noncompartmental pharmacokinetic parameters for study 411-056-001

*** CEFEPIM DOSING ***

PHARMACOKINETIC PARAMETER VALUES

SUBJ NUMBER	CHAR (ug/ml)	TIME (hr)	MT (hr)	TIME (hr)	AUCINF (ug.hr/ml)	CLT (ml/min)	VSS (L)
MEAN	123.0	0.31	2.30	1.00	**225	**150	**20.6
SD	32.1	0.07	0.20	0.22	32	23	2.0

... TREATMENT = 15 MIN INFUSION ...

... TREATMENT = 10 MIN INFUSION ...

SUBJ NUMBER	CHAR (ug/ml)	TIME (hr)	MT (hr)	TIME (hr)	AUCINF (ug.hr/ml)	CLT (ml/min)	VSS (L)
MEAN	135.5	0.22	**2.35	1.91	261	131	**10.6
SD	39.3	0.04	0.21	0.23	43	23	3.2

... TREATMENT = 5 MIN INFUSION ...

... TREATMENT = 3 MIN INFUSION ...

SUBJ NUMBER	CHAR (ug/ml)	TIME (hr)	MT (hr)	TIME (hr)	AUCINF (ug.hr/ml)	CLT (ml/min)	VSS (L)
MEAN	175.7	0.12	2.34	2.04	245	137	**10.2
SD	10.6	0.00	0.09	0.20	26	14	1.6

... TREATMENT = 3 MIN INFUSION ...

*** CEFIZADIME DOSING ***

PHARMACOKINETIC PARAMETER VALUES

SUBJ NUMBER	CHAR (ug/ml)	TIME (hr)	MT (hr)	TIME (hr)	AUCINF (ug.hr/ml)	CLT (ml/min)	VSS (L)
MEAN	155.6	0.26	2.25	1.60	**274	**125	**16.6
SD	33.6	0.02	0.41	0.30	50	26	2.4

... TREATMENT = 15 MIN INFUSION ...

... TREATMENT = 10 MIN INFUSION ...

SUBJ NUMBER	CHAR (ug/ml)	TIME (hr)	MT (hr)	TIME (hr)	AUCINF (ug.hr/ml)	CLT (ml/min)	VSS (L)
MEAN	152.5	0.23	**2.31	1.01	272	126	**16.5
SD	34.9	0.05	0.10	0.44	54	27	2.1

... TREATMENT = 5 MIN INFUSION ...

... TREATMENT = 3 MIN INFUSION ...

SUBJ NUMBER	CHAR (ug/ml)	TIME (hr)	MT (hr)	TIME (hr)	AUCINF (ug.hr/ml)	CLT (ml/min)	VSS (L)
MEAN	167.4	0.19	2.16	2.10	252	133	**17.3
SD	27.4	0.10	0.12	0.30	26	13	1.6

... TREATMENT = 3 MIN INFUSION ...

a) AUC corrected for infusion interval.
 b) Individual did not receive this treatment.
 c) no reliable value.

** Significantly different from corresponding mean value for other test compound based on Bonferroni multiple comparison procedure, $\alpha = 0.05$ (or $\alpha = 0.10$ for MTI).

Table 10

Reference parameters for RC_{MAX} (reference C_{MAX}) calculations. Coefficients and exponential terms based on biexponential characteristic functions for subjects of reference study 411-038-001, who each received 1000 mg cefepime as a 30-min infusion. Dose-dependent terms have been normalized to a 2000 mg level.

SUBJ	EXPONENTIALS		COEFFICIENTS		RC _{MAX} (ug/ml) by value of TAU				
	ALPHA	BETA	A	B	3 min	5 min	10 min	15 min	30 min
MEAN					171.0	167.0	158.0	150.2	131.7

EDIT: 3/27/87

Table 11 Comparison of observed and reference CMAX values for cefepime.
Reference values, denoted RCMAX, were derived as noted in Table 4.

INFUSION				
TIME (min)	CMAX (ug/ml)			RCMAX
	N	MEAN	C.I. ^a	
15	3	125	70-180	150
10	4	135	73-198	158
5	3	176	129-222	167
3	4	182	119-244	171

a) 95 % confidence interval

Table 12

Mean cumulative urinary excretion of cefepime after 500 mg tid dosing. Study 411-044-001.

MEAN SUBJECT EXCRETION DATA
CEFEPIME STUDY 411-044-001 (CEP042)
URINARY EXCRETION OF MW-20142
CEFEPIME FORM IV

TIME AFTER ADMINISTRATION	MEAN CUMULATIVE PERCENT URINARY EXCRETION							
	DAY	HR	LOT 20757			LOT 20759		
			N	MEAN	SD	N	MEAN	SD
0	0	3	10.6	0.0	3	22.1	4.8	
0	30	3	42.1	2.6	3	45.9	3.6	
0	60	3	69.0	2.2	3	67.8	6.2	
0	90	3	69.0	4.3	3	73.2	8.2	
0	120	3	75.3	3.4	3	79.9	7.4	
0	150	3	78.4	3.4	3	83.2	6.2	
0	180	3	79.5	3.2	3	84.2	6.4	
0	240	3	79.7	3.5	3	84.2	6.4	
0	300	3	81.7	4.6	3	84.6	2.7	
0	360	3	89.0	7.9	3	88.7	2.5	
0	420	3	88.4	9.7	3	84.7	9.1	
0	480	3	77.3	3.5	3	86.6	9.0	
0	540	3	85.4	4.0	3	79.5	9.2	
1	0	3	28.2	4.8	3	26.5	4.2	
1	30	3	41.4	3.2	3	38.3	3.6	
1	60	3	64.8	4.4	3	66.2	8.7	
1	90	3	77.3	1.9	3	78.9	6.6	
1	120	3	82.3	0.2	3	80.9	1.0	
1	150	3	89.4	1.1	3	85.7	1.0	
1	180	3	86.4	1.2	3	84.2	1.5	
1	240	3	86.9	1.6	3	84.2	1.5	

Mean cumulative urinary excretion of cefepime after 1000 mg tid, and 2000 mg tid dosing. Study 411-043-001.

MEAN SUBJECT EXCRETION DATA
CEFEPIME STUDY 411-043-001 (CEP042)
URINARY EXCRETION OF MW-20142

TIME AFTER ADMINISTRATION	MEAN CUMULATIVE PERCENT URINARY EXCRETION							
	DAY	HR	1 & 100			2 & 100		
			N	MEAN	SD	N	MEAN	SD
0	0	7	0.0	0.0	7	0.0	0.0	
0	1	7	26.6	7.4	7	27.7	8.4	
0	2	7	44.5	7.9	7	44.7	9.0	
0	4	7	50.5	9.2	7	63.9	12.0	
0	6	7	70.4	8.9	7	71.5	13.0	
0	8	7	74.9	8.0	7	74.9	13.2	
0	12	7	78.1	8.4	7	77.4	12.9	
0	16	7	79.2	8.6	7	78.2	12.7	
0	24	7	79.8	8.3	7	78.4	12.7	
0	30	7	11.1	11.9	7	2.9	1.9	
1	1	7	33.7	3.2	7	26.4	2.1	
1	2	6	51.9	4.8	7	37.4	5.4	
1	4	7	60.3	6.1	7	70.7	5.4	
1	6	7	77.4	7.0	7	80.7	7.9	
1	8	7	81.4	7.6	7	90.2	7.2	
1	10	7	8.9	14.8	7	7.9	6.2	
1	12	7	31.5	4.8	6	48.7	8.3	
1	14	7	52.2	9.5	6	69.7	7.4	
1	16	7	68.1	14.4	6	78.1	12.1	
1	18	7	78.3	14.2	6	88.2	7.4	
1	20	7	79.3	14.7	6	92.3	6.1	
1	22	7	83.1	14.6	6	94.9	8.2	
1	24	7	86.2	14.9	6	93.8	7.9	
1	26	7	88.2	14.9	6	90.2	7.4	

Table 13 Pharmacokinetics for single and repeated (tid) administration of 1000 mg cefepime.

INDIVIDUAL PHARMACOKINETIC DATA
 CEFEPIME STUDY 411-043-001-CEF (PK8612)

TREATMENT = GROUP 1, 1000 mg t.i.d

PHARMACOKINETIC PARAMETER VALUES

SUBJ NBR	C _{MAX} (ug/ml)	T _{MAX} (hr)	T _{RT(1V)} (hr)	T _{HALF} (hr)	AUC(1NF) (hr.ug/ml)	AUC(0-1) (hr.ug/ml)	CL _T (ml/min)	CL _R (ml/min)	V _{SS} (L)

ANALYSIS INTERVAL = DAY 1 DOSE 1

MEAN	65.1	0.50	2.45	2.34	135	127	126	100	18.3
SD	0	0.00	0.31	0.24	23	20	17	18	2.0

ANALYSIS INTERVAL = DAY 6 DOSE 16

MEAN	70.5	0.51	.	.	150	142	.	.	.
SD	8.5	0.02	.	.	23	21	.	.	.

ANALYSIS INTERVAL = DAY 11 DOSE 29

MEAN	66.9	0.51	2.45	2.23	145	137	125	99	18.2
SD	12.4	0.02	0.33	0.35	28	24	21	24	3.0

ANOVA p-value*	0.11	NA	0.94	0.22	0.34*		0.09	NA	0.04

*Repeated measures ANOVA p-value testing day differences. NA = Not Analysed.
 *AUC(1NF) utilized on Day 1.

Edit 11/21/87

Table 14 Pharmacokinetics for single and repeated (tid) administration of 2000 mg cefepime.

INDIVIDUAL PHARMACOKINETIC DATA
 CEFEPIME STUDY 411-043-001-CEF (PKS435)

TREATMENT = GROUP 11, 2000 mg t.i.d

PHARMACOKINETIC PARAMETER VALUES

SUBJ NO#	C _{MAX} (µg/ml)	T _{MAX} (hr)	WRT(IV) (hr)	T _{1/2} F (hr)	AUC(0-12) (hr.µg/ml)	AUC(0-24) (hr.µg/ml)	CLT (ml/min)	CLR (ml/min)	VSS (L)

ANALYSIS INTERVAL = DAY 1 DOSE 1

MEAN	125.7	0.49	2.34	2.20	245	233	138	110	19.3
SD	21.7	0.07	0.37	0.31	35	32	22	31	3.4

ANALYSIS INTERVAL = DAY 6 DOSE 14

MEAN	129.5	0.51	.	.	250	238	.	.	.
SD	27.1	0.02	.	.	43	40	.	.	.

ANALYSIS INTERVAL = DAY 11 DOSE 29

MEAN	137.2	0.51	2.16	2.32	250	239	143	132	18.4
SD	30.7	0.20	0.30	0.39	43	39	25	24	3.8
ANOVA p-value*	0.41	NA	0.24	0.40	0.66*	0.52	NA	0.39	

*Repeated measures ANOVA p-value testing day differences. NA = Not Analyzed.
 *AUC(12F) utilized on Day 1.

Edit 11/21/87

Table 15 Mean ($\pm$ SD) Pharmacokinetic Parameters for Single and Repeated (q8h) Administration of 2000 mg Cefepime

<u>Parameter</u>	<u>Day 1</u>	<u>Day 6*</u>	<u>Day 11</u>	<u>Paired t</u>	<u>P-value</u>
N	7	7	7		
C _{MAX} (μ g/ml)	142 (32.7)	142 (22.4)	145 (17.9)	0.51	0.628
MRT(IV) (Hour)	2.41 (0.64)	-	2.23 (0.30)	0.94	0.386
T-HALF (Hour)	2.46 (0.66)	1.83 ^{**} (0.09)	2.39 (0.49)	0.46	0.666
AUC(INF) (μ g.hr/ml)	281 (43.3)	274 (45)	281 (54.8)	0.06	0.954
CLR (ml/min)	108 (14.4)	-	117 (26.1)	1.27	0.250
CLT (ml/min)	121 (17.5)	-	122 (22.2)	0.59	0.577
VSS (L)	17.6 (5.8)	-	16.1 (2.1)	0.97	0.369

* Day 6 values excluded from statistical comparison.

** The half-life estimate does not represent true elimination phase. Blood samples were taken only up to 8 hours because of q8h dosing schedule.

Table 16b Individual pharmacokinetic data.

DAY	SUBJ NBR	PHARMACOKINETIC PARAMETER VALUES					
		C _{MAX} (UG/ML)	T _{RT(IV)} (HRS)	T _{1/2} (HRS)	AUC ^a (NR.UG/ML)	CLT (ML/MIN)	CLR (ML/MIN)

1

MEAN	279	2.20	2.18	545	125	117	16.5
SD	55	0.31	0.22	93	20	16	3.4
N	7	7	7	7	7	7	7

6

MEAN	321	.	.	559	.	.	.
SD	61	.	.	97	.	.	.
N	7	.	.	7	.	.	.

11

MEAN	338	2.20	2.29	407	111	104	14.9
SD	54	0.26	0.33	127	22	28	2.7
N	7	7	7	7	7	7	7

^a AUC values are AUC(INF) for day 0 data and AUC(0-6) for days 5 and 10 data.

Table 17 Observed cefepime accumulation ratios following 4000 mg, q8h dosing.

Subject no.	Accumulation ratios		
	$R_1 = \frac{AUC_{(0-8)}^{1st}}{AUC_{(0-8)}^{2nd}}$	$R_2 = \frac{C_{min}^{1st}}{C_{min}^{2nd}}$	$R_3 = \frac{C_{max}^{1st}}{C_{max}^{2nd}}$
Mean	1.17	1.24	1.23
SD	0.11	0.31	0.11
n	7	7	7

Table 18 Mean Pharmacokinetic Parameters of Cafepime After Intramuscular and Intravenous Doses

TREATMENT	PHARMACOKINETIC PARAMETER VALUES							
	C _{MAX} (UG/ML)	T _{MAX} (HRS)	PERI (1/2) (HRS)	T _{1/2} (HRS)	T-1/2 _B (HRS)	AUC (1/2) (MG·UG/ML)	CL _R (ML/MIN)	CL _T (ML/MIN)
250 MG								
MEAN	7.8	1.06	3.85	1.54	2.35	33	90	129
SD	2.0	0.27	0.55	0.55	0.50	6	17	24
N	6	6	6	6	6	6	6	6
500 MG								
MEAN	13.9	1.42	3.77	1.44	2.05	40	117	141
SD	3.4	0.84	0.76	0.76	0.17	8	24	17
N	6	6	6	6	6	6	6	6
1000 MG								
DAY 1								
MEAN	29.6	1.56	4.03	1.72	2.37	137	104	122
SD	4.4	0.38	0.24	0.24	0.35	11	10	10
N	6	6	6	6	6	6	6	6
1000 MG								
DAY 7								
MEAN	28.4	1.50	.	.	2.30	136	108	123
SD	4.1	0.80	.	.	0.30	8	5	7
N	6	6	6	6	6	6	6	6
1000 MG								
DAY 12								
MEAN	32.4	1.21	3.41	1.10	2.18	127	112	132
SD	7.1	0.44	0.69	0.69	0.29	12	11	15
N	6	6	6	6	6	6	6	6
2000 MG IV								
MEAN	132.2	0.54	2.54	.	2.07	248	109	125
SD	20.8	0.87	0.31	.	0.22	27	13	11
N	12	12	12	6	12	12	12	12
2000 MG IM								
MEAN	57.5	1.52	3.88	1.57	2.05	262	109	128
SD	9.5	0.43	0.63	0.65	0.22	23	20	11
N	12	12	12	12	12	12	12	12

Table 19 Mean Urinary Excretion Profile of Cefepime After Intramuscular and Intravenous Doses

TIME AFTER ADMINISTRATION DAY HR MIN	MEAN CUMULATIVE PERCENT URINARY EXCRETION														
	250 MG		500 MG		1000 MG		2000 MG IV		2000 MG IM		2000 MG IM				
	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD
0 0 0	6	0.0	0.0	6	0.0	0.0	6	0.0	0.0	12	0.0	0.0	12	0.0	0.0
0 0 0	6	42.0	4.3	6	24.3	12.0	6	24.0	4.2	12	39.3	5.9	12	24.4	12.0
0 0 0	1	30.5	.	.	.	.	.	.	.	.	.	.	.	.	.
0 0 0	4	50.7	3.6	6	26.1	13.4	6	76.3	3.7	12	81.3	4.9	12	75.3	12.0
0 12 0	6	45.6	1.9	6	79.2	13.0	6	82.2	3.5	12	84.3	5.0	12	81.6	22.3
0 24 0	6	65.6	1.9	6	80.8	14.2	6	84.4	3.9	12	85.5	5.0	12	81.2	11.8
0 0 0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
0 0 0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
0 0 0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
0 0 0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
0 12 0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
0 24 0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
0 0 0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
0 0 0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
0 0 0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
0 12 0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
0 24 0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Table 21

Individual subject non-compartmental pharmacokinetics for study AI411-086-001.

BNV-20142 STUDY AI411-086-001 (PKA161)
COMPARATIVE PHARMACOKINETICS

SUBJ SEQ		PHARMACOKINETIC PARAMETER VALUES						
NBR	NBR	C _{MAX} (ug/ml)	T _{MAX} (hr)	MRT(IV) (hr)	T _{1/2} (hr)	AUC(INF) (ug-hr/ml)	CLT (ml/min)	VSS (L)

TREATMENT = ZWITTERION/NACL

b

MEAN (N = 11)	134.2	0.49	2.38	2.03	272	125.4	17.7
SD	19.6	0.05	0.21	0.20	46	18.4	1.8

TREATMENT = DI.NCL/ARGININE

b

** MEAN (N = 11)	139.1	0.52	2.43	2.16	269	126.6	18.5
SD	32.1	0.09	0.21	0.24	41	19.1	3.2

a) Value does not correspond to the smallest NBE regression term.
b) Subject 8 data excluded from calculation of treatment group means.

Table 22 Summary of pharmacokinetic parameters and statistical comparisons between formulations.

PARAMETER	MEAN (SD) BY FORMULATION TYPE		POINT ESTIMATE OF RATIO (%)	90 % CONFIDENCE INTERVAL
	ZW	ARG		
N	11	11		
C _{MAX} (ug/ml)	134.2 (19.6)	139.1 (32.1)	102	94 to 111
T _{MAX} (hr) Median (Min, Max)	0.50 (0.33, 0.55)	0.50 (0.33, 0.65)		
T _{HALF} (hr)	2.03 (0.20)	2.16 (0.24)	106	100 to 114
MRT(IV) (hr) Sequence 1 (N = 6)	2.46 (0.19)	2.34 (0.18)	95	92 to 99
Sequence 2 (N = 5)	2.29 (0.21)	2.54 (0.21)	111	107 to 116
AUC(INF) (ug.hr/ml)	271.9 (45.8)	268.9 (41.2)	99	94 to 104
CLT (ml/min)	125.4 (18.4)	126.6 (19.1)	101	96 to 106
VSS (L)	17.7 (1.8)	18.5 (3.2)	103	97 to 109
UR (N=10) (% dose)	82.1 (5.9)	79.2 (14.2)	95	83 to 108

Table 24 Mean (SD) Cefepime C_{MIN} Concentration Values in Cystic Fibrosis Patients after Multiple 50 mg/kg IV Doses

Study Day	N	Mean (SD) Conc (µg/ml)
3	8	7.2 (7.1)
6	8	6.6 (5.8)
9	5	6.4 (6.9)
12	5	7.1 (7.9)

Table 25 Mean (SD) Sputum Concentrations of Cefepime in Cystic Fibrosis Patients after Single and Multiple 50 mg/kg IV Doses

Sampling Time (hr)	N	Concentration (µg/ml)
<u>First Dose</u>		
Predose	10	< LLQ
1	9	4.1 (2.5)
4	9	4.7 (3.0)
8	6	4.1 (3.0)
<u>Intermediate Dose</u>		
Predose	4	5.8 (4.3)
1	1	9.8
4	1	5.9
8	1	3.8
<u>Last Dose</u>		
Predose	5	6.2 (5.2)
1	6	6.3 (5.4)
4	5	7.4 (5.7)
8	5	4.8 (2.3)

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Table 26 Individual and Mean (SD) Sputum Concentrations ($\mu\text{g/ml}$) of Cefepime in Cystic Fibrosis Patients after a Single 2000 mg IV Dose

Patient No.	Pre-dose	Sputum Concentration ($\mu\text{g/ml}$)							
		Time After Dosing (hr)							
		1	2	4	6	8	12	16	24
	NC*								
	NC								
	<LLQ								
	<LLQ								
	<LLQ								
	<LLQ								
	<LLQ								
	<LLQ								
	1.0								
	<LLQ								
	<LLQ								
Mean	1.0	1.5	2.4	3.4	1.2	.	1.3	.	.
SD		0.7	0.8	1.7					

- * NC = not collected
- * <LLQ = less than the assay lower limit of quantitation (0.5 $\mu\text{g/ml}$)

Table 27 Individual and Mean (SD) Pharmacokinetic Parameter Values of Cefepime in Normal Subjects after a Single 2000 mg IV Dose

SUBJ NO.	PHARMACOKINETIC PARAMETER VALUES											
	C _{MAX} (μG/ML)	T _{MAX} (H)	AUC(0-∞) (μG.H/ML)	MRT(I.V.) (H)	T-1/2 (H)	CLT (ML/MIN/KG)	CLT (ML/MIN/M ²)	CLR (ML/MIN/KG)	CLR (ML/MIN/M ²)	V _{SS} (L/KG)	V _{SS} (L/M ²)	Z _{UR}
MEAN	148.1	0.50 ^a	327	2.39	2.41	1.79	64.4	1.47	52.0	0.25	9.11	82.0
SD	19.0	(0.50,0.65)	50	0.37	0.62	0.29	10.9	0.32	11.3	0.04	1.30	10.2
N	12	12	12	12	12	12	12	12	12	12	12	12

^a MEDIAN (MINIMUM, MAXIMUM)

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Table 28 Individual and Mean (SD) Pharmacokinetic Parameter Values of Cefepime in Cystic Fibrosis Patients after a Single 2000 mg IV Dose

SUBJ NO.	PHARMACOKINETIC PARAMETER VALUES											
	C _{MAX} (µG/ML)	T _{MAX} (H)	AUC(0-∞) (µG.H/ML)	MRT(INF) (H)	T-1/2 (H)	CLT (ML/MIN/KG)	CLT (ML/MIN/M ²)	CLR (ML/MIN/KG)	CLR (ML/MIN/M ²)	VSS (L/KG)	VSS (L/M ²)	UR
MEAN	154.5	0.50*	286	2.03	2.28	2.20	74.3	1.73	50.4	0.27	0.96	79.5
SD	23.2	(0.50,0.57)	51	0.26	0.49	0.36	11.1	0.21	6.41	0.04	1.12	8.0
N	11	11	11	11	11	11	11	10	10	11	11	10

* MEDIAN (MINIMUM, MAXIMUM)

♦ CLR and UR excluded from the calculation of the mean (SD) values

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Table 29 Mean ($\pm$ SD) Cefepime Pharmacokinetic Data in Subjects with Normal and Impaired Renal Function

Parameter	Group I (>90 ml/min*)	Group II (61-90 ml/min*)	Group III (31-60 ml/min*)	Group IV (11-30 ml/min*)	Group V (<10 ml/min*)	Tukey's Test ^a
C _{MAX} (μ g/ml)	63.5 (7.79)	70.5 (20.8)	73.9 (19.5)	68.9 (16.0)	65.5 (9.18)	<u>III II IV V I</u>
MRT-INF (hr)	2.86 (0.24)	4.60 (0.58)	5.88 (1.16)	14.7 (3.39)	20.0 (3.84)	<u>V IV III II I</u>
T-1/2 (hr)	2.29 (0.55)	3.33 (0.74)	4.89 (0.82)	10.5 (2.96)	13.5 (2.65)	<u>V IV III II I</u>
AUC-INF (μ g.hr/ml)	131 (22.8)	225 (37.7)	292 (89.3)	683 (192)	928 (202)	<u>V IV III II I</u>
VDSS (L)	20.5 (4.84)	19.6 (2.99)	19.8 (3.05)	21.8 (5.10)	21.7 (4.20)	<u>IV V III II I</u>
CLT (ml/min)	131 (24.6)	75.7 (12.9)	61.0 (16.6)	25.9 (6.73)	18.7 (4.18)	<u>I II III IV V</u>
CLR (ml/min)	110 (28.8)	60.8 (8.51)	48.1 (16.0)	15.4 (6.1)	4.22 (3.63)	<u>I II III IV V</u>
CLCR	20.2	14.9	12.9	10.5	16.9	<u>I V II III IV</u>

* CLCR

^a Groups without a common underline are significantly different, $p < 0.05$.

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Table 30 Demographics and Dialysis Data for Five Subjects on Hemodialysis

Subject	Hct (%) ^a	Dialyzer Chamber	Blood Flow (ml/min) ^b	Dialysate Flow (ml/min) ^c	Dialysate Creatinine Clearance (ml/min)	Dialysate Blood Urea Nitrogen Clearance (ml/min)	Mean Dialysis Clearance of Cefepime (ml/min) ^d	Fraction of Cefepime Dose Recovered in Dialysate ^e
	24.8	Travenol-CA-170	475	757	220	295	277	0.43
	26.0	Travenol-CA-170-Tandem	494	718	208	264	175	0.86
	34.1	Travenol-CA-170	400	752	120	172	103	0.77
	25.4	Travenol-CA-210	338	855	147	200	134	0.65
	42.6	Travenol-CA-210	450	747	139	160	118	0.68

- a) Average hematocrit (Hct) value from pre- and post-dialysis samples
- b) Measured by bubble transit time
- c) Measured from total hourly dialysate collections
- d) Determined from mean of Methods 1, 2 and 3 (page 17 of this report)
- e) Fraction of pool of cefepime present in the body at the start of hemodialysis

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Subject nr	C_{max} (ug/ml)	λ_{z1} (h ⁻¹)	AUC (ugxh/ml)	(1) V_{ss} (l/kg)	
Mean	102.9	0.3860	153.2	15.4	0.21
SD	22.6	0.0182	30.3	2.7	0.03
Mean	114.9	0.1474	481.9	14.7	0.20
SD	15.3	0.0312	141.8	2.0	0.03
Mean	117.7	0.0914	897.3	13.1	0.20
SD	21.6	0.0242	256.8	2.1	0.02
Mean	130.4	0.0328	2658.7	11.8	0.18
SD	23.4	0.0058	360.8	2.0	0.06

* subjects are not include in calculation of mean C_{max} and AUC

Subject nr	T1/2 (h)	MTT (h)	Clear _{tot} (ml/min)	Clear _{tot} (ml/(minx1.73m ²))
Mean	1.80*	2.39	109.1	97.2
SD	-	0.09	16.6	7.8
Mean	4.70*	6.75	38.5	34.6
SD	-	1.56	12.3	9.6
Mean	7.58*	11.43	20.5	19.8
SD	-	3.68	6.2	6.3
Mean	21.13*	31.56	6.4	6.3
SD	-	6.11	1.5	2.3

* Mean T1/2 were calculated from mean elimination constant, thus SD cannot be given.

Subject nr	U _{rec} * (mg)	U _{rec} * (% of dose)	Clear _{ren} (ml/min)	Clear _{ren} ml/(minx1.73m ²))

Mean	904.9	87.7	91.4	86.2
SD	69.9	4.2	16.2	8.1

Mean	822.1	77.6	35.7	31.9
SD	200.5	12.7	15.1	11.9

Mean	469.4	45.8	12.9	12.8
SD	142.4	13.3	4.5	5.6

-
- * Urine recovery up to 12 h
 - ** Administered dose half of intended due to miscalculation in preparing cefepime vials for infusion
 - *** Not calculated since urine collection incomplete
 - **** Urine not collected at 12 h

Table 33a Pharmacokinetics of cefepime in CAPD patients following single 1000 and 2000 mg doses.

PHARMACOKINETIC PARAMETER VALUES

SUBJECT NO.	C _{MAX} (μG/ML)	MRT (H)	T-HALF (H)	AUC (H. μG/ML)	CLT (ML/MIN)	CLR (ML/MIN)	CLNR (ML/MIN)	CLD (ML/MIN)	VSS (L)
1000 MG									
MEAN	62.9	24.0	17.6	1166	15.4	1.00	14.4	3.86	21.7
SD	15.8	3.1	2.9	356	4.9	1.04	4.2	0.59	4.6
N	5	5	5	5	5	5	5	5	5
2000 MG									
MEAN	124	26.8	18.8	2405	14.0	0.24	13.7	4.35	22.5
SD	14	1.5	1.6	213	1.3	0.23	1.1	0.69	2.8
N	5	5	5	5	5	5	5	5	5

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Table 33b Mean cumulative dialytic excretion of cefepime.

Time (h)		Mean cumulative % of dose					
		1000 mg*			2000 mg*		
Mean	SD	N	Mean	SD	N	Mean	SD
0	0	-	0	----	-	0	----
4.56	0.70	4	5.60	1.08	5	5.56	1.09
8.90	0.32	5	9.80	1.31	5	10.5	1.3
13.70	0.48	5	13.3	1.6	5	14.6	2.2
23.60	0.70	5	16.4	2.6	5	18.7	2.8
28.50	0.71	5	18.6	2.9	4	20.3	3.5
32.70	0.48	5	20.1	3.3	5	22.3	3.5
37.60	0.52	5	21.4	3.6	5	23.9	3.7
47.80	0.42	5	22.6	3.8	5	25.5	3.9
52.35	0.58	5	23.5	4.0	5	26.6	4.1
56.75	0.42	5	23.9	4.4	5	27.4	4.2
61.70	0.48	5	24.4	4.6	5	28.2	4.5
71.90	0.32	5	24.9	4.8	5	28.7	4.5

*Administered doses.

Table 34 Mean Cefepime Plasma Concentrations: HPLC/UV and Total Radioactivity Assays.

TIME AFTER D. SE ADMIN.			MEAN PLASMA CONCENTRATION (µg/ml)												
DAY	HR	MIN	HPLC/UV NORMAL			HPLC/UV RENAL			TAC NORMAL			TAC RENAL			
			N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD	
.	.	0	0	.	.	0	.	.	0	.	.	0	.	.	0
.	.	15	4	44.1	7.6	4	35.2	8.9	4	34.8	8.5	4	33.6	9.0	
.	.	30	4	70.8	8.6	4	62.9	13.0	4	77.2	8.2	4	61.0	12.4	
.	.	33	4	65.4	6.8	4	61.0	9.1	4	68.3	4.2	4	64.5	13.7	
.	.	39	4	57.2	1.6	4	63.0	12.8	4	58.9	2.4	4	59.2	11.2	
.	.	45	4	52.3	0.5	4	60.6	8.8	4	55.2	0.6	4	57.9	9.2	
.	1	0	4	44.7	5.7	4	5.9	11.4	4	45.7	1.3	4	54.2	10.4	
.	1	30	4	32.7	3.6	4	9.8	9.9	4	35.2	1.4	4	49.2	9.4	
.	2	0	3	26.8	3.6	4	48.9	11.2	4	25.2	5.2	4	45.3	9.6	
.	4	0	4	12.5	1.3	4	37.8	10.4	4	13.4	1.4	4	37.4	10.7	
.	6	0	3	6.3	0.5	4	30.5	11.1	4	6.7	1.0	4	31.9	12.5	
.	8	0	4	3.3	0.5	4	26.9	13.7	4	3.8	0.4	4	27.3	12.2	
.	10	0	4	1.5	0.3	4	23.9	14.7	4	2.1	0.4	4	24.0	12.7	
.	16	0	0	.	.	4	12.7	11.0	0	.	.	4	17.0	12.6	
.	24	0	0	.	.	3	10.0	9.5	0	.	.	4	11.5	10.2	
.	36	0	0	.	.	3	5.6	4.3	0	.	.	3	8.0	5.6	
.	48	0	0	.	.	3	3.1	2.9	0	.	.	3	5.5	4.8	
.	60	0	0	.	.	2	2.3	1.7	0	.	.	2	4.7	2.5	
.	72	0	0	.	.	1	1.9	0.0	0	.	.	2	3.6	2.1	
.	84	0	.	.	.	1	0.9	0.0	.	.	.	2	2.4	1.8	
.	96	0	.	.	.	0	.	.	.	.	.	2	2.1	1.3	
.	108	0	.	.	.	0	.	.	.	.	.	2	1.4	0.8	
.	120	0	.	.	.	0	.	.	.	.	.	1	1.5	0.0	

NOTE: VALUES <LLQ = MISSING

Table 35 Pharmacokinetic Parameters of Cefepime in Subjects with Normal and Impaired Renal Functions.

Subject	C _{MAX}	T-HALF	AUC(INF)	CLT	CLR	VDSS
No.	($\mu\text{g/ml}$)	(hr)	($\mu\text{g}\cdot\text{hr/ml}$)	(ml/min)	(ml/min)	(L)

Table 36 INDIVIDUAL PHARMACOKINETIC DATA FOR SUBJECTS AND PATIENTS, CEFEPIME STUDY A1411-114-001.

PHARMACOKINETIC PARAMETER VALUES										
GROUP	PATIENT NO.	C _{MAX} (UG/ML)	MRT(IV) (H)	T-1/2 (H)	AUC(INF) (H.UG/ML)	CL _T (ML/MIN)	CL _R (ML/MIN)	CL _{NR} (ML/MIN)	VSS (L)	URINARY RECOVERY, 0-24 H (% OF DOSE)
NORMAL SUBJECTS										
	MEAN	76.8	2.34	2.16	149.7	114.3	92.4	23.0	15.8	78.7
	SD	10.5	0.37	0.39	24.9	19.8	19.3	11.7	1.8	8.0
	N	11	11	11	11	11	10	10	11	10
HEPATICALLY IMPAIRED PATIENTS										
	MEAN	57.7	2.84	2.40	138.3	128.8	90.3	32.6	20.9	73.4
	SD	11.8	0.78	0.53	36.6	35.2	23.7	18.4	3.9	14.5
	N	11	11	11	11	11	10	10	11	10

* THESE VALUES WERE EXCLUDED FROM CALCULATIONS OF THE RESPECTIVE MEANS.

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Table 37 Individual Subject Cefepime Pharmacokinetic Data

SUBJ NBR	C _{MAX} (μ G/ML)	MRT(IV) (H)	T-HALF (H)	AUC(INF) (H. μ G/ML)	CLT (ML/MIN)	CLR (ML/MIN)	VSS (L)	AMOUNT EXCRETED (MG)	
								URINE	BREAST MILK
MEAN	78.5	2.27	2.08	151.2	111.6	94.0	15.1	839	0.095
SD	13.7	0.30	0.34	17.2	13.6	14.0	2.4	60	0.063
N	9	9	9	9	9	9	9	9	9

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Table 38 Mean Cefepime Breast Milk Concentrations and Cumulative Excretion of Cefepime in Milk

Time Interval (h)	N	<u>Concentration (ug/ml)</u>		<u>Cumulative Excretion (% of Dose)</u>	
		Mean	SD	Mean	SD
9		0.00	0.00	0.000	0.000
9		0.45	0.18	0.039	0.040
9		0.53	0.15	0.062	0.051
9		0.45	0.17	0.077	0.057
9		0.39	0.18	0.086	0.062
9		0.20	0.12	0.094	0.063
9		0.00	0.07	0.095	0.063

NOTE: VALUES <LLQ = 0

Table 39 Concentrations and Penetration Ratios of Cefepime in Plasma, Peritoneal Fluid and Appendix Tissue Samples Collected from Individual Patients at Various Times After a 2000 mg Intravenous Dose

Patient Number	Hours Post Dose	Plasma Conc (µg/ml)	Peritoneal Fluid Conc (µg/ml)	PF/Pl. Ratio	Appendix Conc (µg/g ^a)	AP/Pl. Ratio
	Control					
	Control					
	4.33					
	4.00					
	6.55					
	2.37					
	7.83					
	1.47					
	2.47					
	9.45					
	Control					
	9.72					
	6.20					
	3.38					
	8.55					
	8.80					
	1.80					
	8.22					
	3.50					
	1.17					
	1.50					
	21.4					
	1.40					
	7.33					
	4.13					
	5.80					
	12.0					
	1.38					
	7.42					
	1.85					
	1.50					
	14.2					
	8.70					
	5.70					
	1.32					
	14.7					
	13.9					
	11.4					
	10.8					
	0.95					
	2.80					
	Control					
	10.3					
	Control					
	Control					

* Plasma concentration data inconsistent with the value reported at this time point after a 2000 mg dose

NA Not available, due to lack of sample collection

††† Less than the assay lower limit of quantitation

Since the concentration values suggest that an unrecorded dose of cefepime was given prior to surgery, the data from this patient are not included in the calculation of any mean values

Table 40 Mean (SD*) Concentrations and Penetration Ratios of Cefepime in Plasma, Peritoneal Fluid and Appendix Tissue over Various Intervals Post-Dose

Range of Sample Collection Time (hr)	N†	Time (hr)	N	Plasma Conc (µg/ml)	N	Peritoneal Fluid Conc (µg/ml)	N	PF/PL Ratio	N	Appendix Conc (µg/ml)	N	AP/PL Ratio
0-2	10	1.49 (0.30)	9	45.4 (20.2)	8	34.1 (32.5)	6	0.74 (0.63)	10	10.6 (8.4)	9	0.24 (0.17)
2-4	6	3.09 (0.64)	6	20.1 (17.9)	3	13.8 (6.7)	3	0.66 (0.23)	5	6.7 (3.1)	5	0.49 (0.19)
4-6	4	5.1 (0.79)	3	8.9 (6.5)	3	6.9 (5.3)	2	0.84	3	2.6 (1.5)	2	0.71
6-8	5	7.07 (0.67)	4	4.9 (2.7)	3	6.1 (1.4)	2	1.06	5	2.2 (1.2)	4	0.43 (0.36)
8-10	6	8.91 (0.57)	6	1.8 (1.0)	2	2.0	2	0.76	6	1.4 (0.8)	6	0.82 (0.36)
>10	7	12.0 (1.5)	5	1.4 (1.0)	2	1.6	2	0.64	7	1.7 (1.0)	5	1.45 (0.63)

* SD not reported for less than 3 observations

† N represents the number of patients with quantifiable drug levels in a particular sample type. In two cases (one each in the 4-6 and 6-8 hr intervals), cefepime was not detected in the patient plasma sample, resulting in the inability to calculate a fluid or tissue to plasma ratio.

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Table 41 Individual and mean subject pharmacokinetic parameter values for cefepime, ceftazidime and cefoperazone in serum

SUBJ NBR	SEQ NBR	PHARMACOKINETIC PARAMETER VALUES						
		C _{MAX} (µG/ML)	T _{MAX} (HRS)	MRT (INF) (HRS)	T-1/2 (HRS)	AUC (INF) (HR. µG/ML)	CLT (ML/MIN)	CH ₁₂ * (µG/ML)
CEFEPIME								
	1							
	2							
	1							
	3							
	4							
	1							
MEAN		86.7	0.50	2.33	1.59	188.1	179	0.6
SD		14.1	0.00	0.16	0.07	72.8	21	0.1
CEFTAZIDIME								
	1							
	2							
	1							
	3							
	4							
	1							
MEAN		76.2	0.50	2.38	1.78	157.9	228	0.5
SD		25.8	0.00	0.09	0.24	50.3	65	0.1
CEFOPERAZONE								
	1							
	2							
	1							
	3							
	4							
	1							
MEAN		178.1	0.50	2.44	1.80	369.3	92	2.1
SD		29.5	0.00	0.47	0.38	54.0	15	1.2

* Defined as the concentration at 12 hr

Table 42 Individual and mean subject pharmacokinetic parameter values for cefepime, ceftazidime and cefoperazone in blister fluid

SUBJ NBR	SEQ NBR	PHARMACOKINETIC PARAMETER VALUES						
		C _{MAX} (µG/ML)	T _{MAX} (HRS)	MRT(INF) (HRS)	T- _{HALF} (HRS)	AUC(INF) (HR.µG/ML)	CLT (L/MIN)	C _{MIN} * (µG/ML)
CEFEPIME								
	1							
	2							
	1							
	3							
	4							
	1							
MEAN		26.3	3.33	4.89	2.81	147.3	250	3.0
SD		11.2	2.42	0.96	0.47	54.0	88	1.6
CEFTAZIDIME								
	1							
	2							
	1							
	3							
	1							
MEAN		40.2	2.40	5.04	2.33	242.3	151	3.0
SD		13.7	0.89	0.59	0.46	73.3	55	1.8
CEFOPERAZONE								
	1							
	2							
	1							
	1							
MEAN		13.3	4.50	18.37	11.68	207.1	178	6.5
SD		5.0	2.52	14.11	9.59	69.5	74	2.6

* Defined as the concentration at 12 hr



Table 43 Individual and mean (SD) cefepime concentration values for serum and prostate tissue

Patient Number	Time Post Dose (hr)	Serum Conc (µg/ml)	Prostate Conc (µg/g)	Prostate/Serum Ratio
Mean (SD)		61.2 (8.7)	31.5 (6.8)	0.51 (0.07)
Mean (SD)		42.6 (12.6)	17.8 (6.7)	0.42 (0.15)
Mean (SD)		17.4 (10.1)	8.4 (8.0)	0.43 (0.32)
Mean (SD)		8.9 (4.3)	6.4 (3.8)	0.76 (0.26)
Mean (SD)		14.6 (20.7)	6.6 (8.0)	0.79 (0.90)
Mean (SD)		1.5 (1.1)	1.5 (1.0)	1.38 (1.35)

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Table 44 Concentrations and Penetration Ratios of Cefepime in Plasma, Peritoneal Fluid, Bile and Gallbladder Tissue Samples Collected from Individual Patients at Various Times After a 2000 mg Intravenous Dose

Patient No.	Time Post Dose (Hr:Min)	PL Conc ¹ (µg/ml)	PF Conc ² (µg/ml)	Ratio PF/PL	Bile Conc (µg/ml)	Ratio Bile/PL	Gallbladder Conc (µg/gm)	Ratio GB/PL

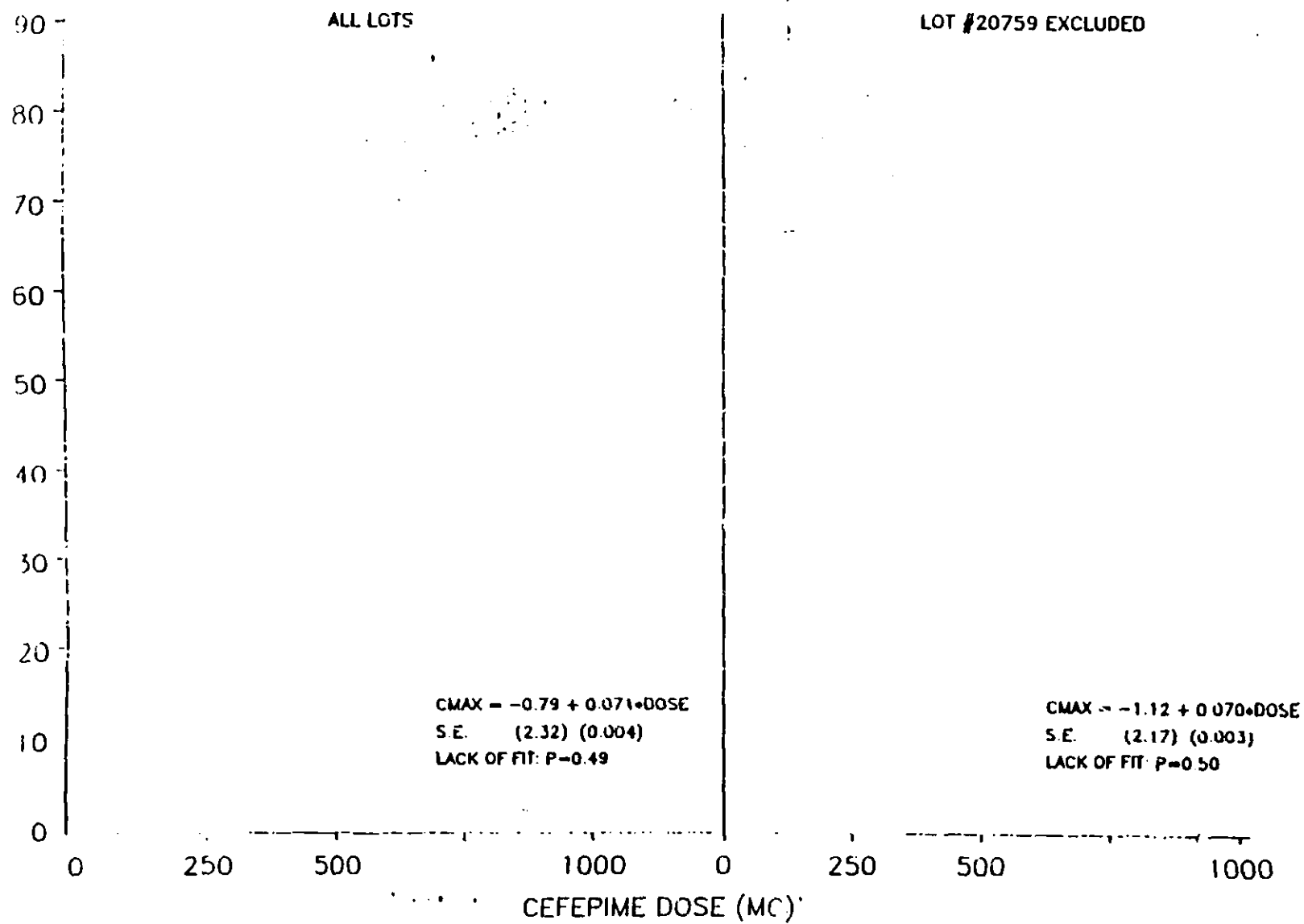
59

Patient No.	Time Post Dose (hr:Min)	Pl Conc ¹ (ng/ml)	Pl Conc ² (ng/ml)	Ratio Pl/Pl	Blk Conc (ng/ml)	Ratio Blk/Pl	Cellbladder Conc (ng/ml)	Saliv Conc

Patient No.	Time Post Dose (hr:min)	P1 Conc ¹ (µg/ml)	P2 Conc ² (µg/ml)	Ratio P2/P1	Bile Conc (µg/ml)	Ratio Bile/P1	Gallbladder Conc (µg/gm)	Ratio Gall/P1

1. P1c plasma
2. P1c Peritoneal fluid
3. ckg Gallbladder
4. ckg+ Gentamicin control patient
5. ckg+ Gent not collected
6. ckg+ Gent not analyzed

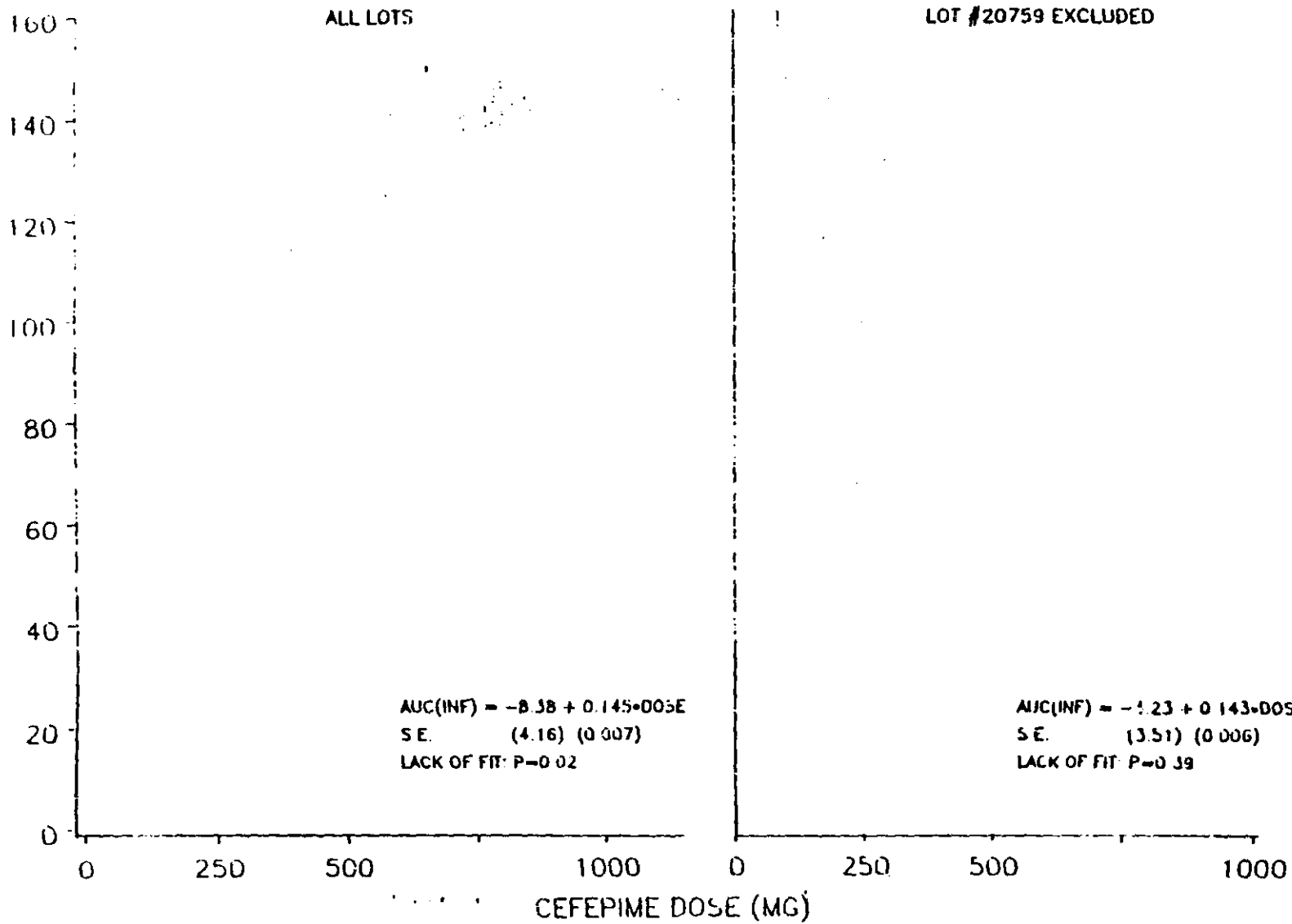
Fig. 2 REGRESSION OF CMAX ON CEFEPIME DOSE ON DAY 1



MG LOT# 20759 (o)

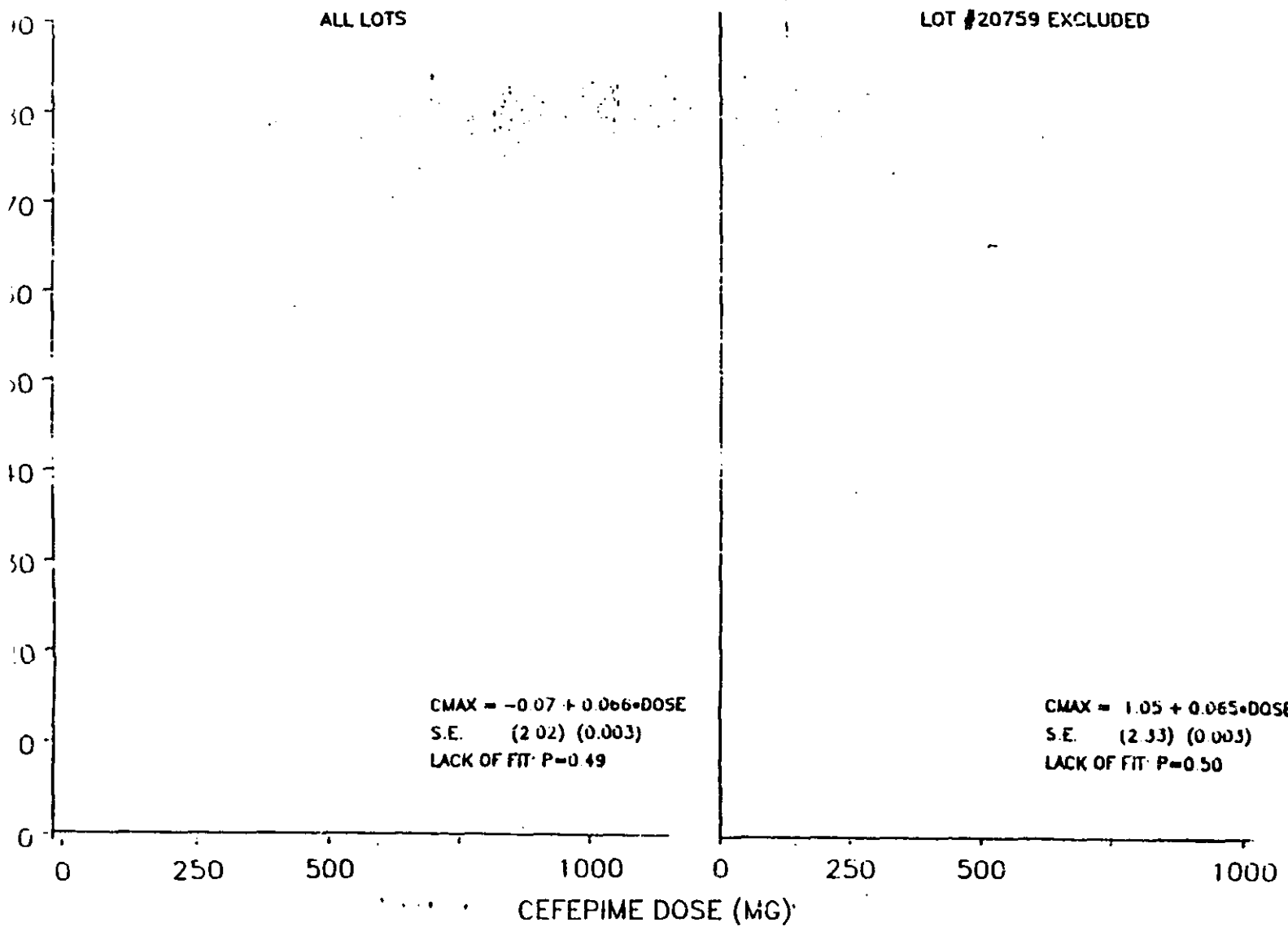
68

Fig. 3 REGRESSION OF AUC(INF) ON CEFEPIME DOSE ON DAY 1



AG LOT# 20759 (o)

Fig. 4 REGRESSION OF CMAX ON CEFEPIME DOSE ON DAY 11



MG LOT# 20759 (o)

70

Fig. 5 REGRESSION OF AUC(0-T) ON CEFEPIME DOSE ON DAY 11

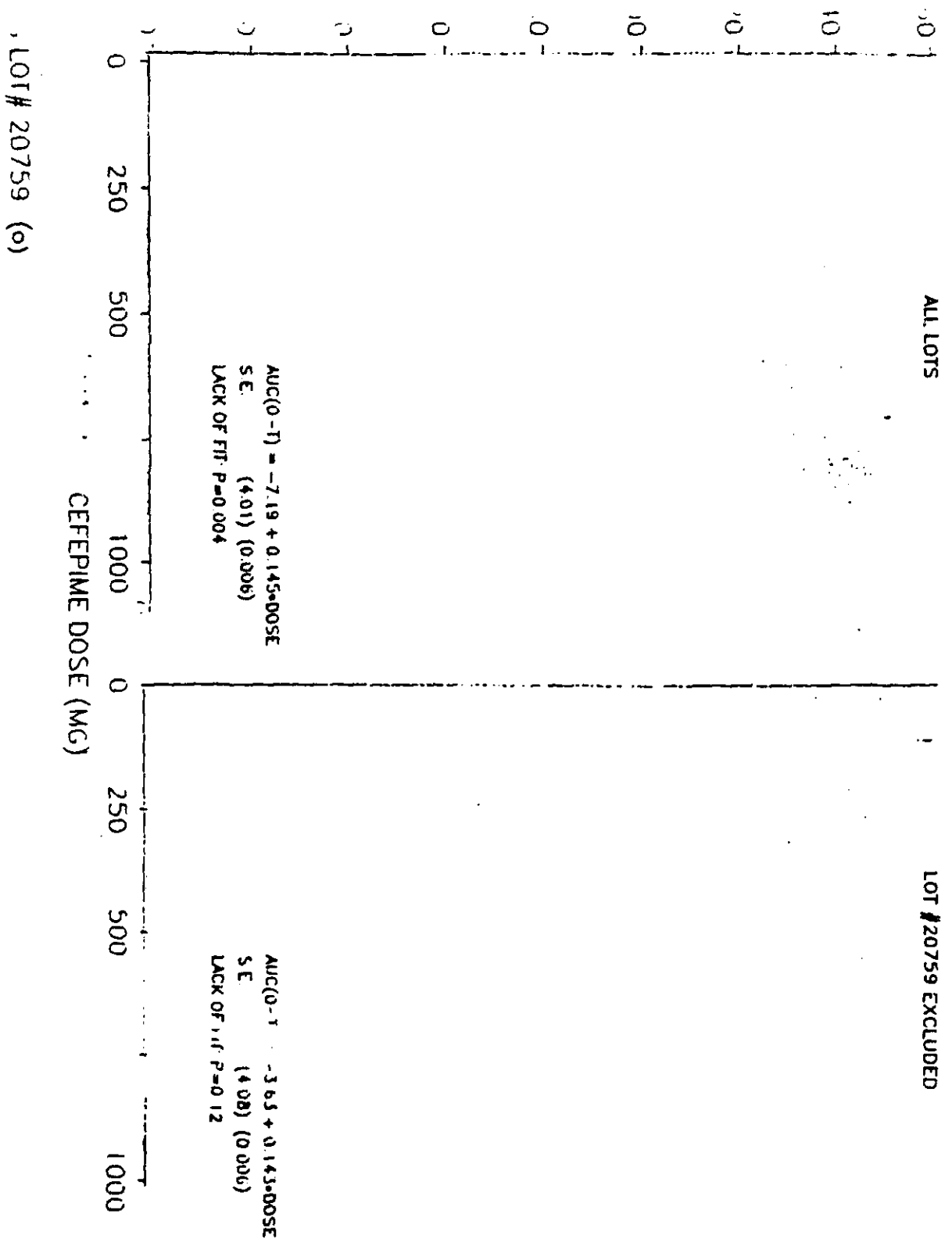


Fig. 6 Dose-group mean Plasma CMAX Concentrations vs. Treatment Day.
Study 411-059-001

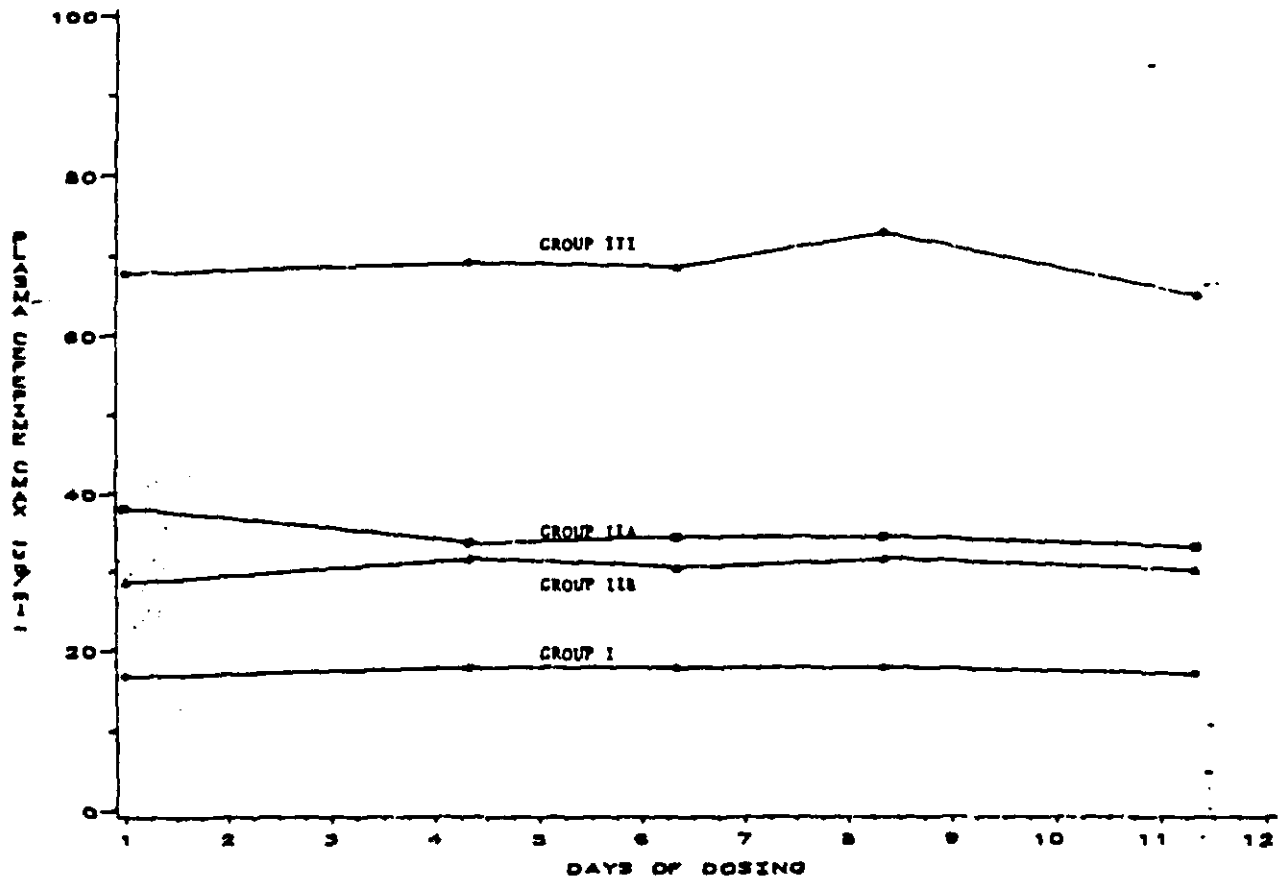


Fig. 7 REGRESSION OF CMAX ON CEFEPIME DOSE ON DAY 1

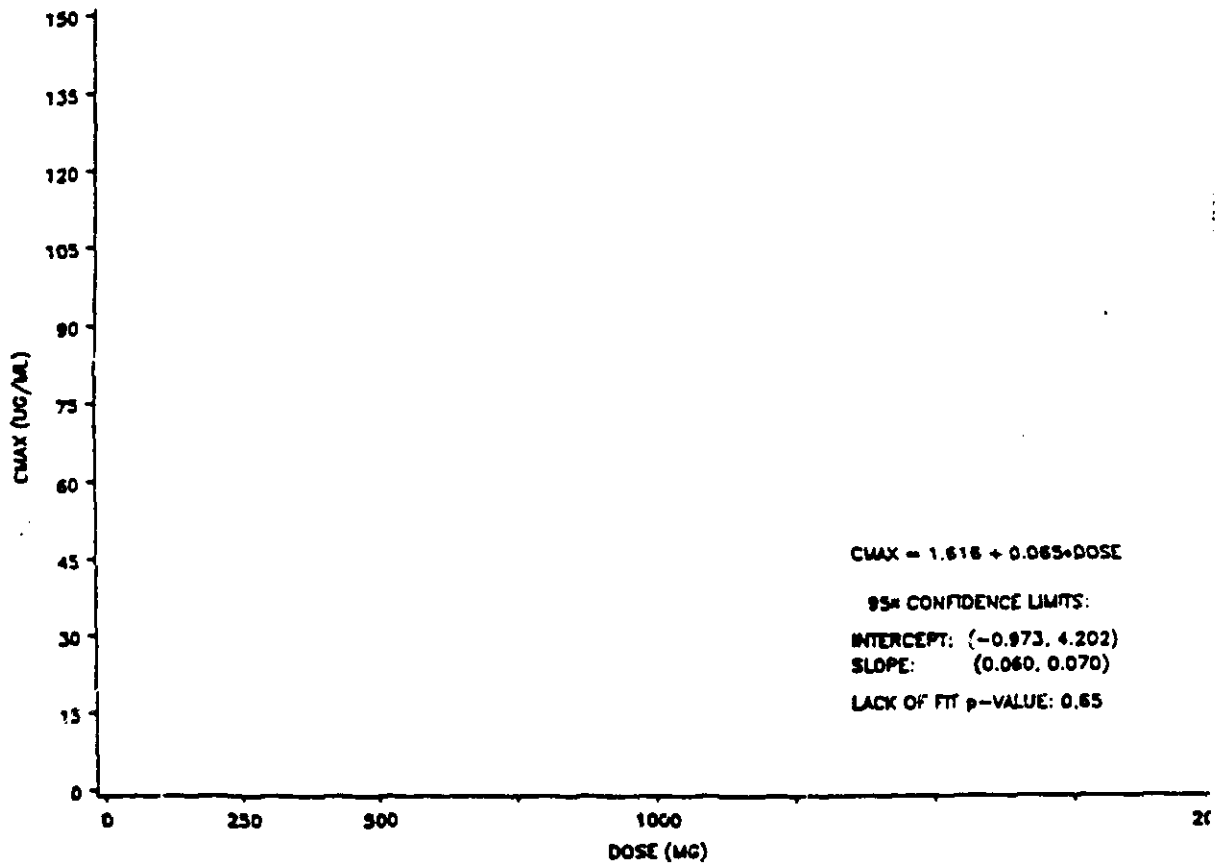
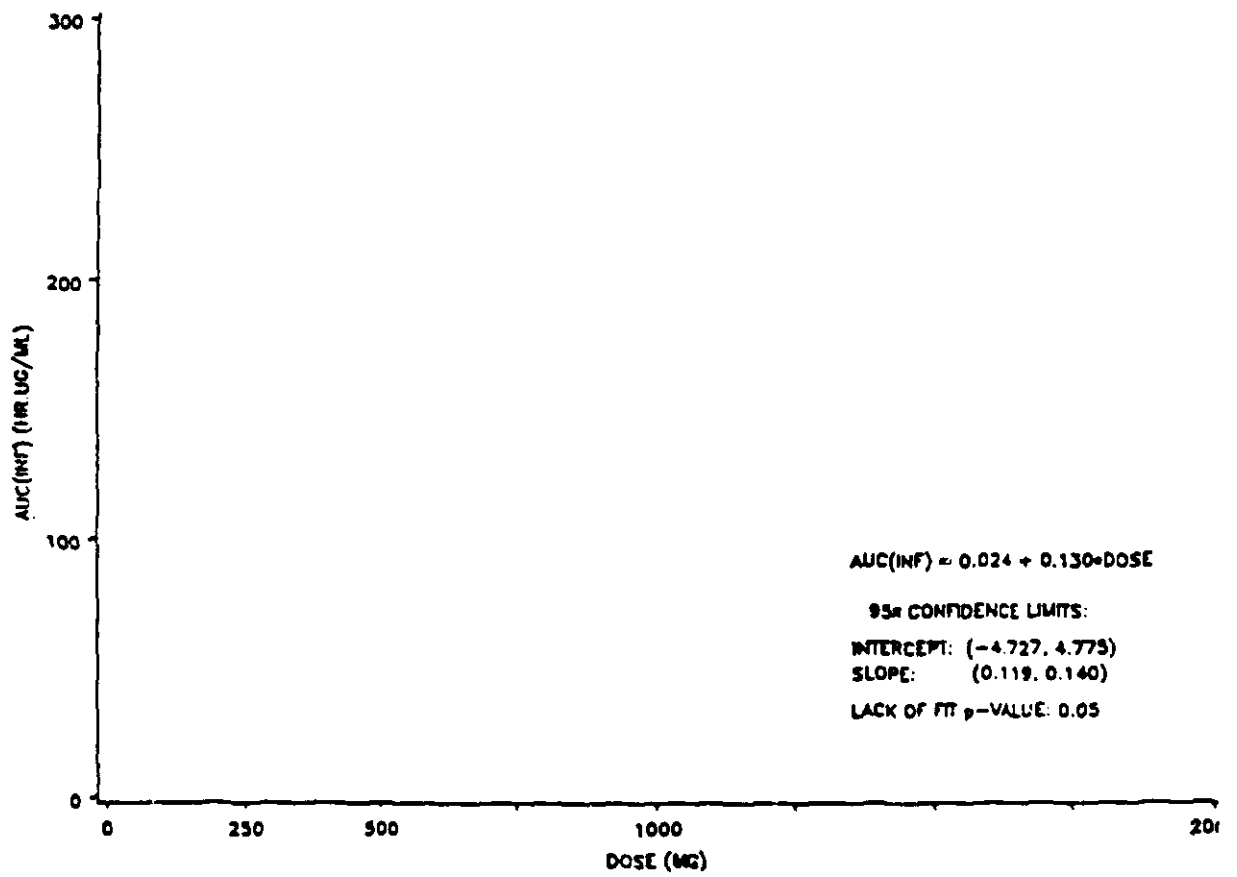


Fig. 8 REGRESSION OF AUC(INF) ON CEFEPIME DOSE ON DAY 1



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Fig. 9

PLASMA CMIN vs. TREATMENT DAY
Data for 31 subjects on tid dose schedule
(Studies 411-058-001 and 411-063-001)

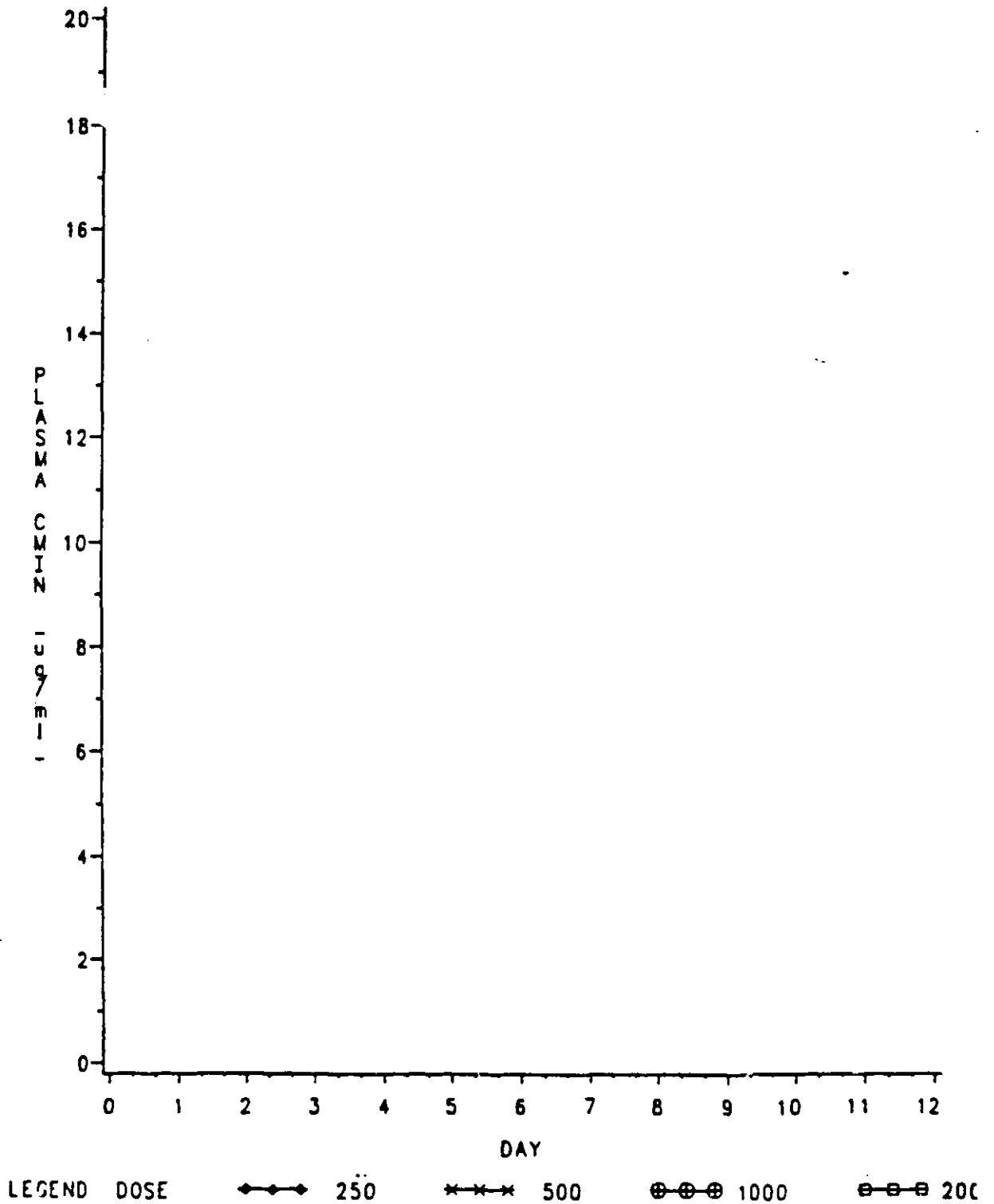


Fig. 10

PLASMA CMAX vs. TREATMENT DAY
Data for 31 subjects on tid dose schedule
(Studies 411-058-001 and 411-063-001)

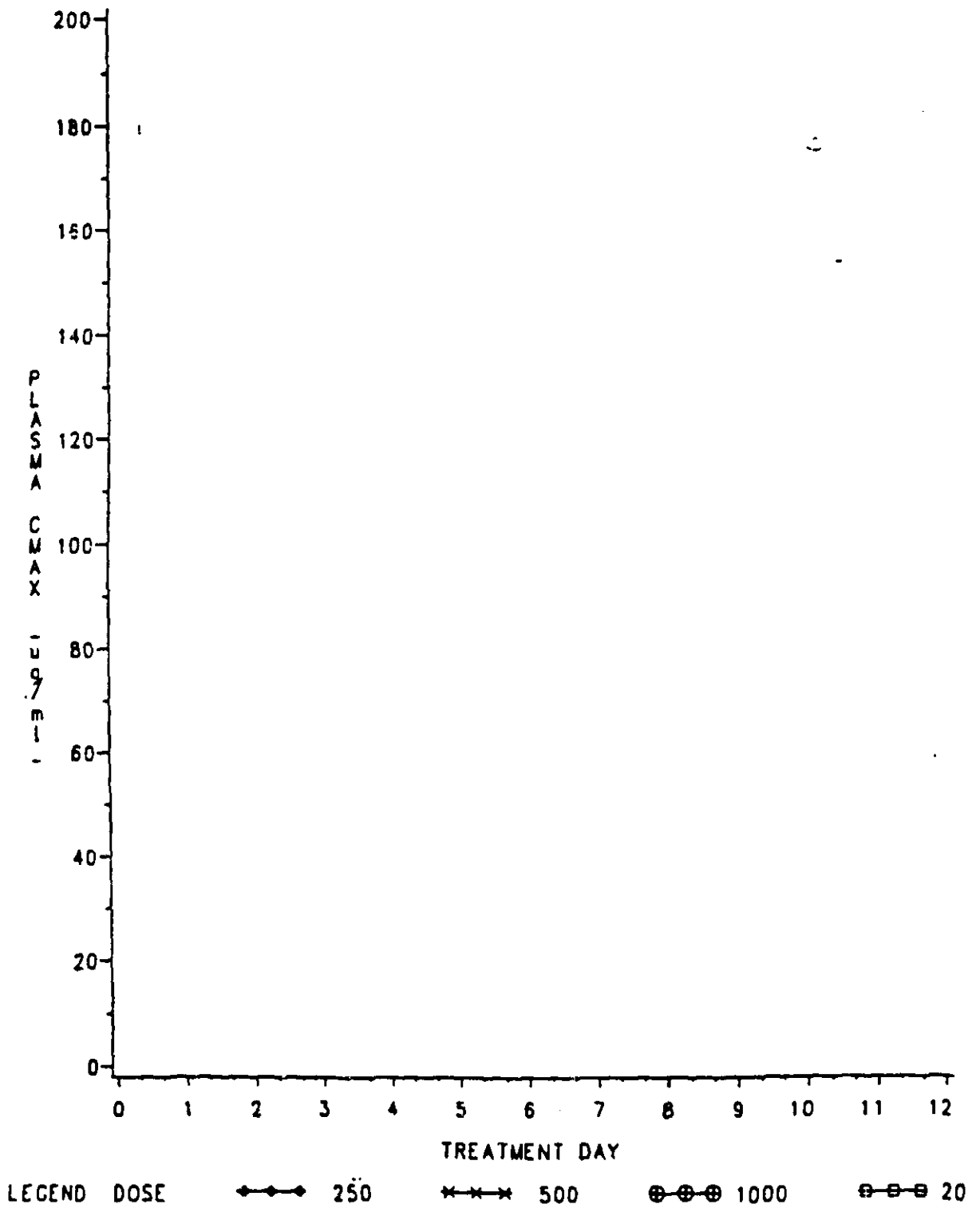


Fig. 11 REGRESSION OF CMAX ON CEFEPIME DOSE ON DAY 11

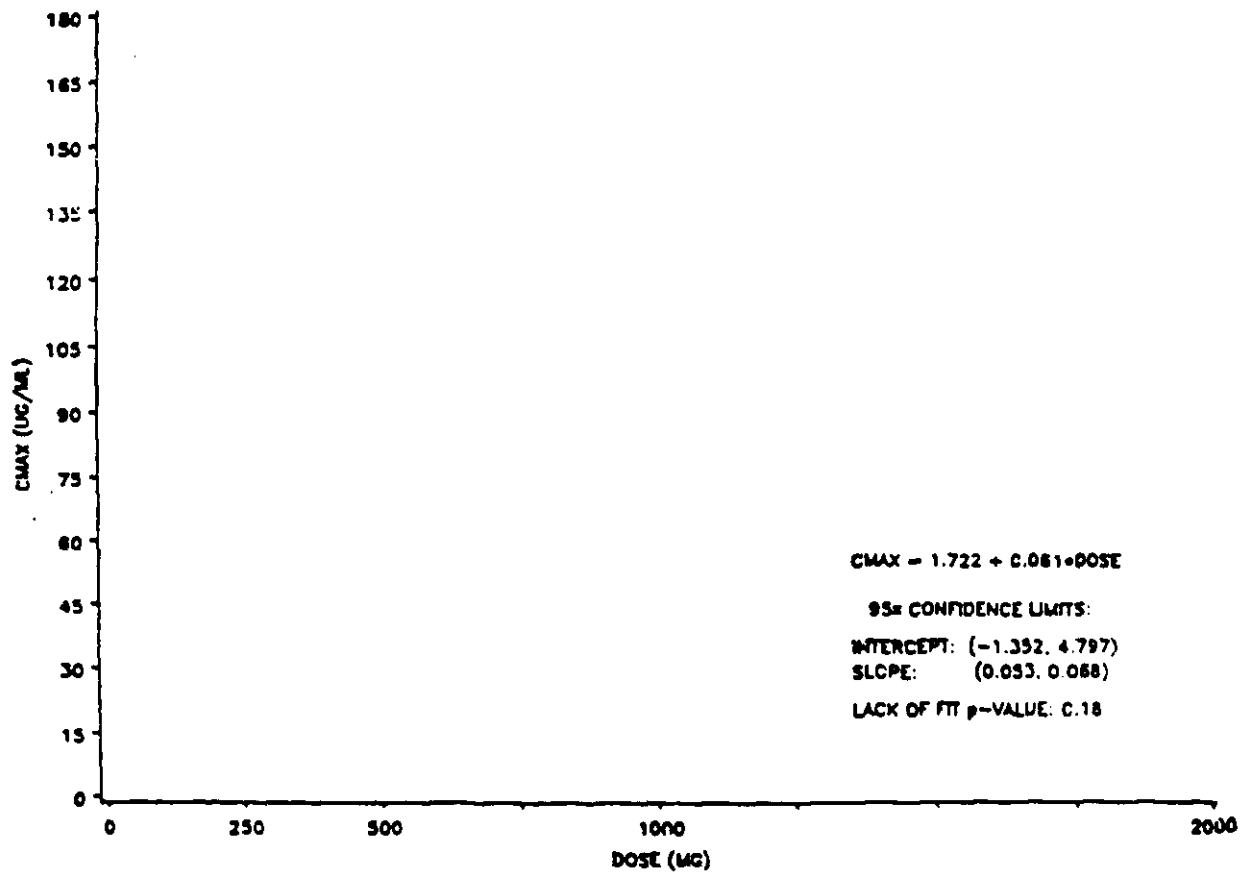
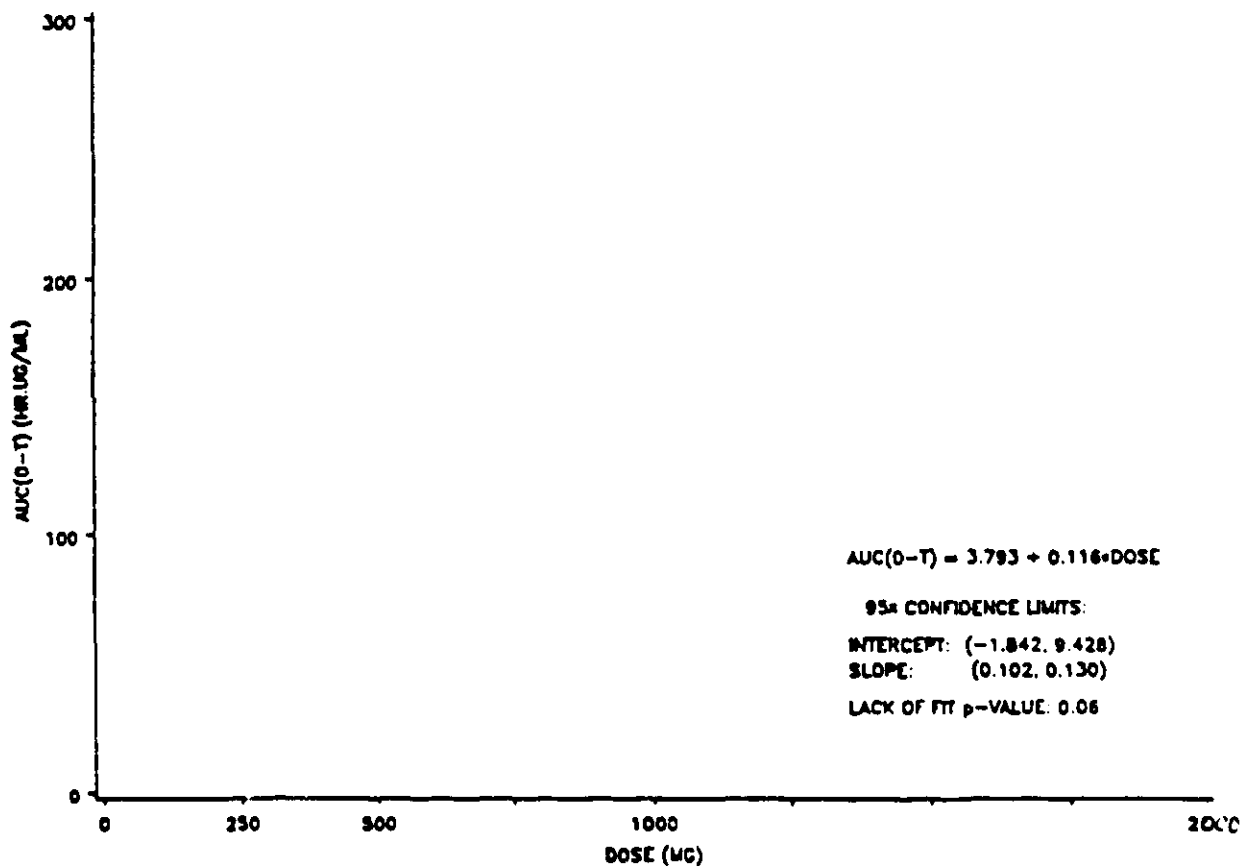


Fig. 12 REGRESSION OF AUC(0-T) ON CEFEPIME DOSE ON DAY 11



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DOSE-GROUP MEAN (SD) CEFEPIME URINARY RECOVERY BY TREATMENT DAY

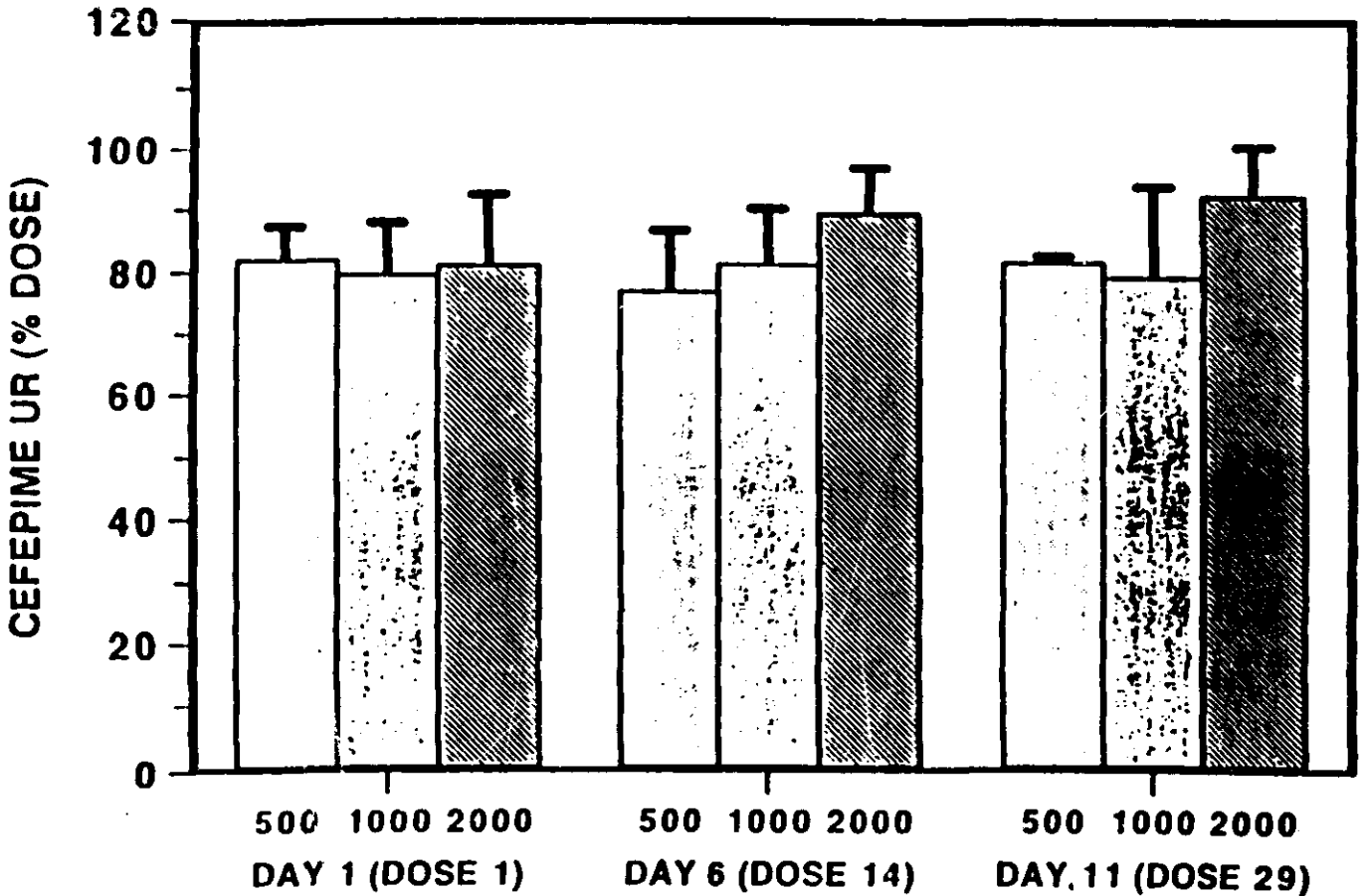
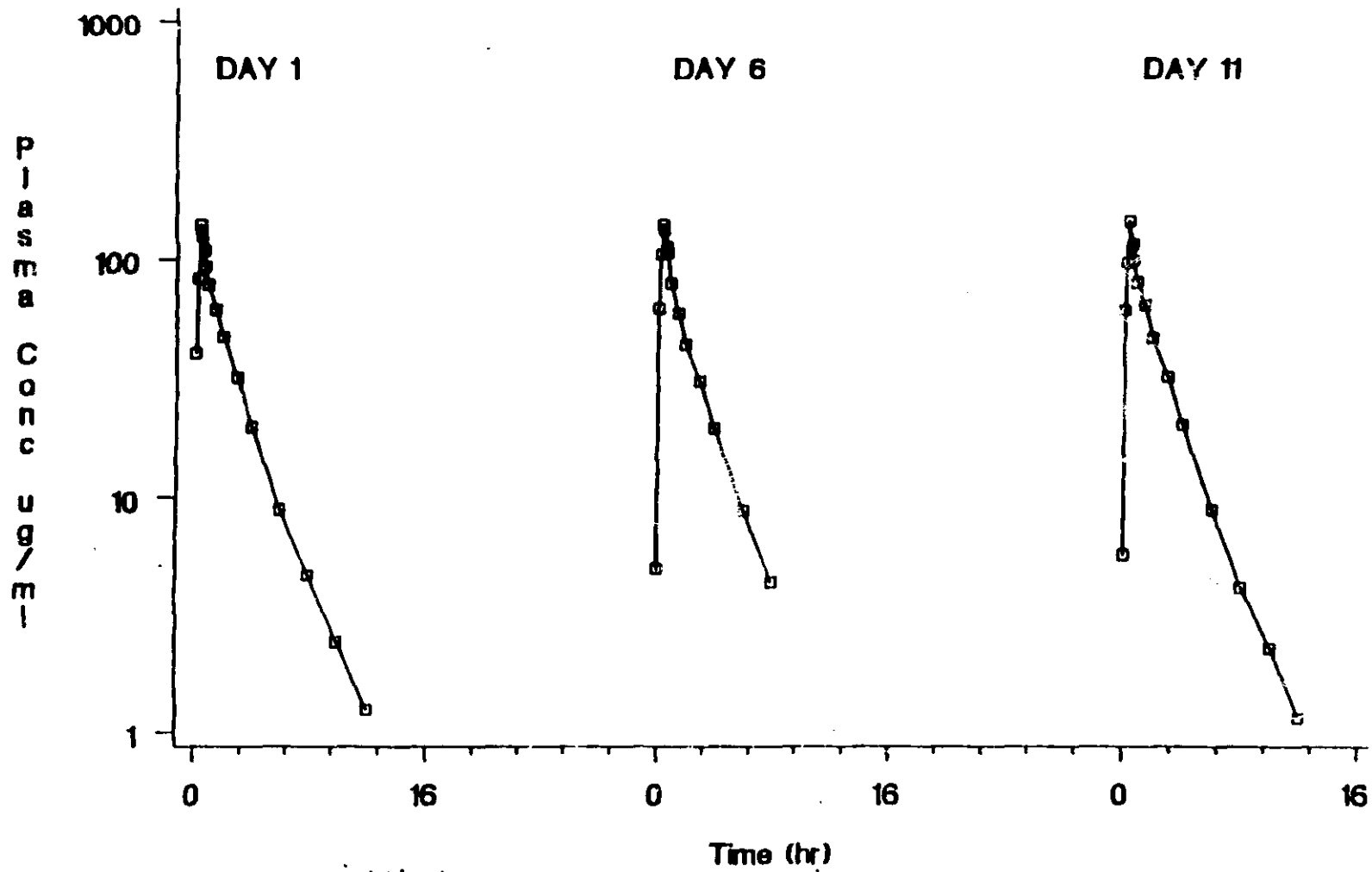


Fig. 13 Cefepime urinary recovery as a function of dose level and treatment day. Study 411-064-001 (500 mg) and 411-063-001 (1000 and 2000 mg, subject 13 excluded).

Fig. 14 Mean Plasma Concentration Of Cefepime Following 2000 mg Intravenous Dose Administered Every 8 Hours to 7 Subjects



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Fig. 15 Mean Plasma Cefepime CMAX vs Treatment Day
Data for 7 Subjects on a q8h Dose Schedule

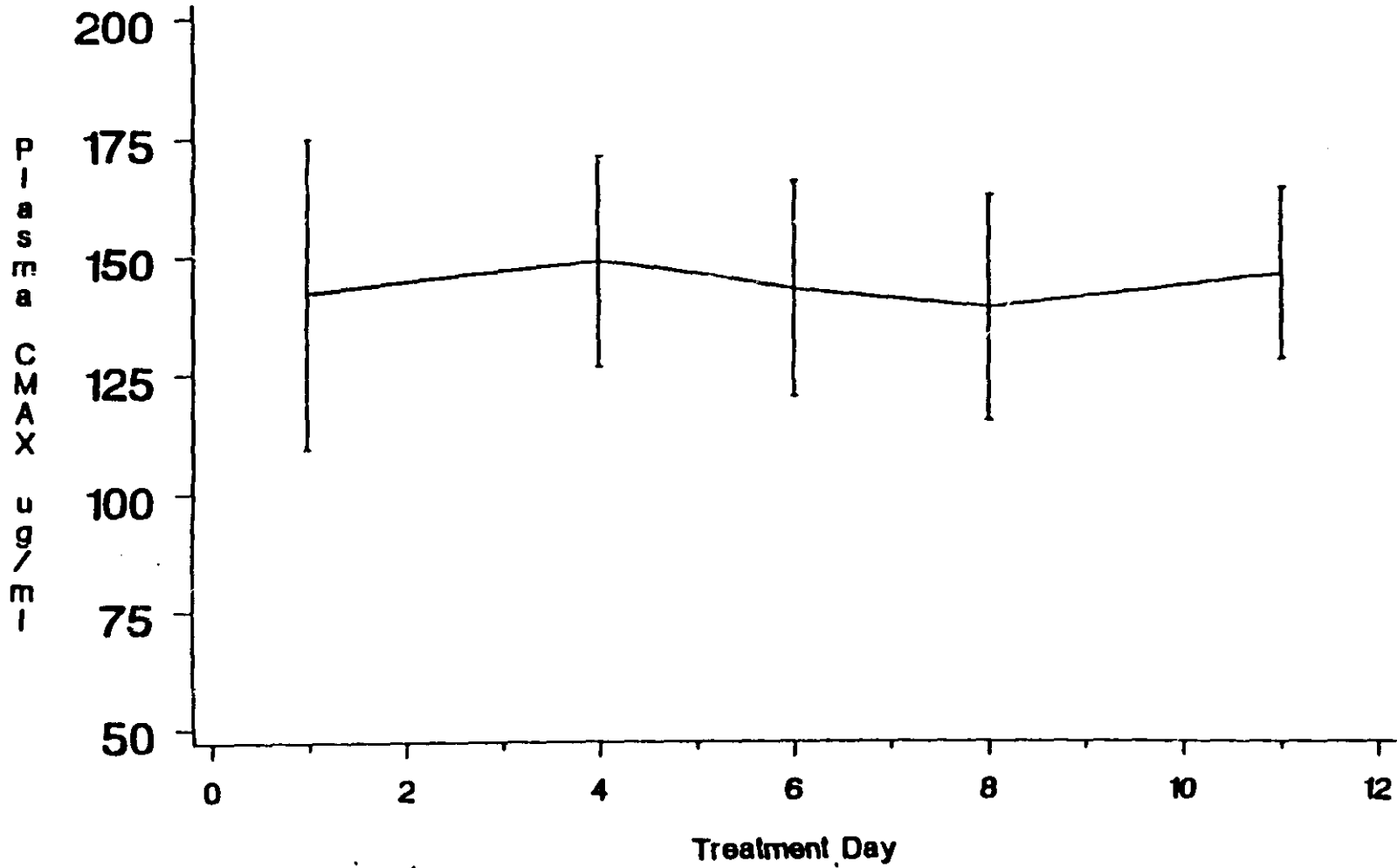
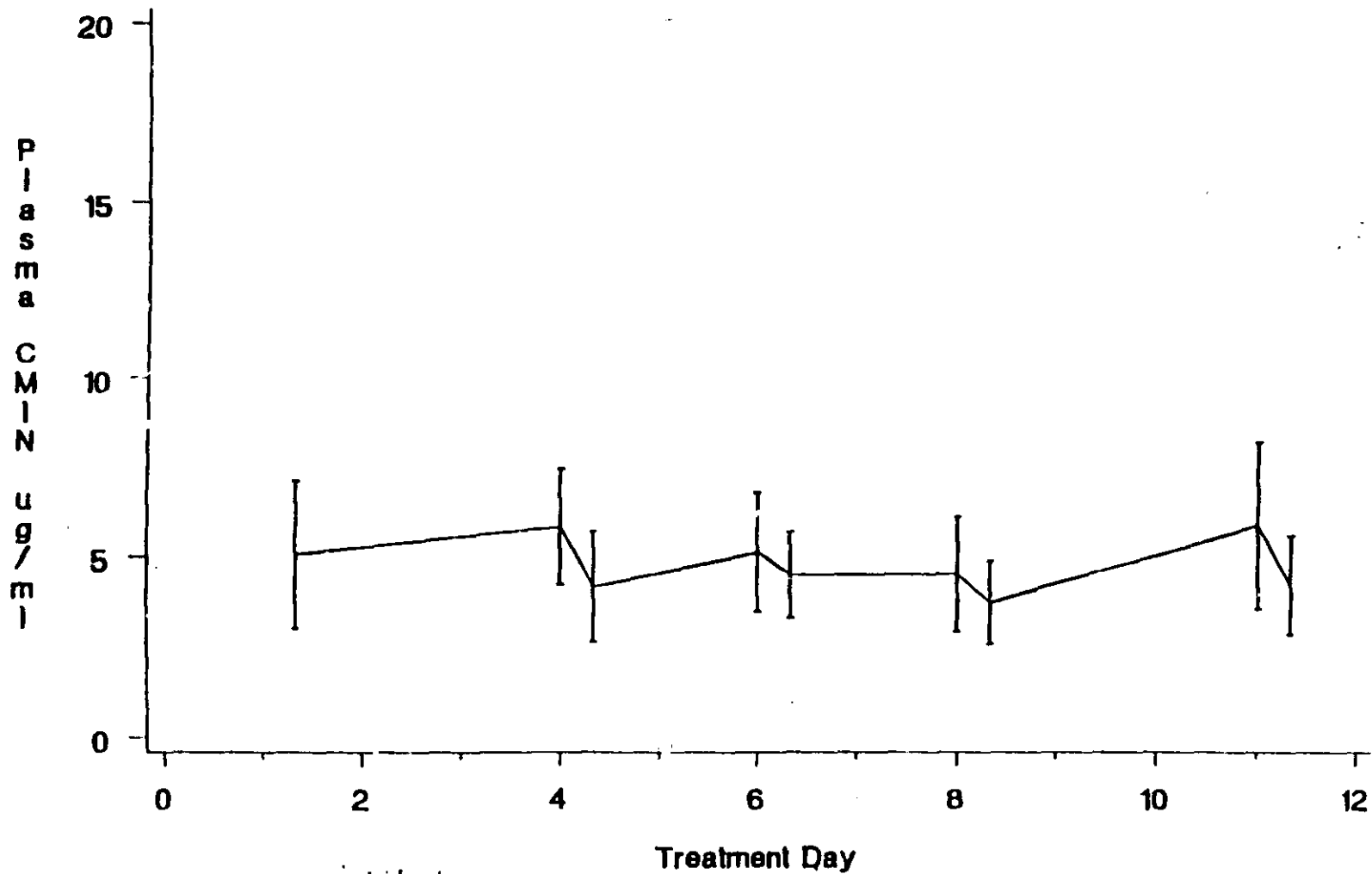


Fig. 16 Mean Plasma Cefepime CMIN vs Treatment Day
Data for 7 Subjects on a q8h Dose Schedule



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Fig. 17 Mean plasma concentrations.

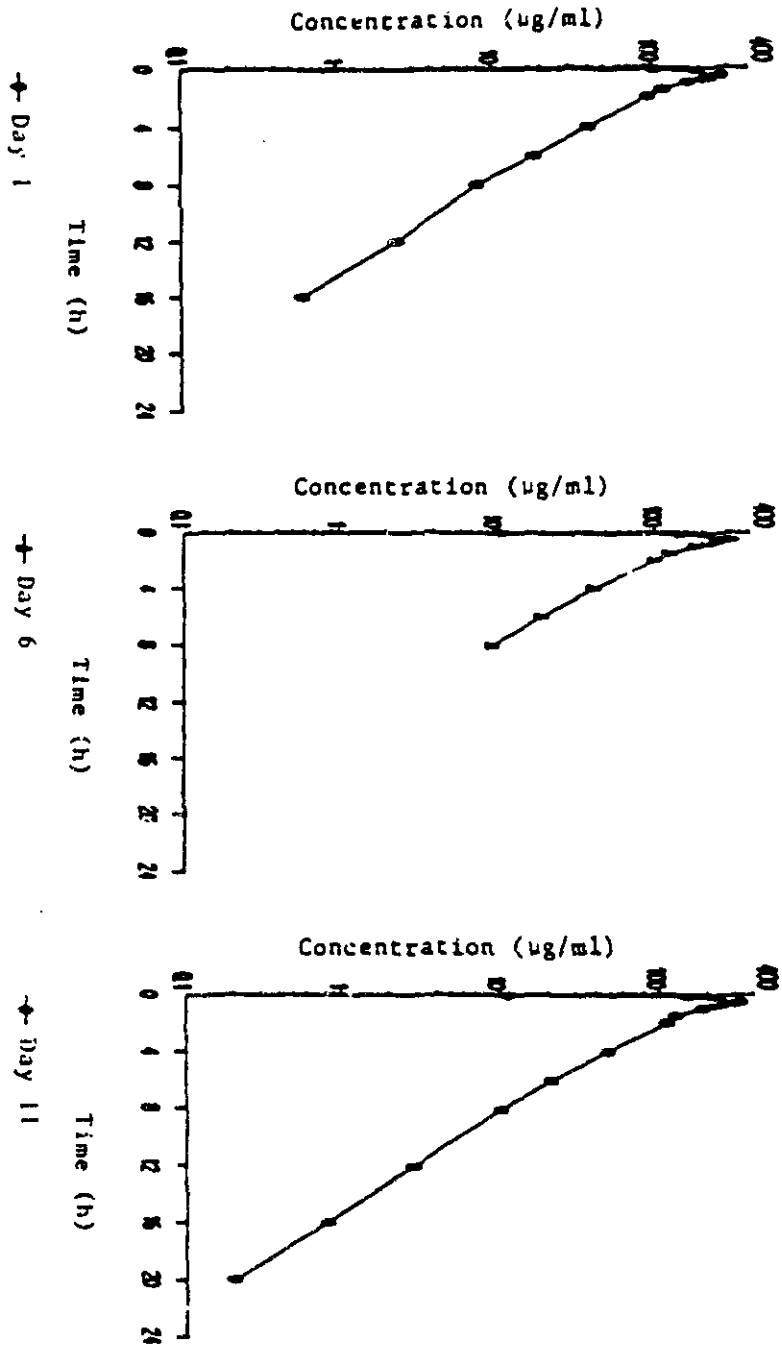
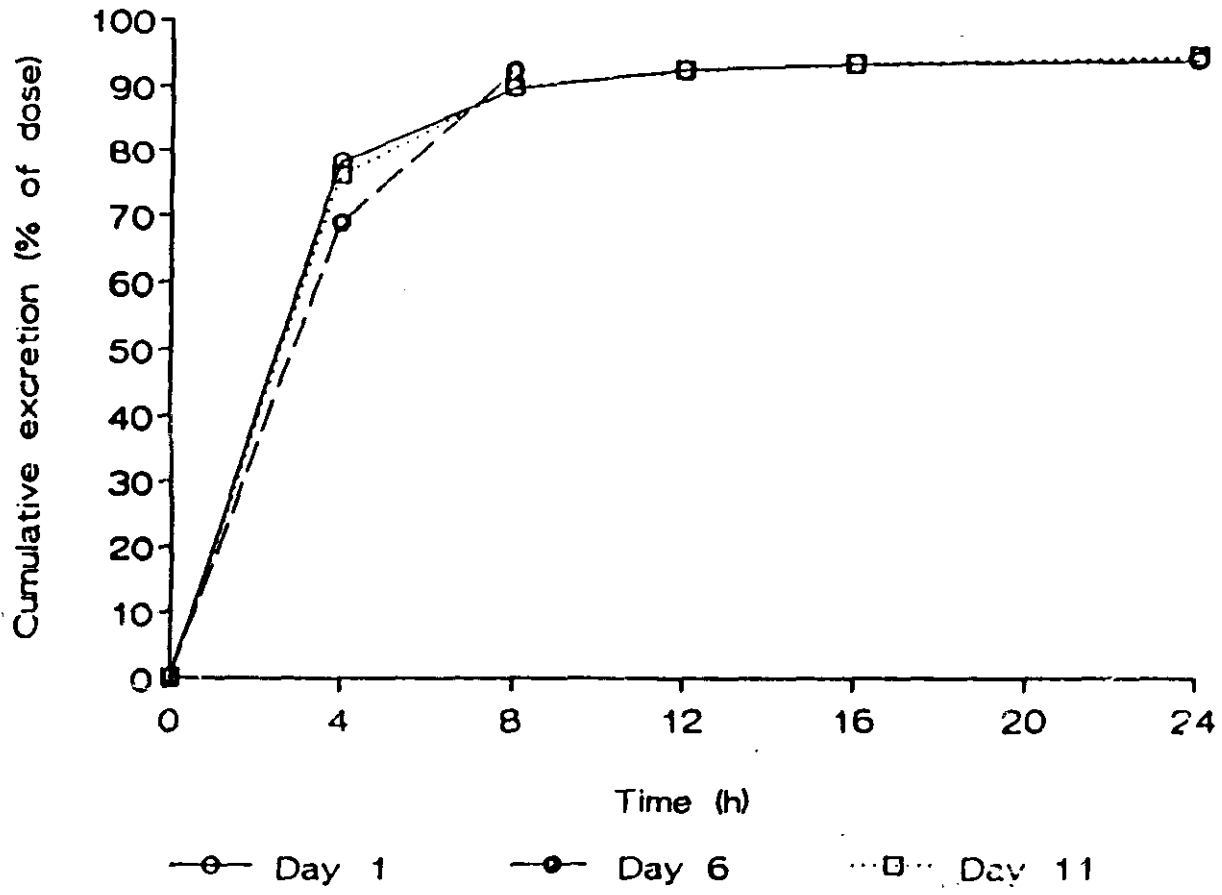


Fig. 18 Mean cumulative urinary excretion of cefepime.



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Fig. 19 Regression of CMAX on Cefepime Dose

CEFEPIME STUDY AI411-096-001
CMAX as a Function of IM Dose (mg)

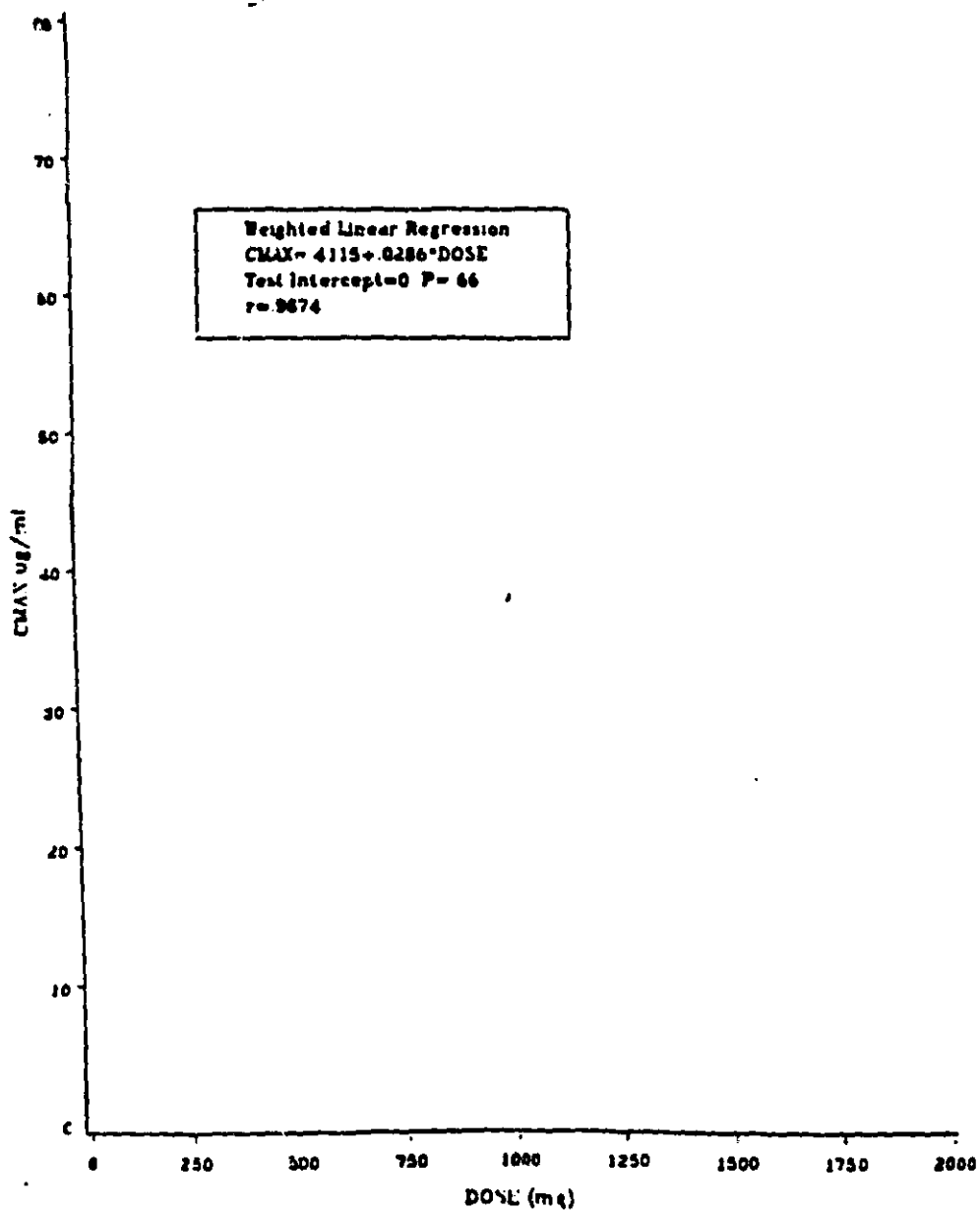


Fig. 20 Regression of AUC on Cefepime Dose

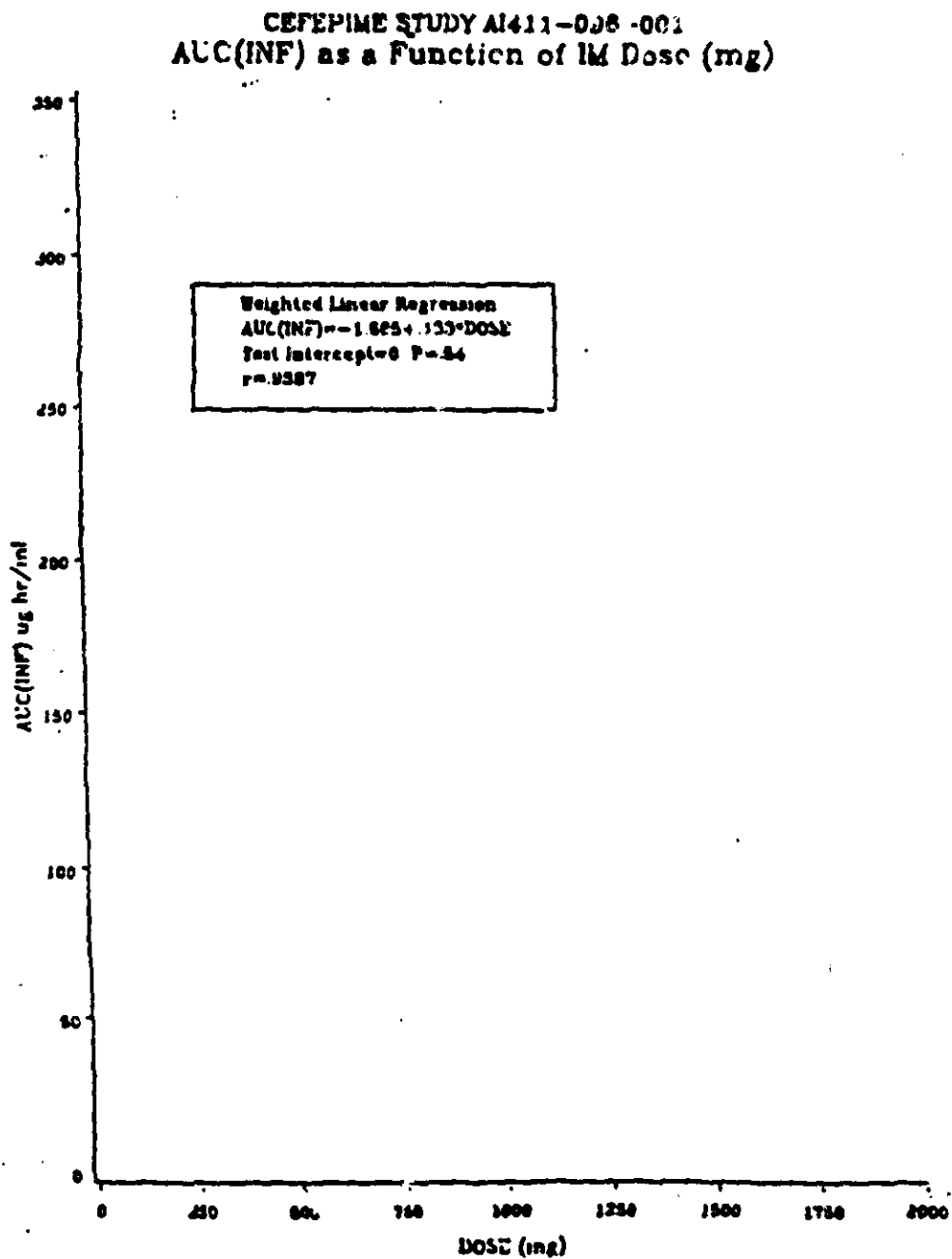


Fig. 21 Mean Plasma Cefepime Concentrations; Multiple-Dose Intramuscular Administration

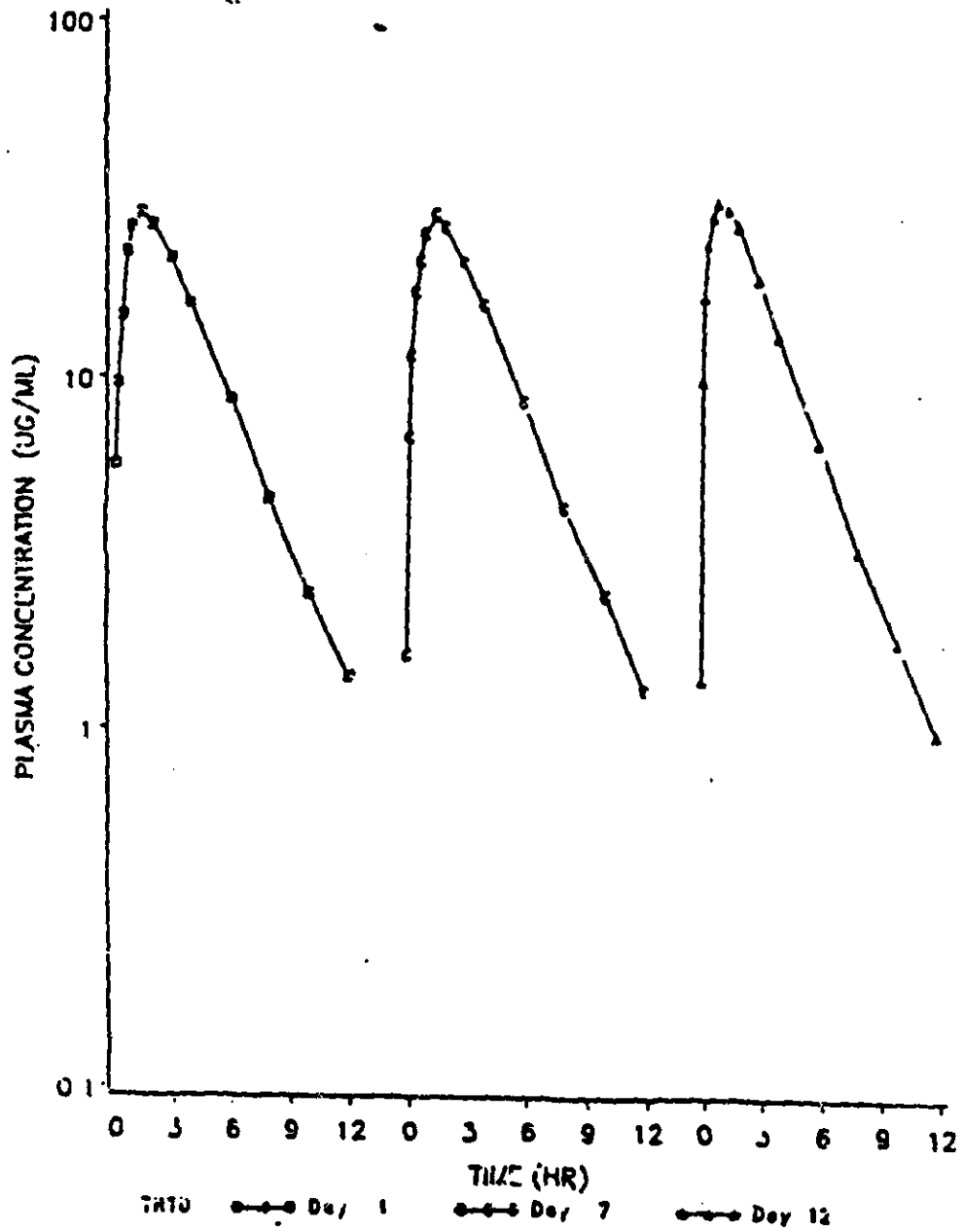


Fig. 22 Mean CMAX and CMIN vs Treatment Day; 1000 mg q12h I.M. Doses

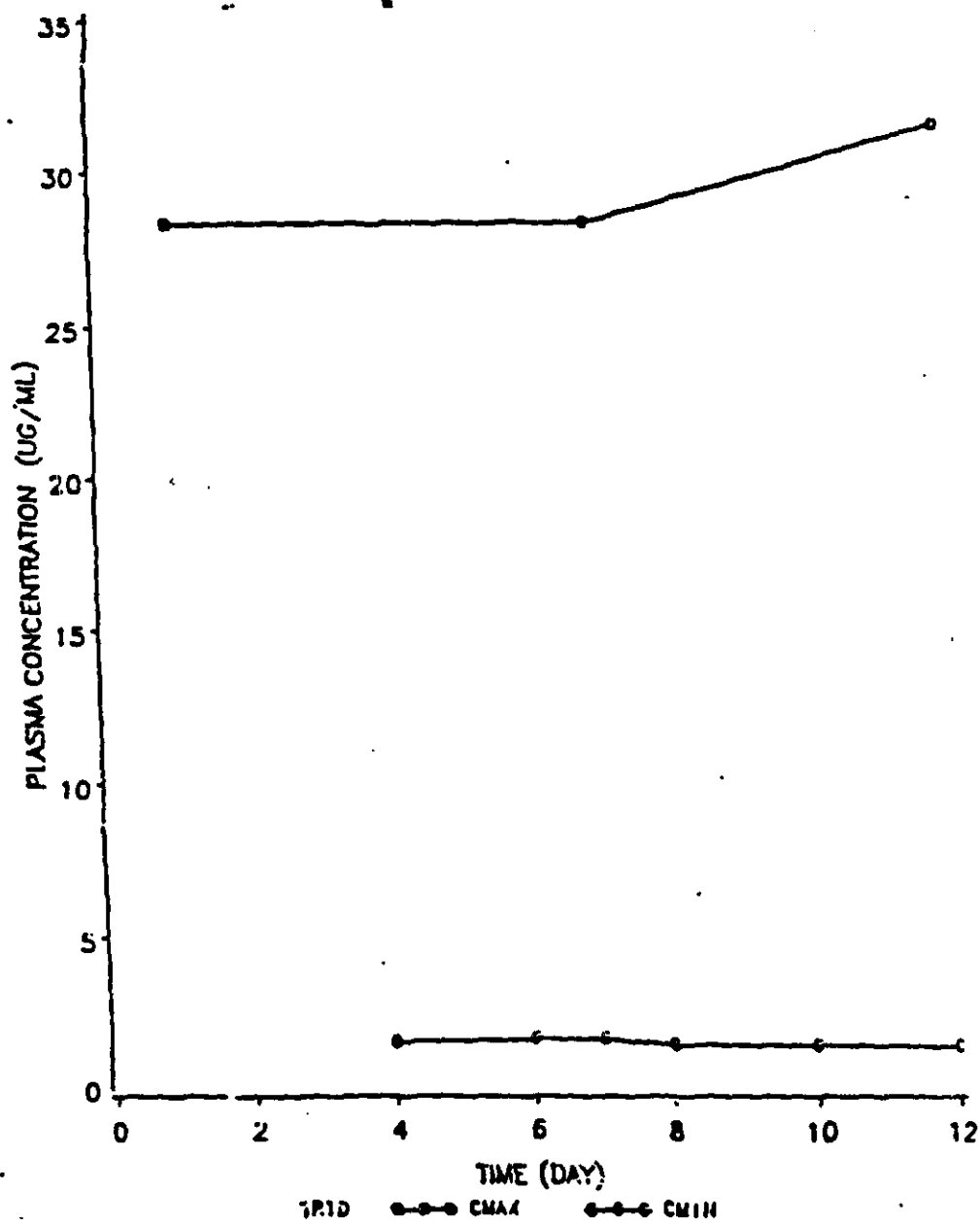


Fig. 23 Mean plasma concentrations of cefepime.

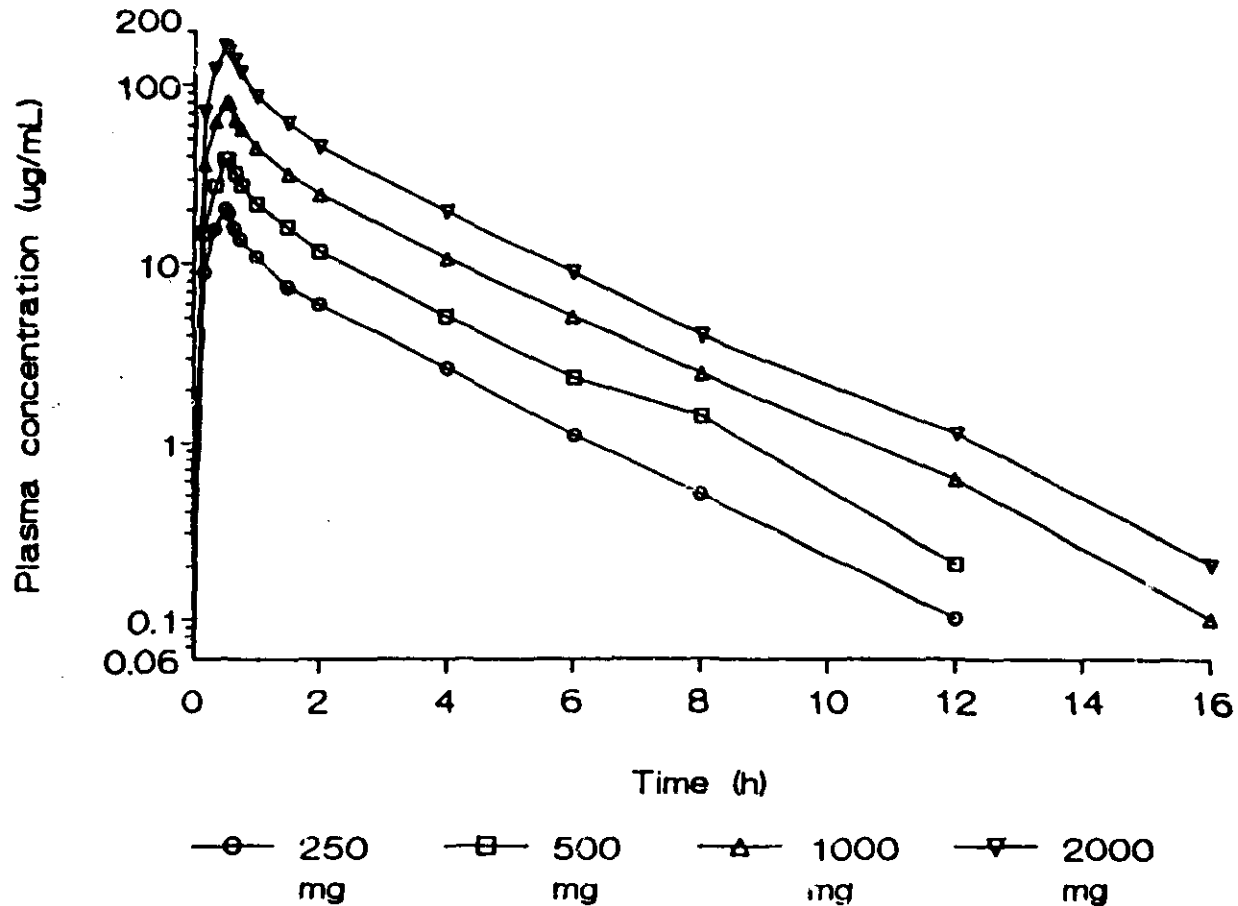


Fig. 24 Peak cefepime plasma levels
as a function of dose.

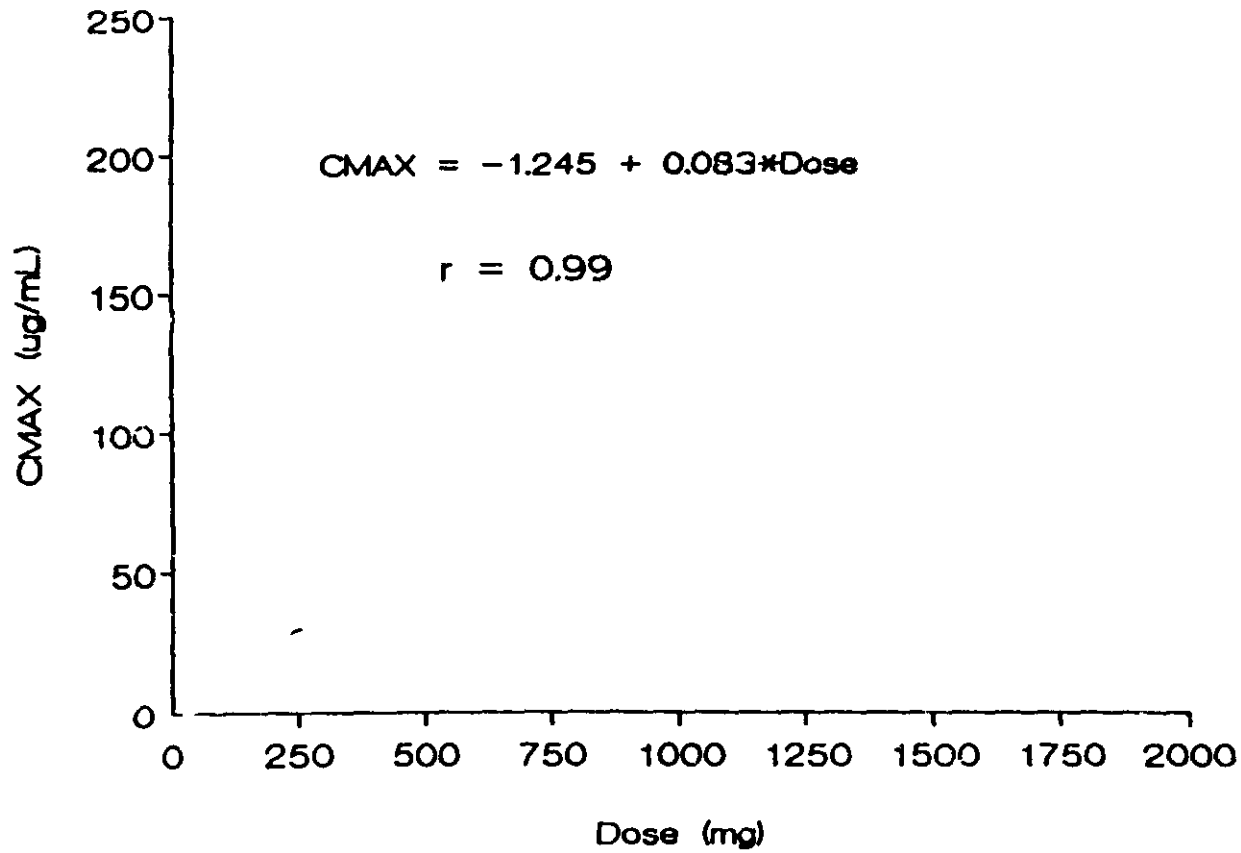
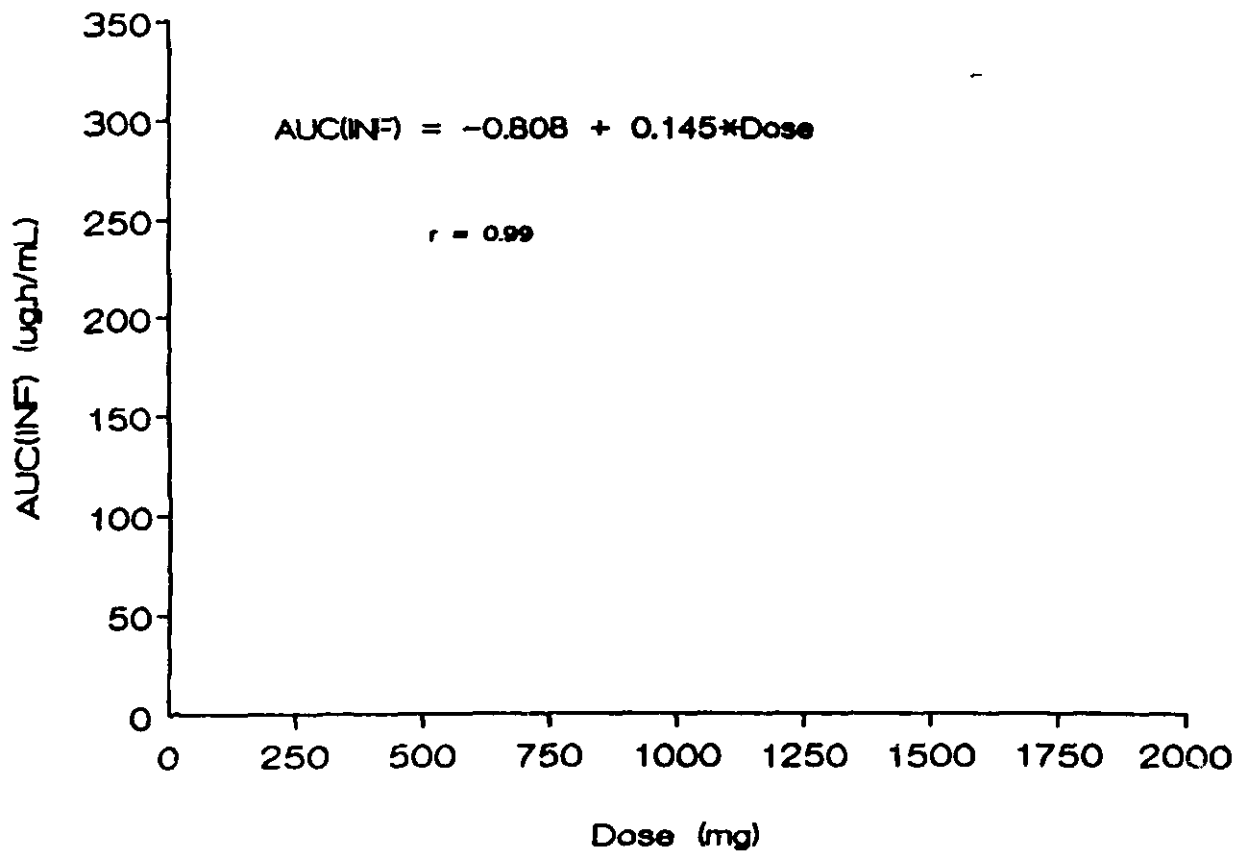


Fig. 25 Area under the curve as a function of dose.



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Fig. 26

Statistical comparison of pharmacokinetic parameters.

Study No. A1011 0M6-001
 Comparison of Two Cefepime (DMY-28142) Formulations
 Dihydrochloride/Arginine and Zwitterion/Sodium Chloride

90% Confidence Intervals
 (Based on Two One-Sided t-tests)

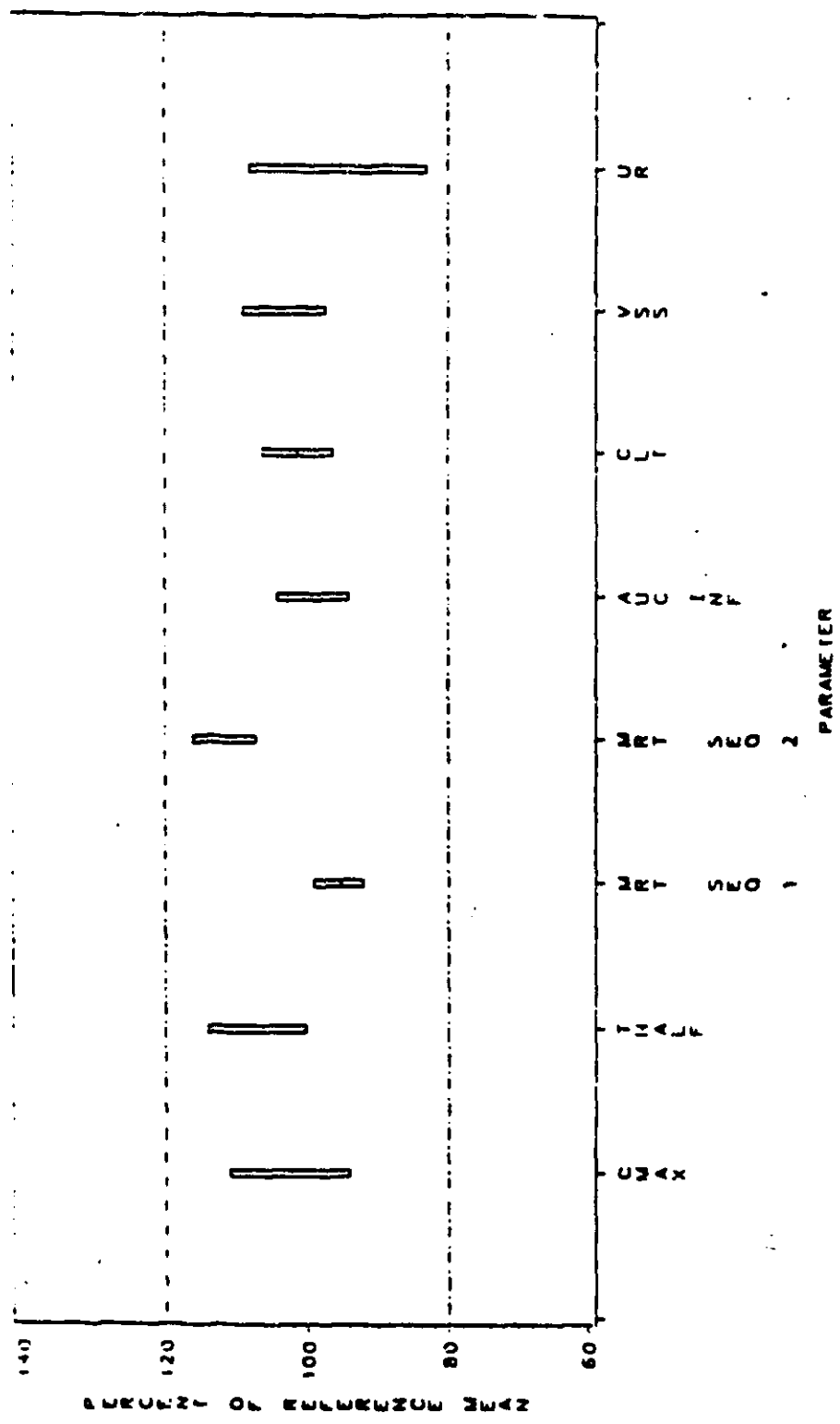


Fig. 27 Proportions of Cefepime, 7-Epimer of Cefepime, NMP and NMP-N-Oxide Excreted in Normal and Renally Impaired Subjects after 1000 mg IV Dose of Radiolabelled Cefepime.

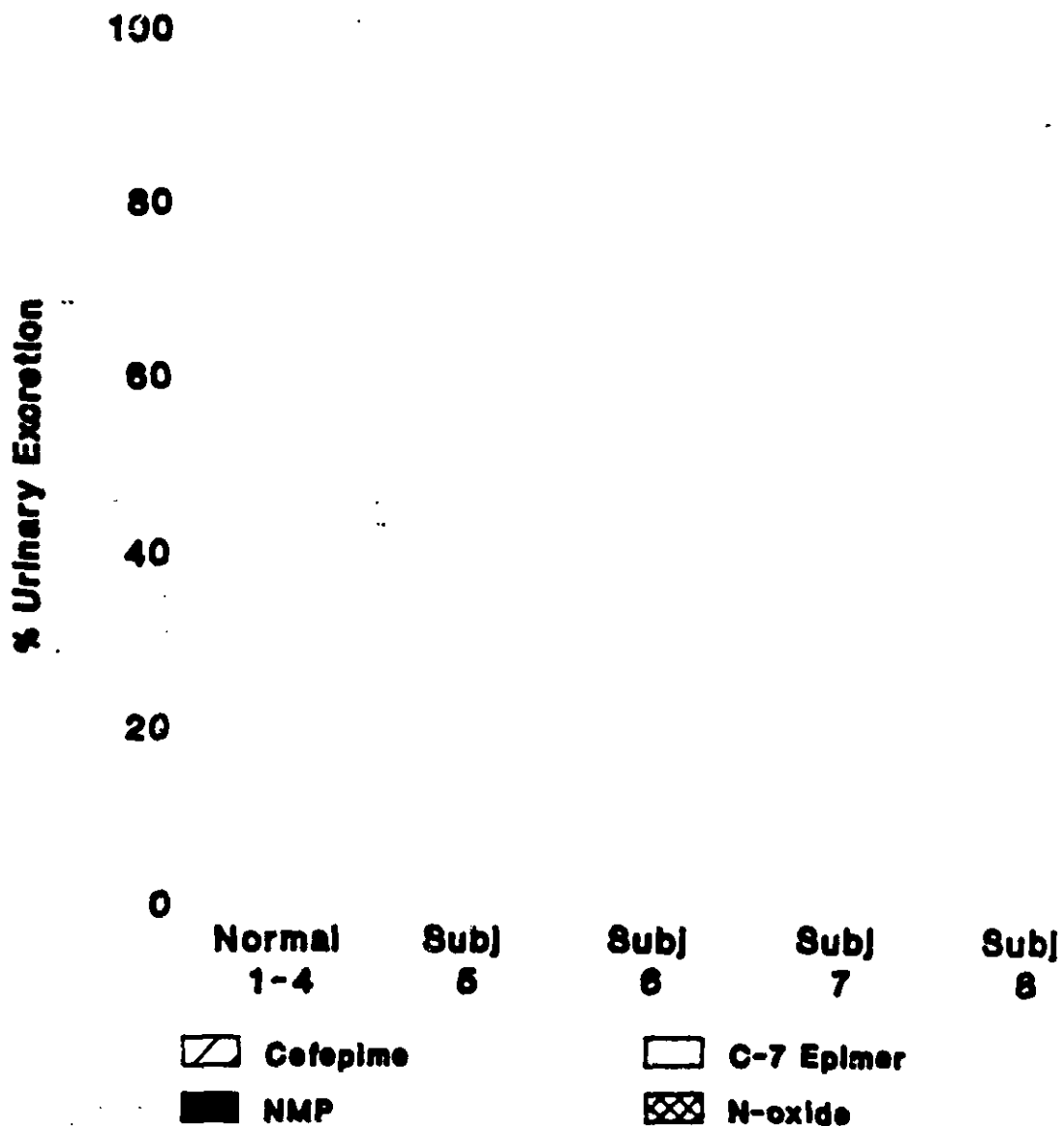


Fig. 28 Mean Plasma Concentrations of Cefepime.

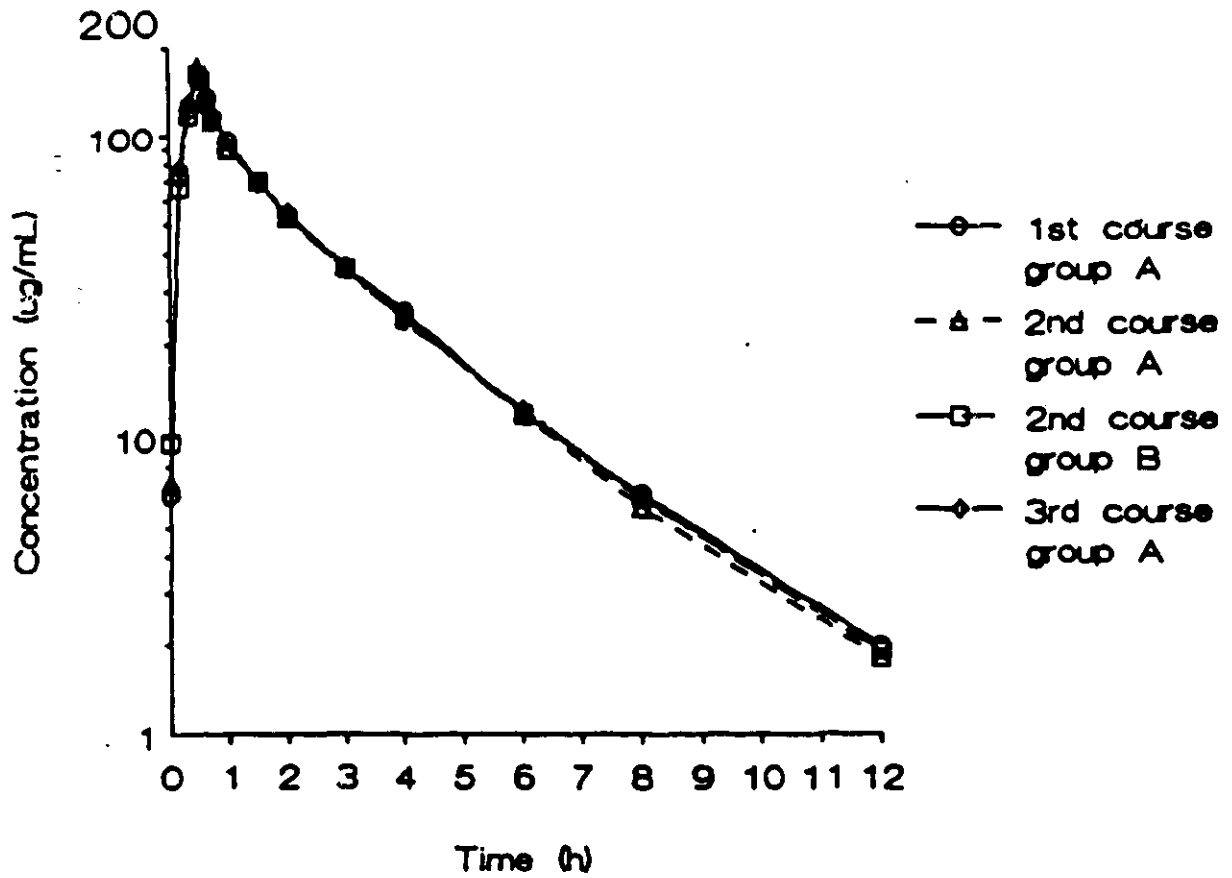
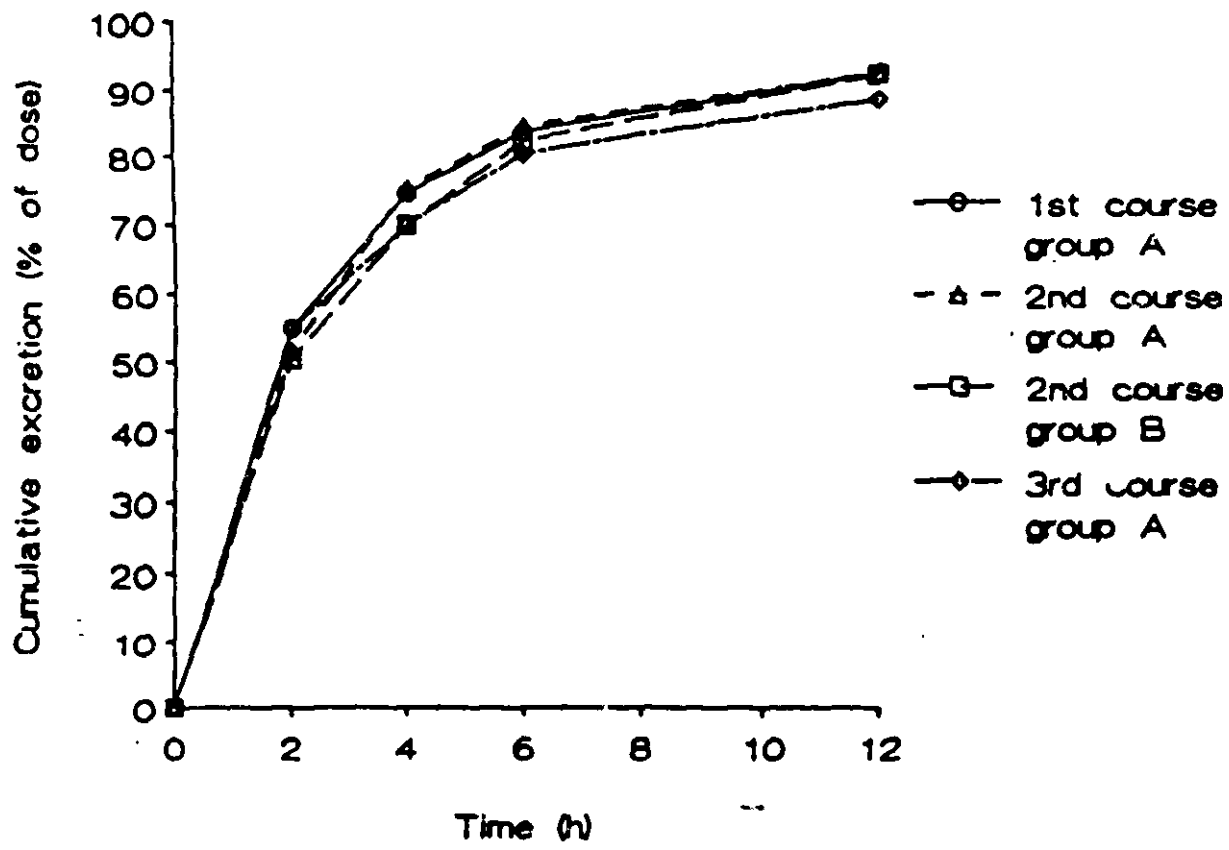


Fig. 29 Mean Cumulative Urinary Excretion of Cefepime.



NDA 50679

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Fig. 30 Mean Plasma Concentrations of Amikacin.

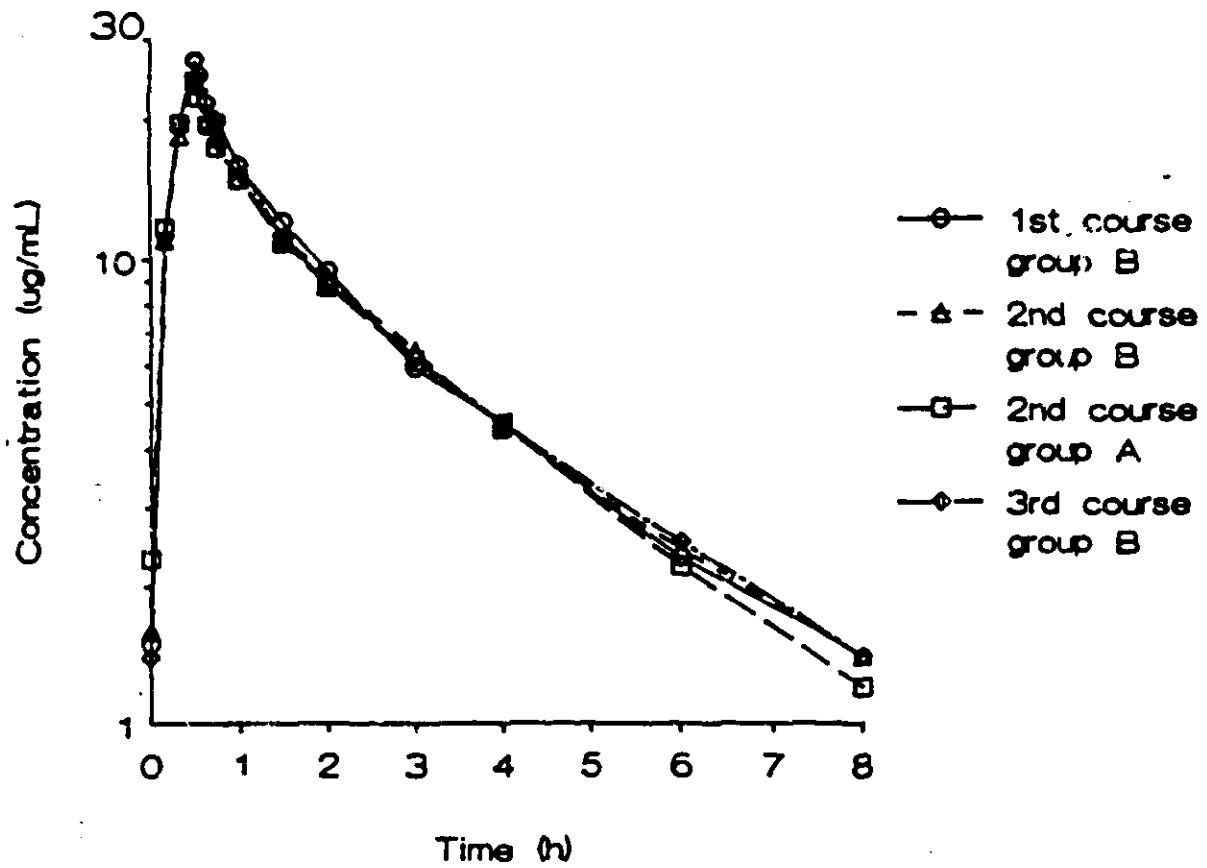


Fig. 31 Mean Cumulative Urinary Excretion of Amikacin.

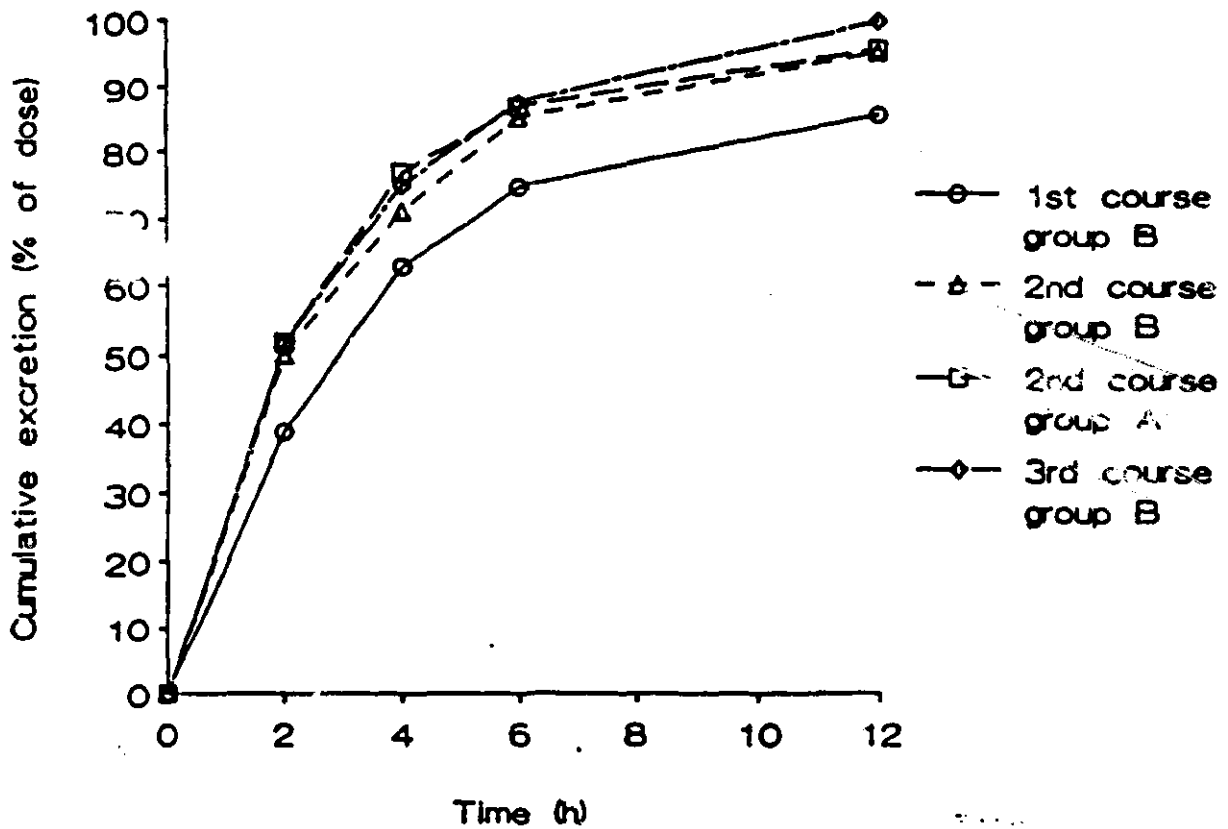
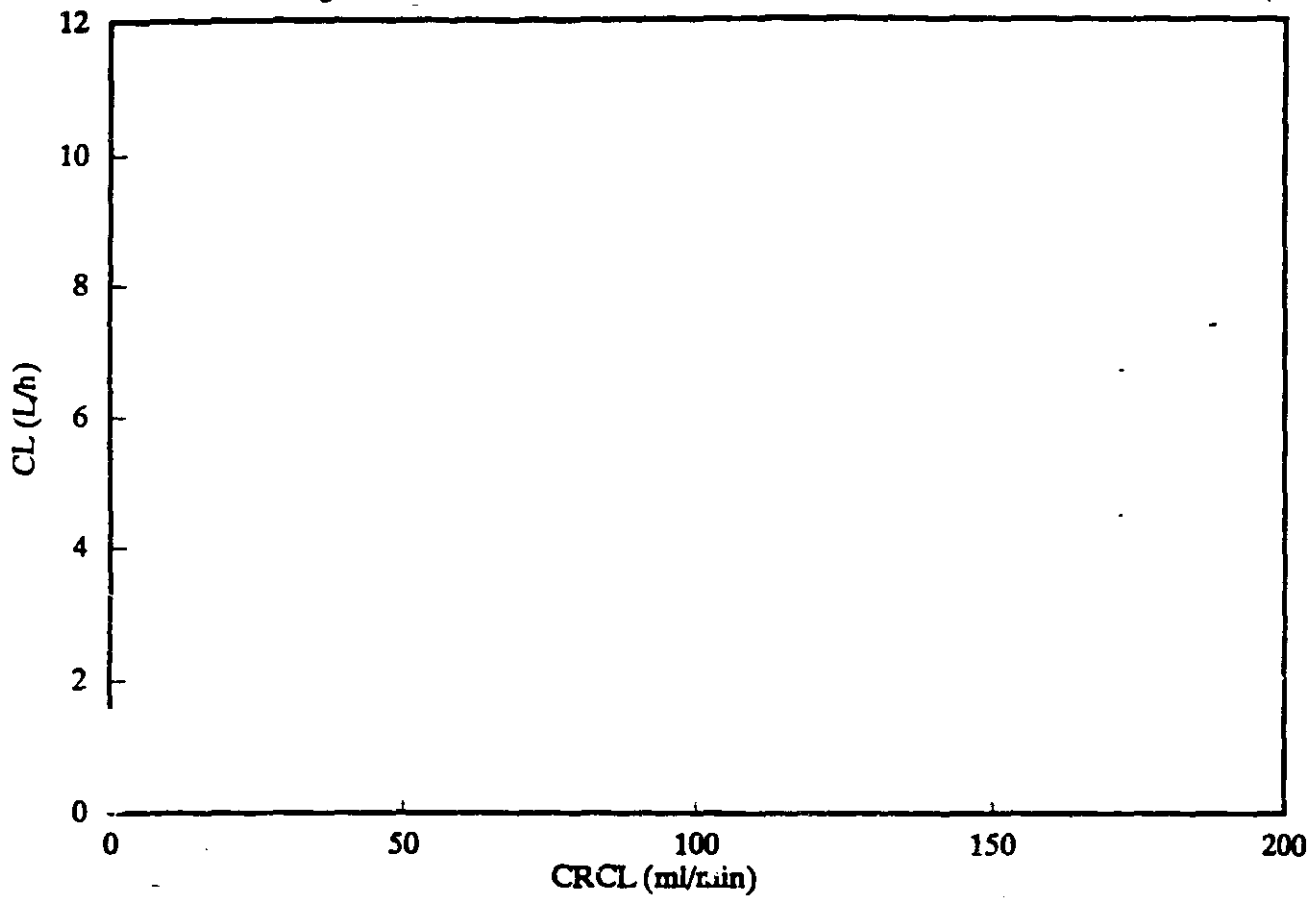
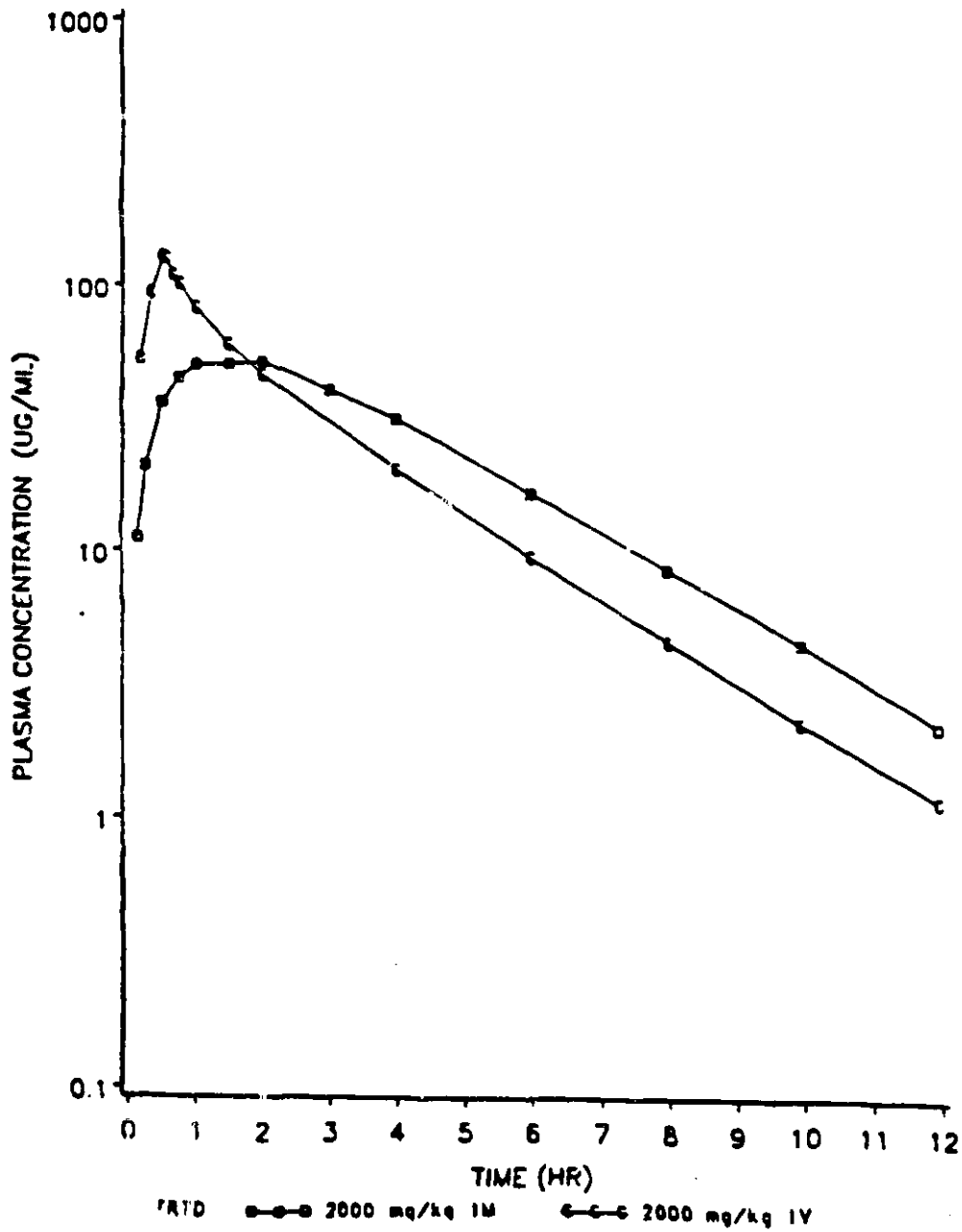


Fig. 32

Total Body Clearance Vs Creatinine Clearance



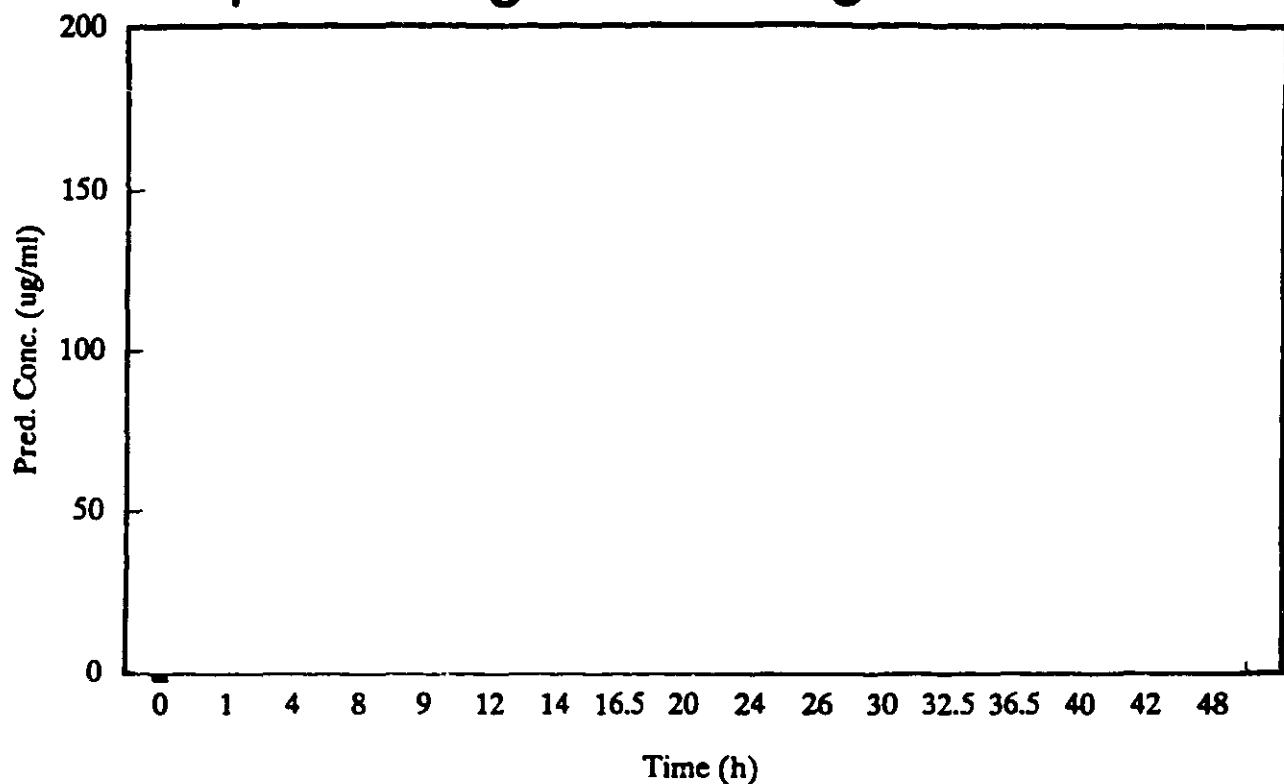
Mean Plasma Cefepime Concentrations; Single 2000 mg
Intramuscular and Intravenous Administration



g8a?

Fig. 33

Multiple Dosing in Av. 70 Kg Pts.: Diff. CRCL



- 2 g q8h, CRCL = 120 ml/min
- ◆— 2 g q12h, CRCL = 45 ml/min
- ▲— 2 g q24h, CRCL = 15 ml/min

Fig. 34 Multiple Dosing: Different CRCL .

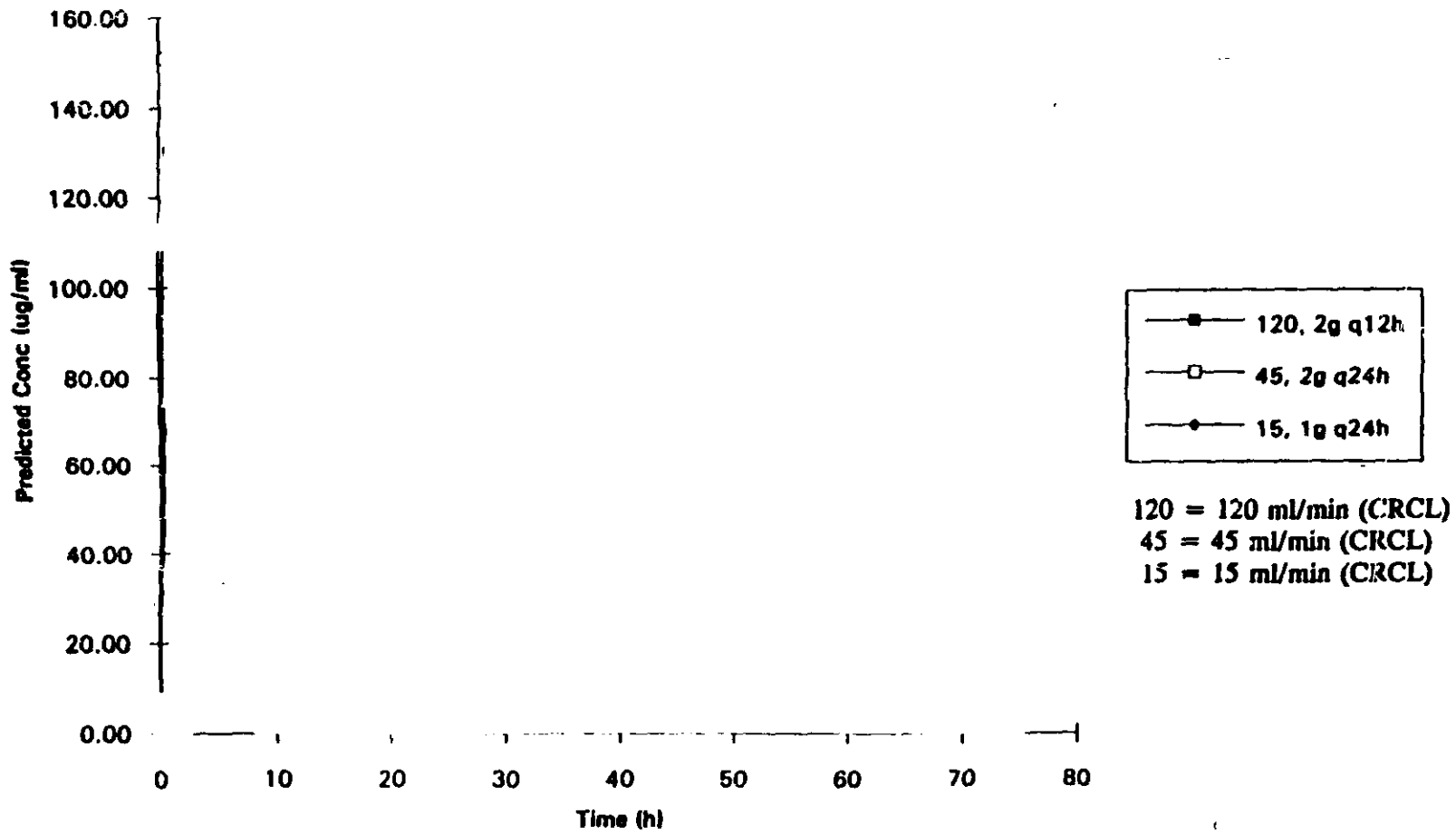


Fig. 35 Dosage Regimens: Different CRCL.

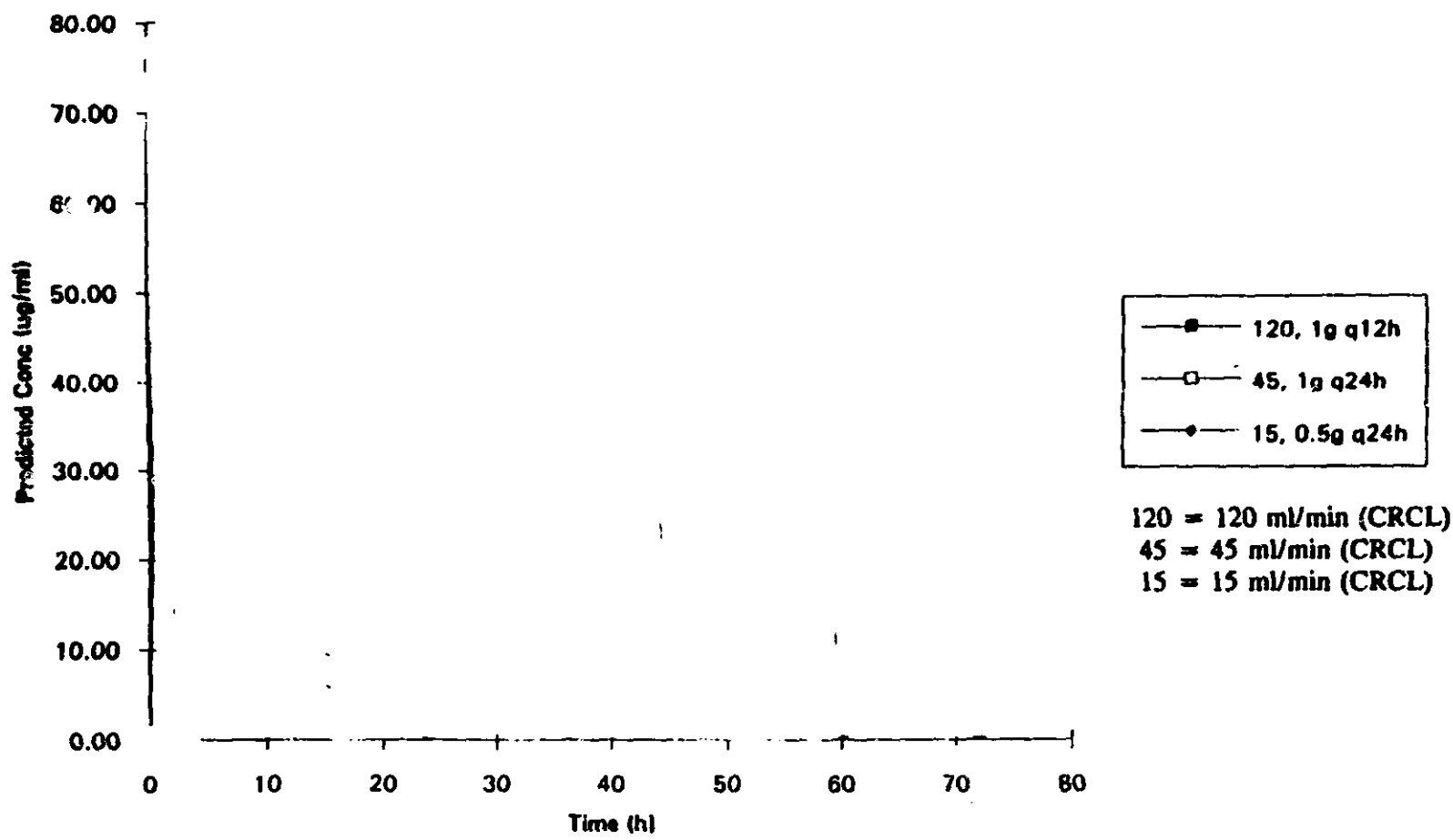


Fig. 36

V1 Vs WT

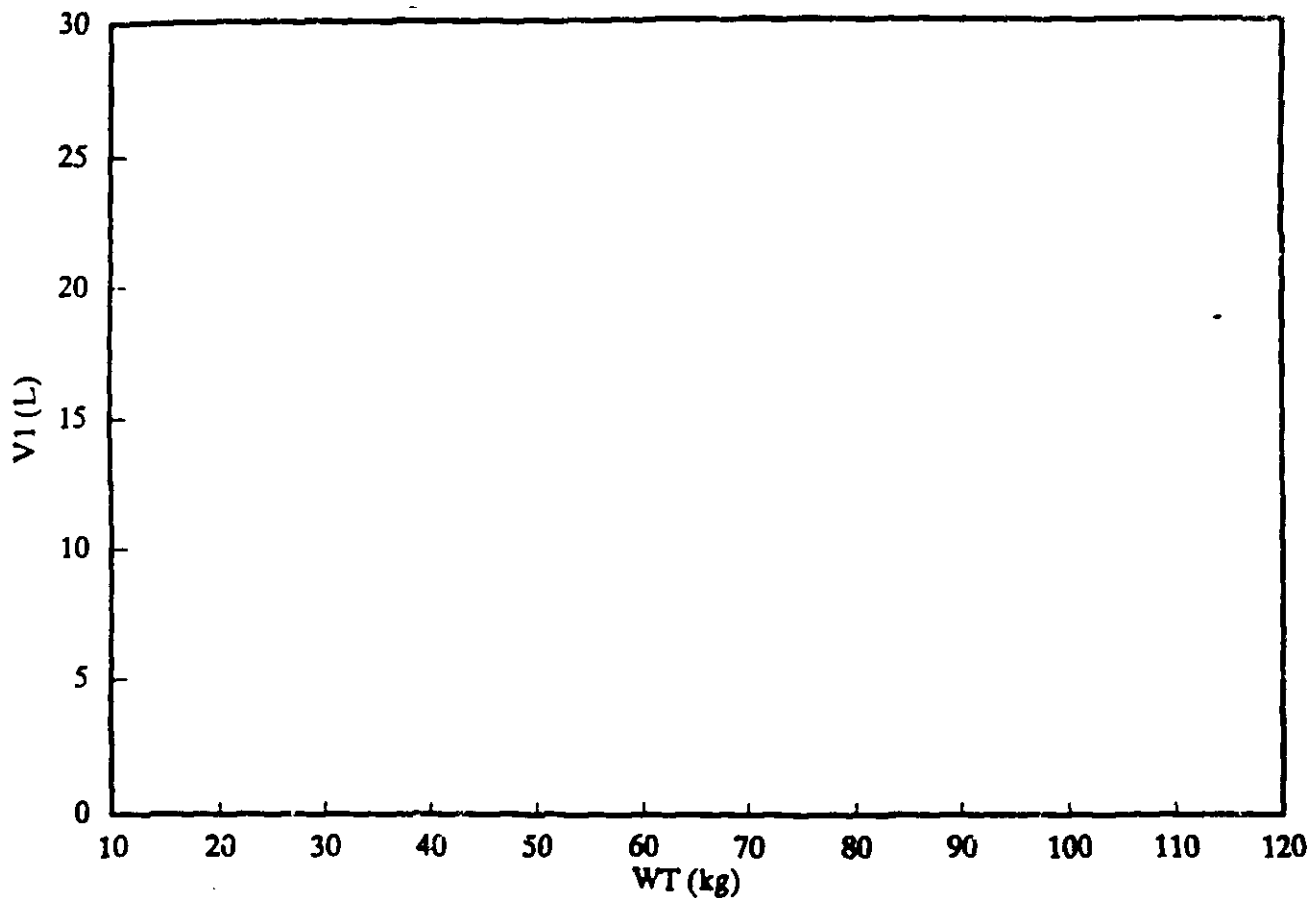


Fig. 37

Intercompartmental Clearance (Q) Vs. Weight

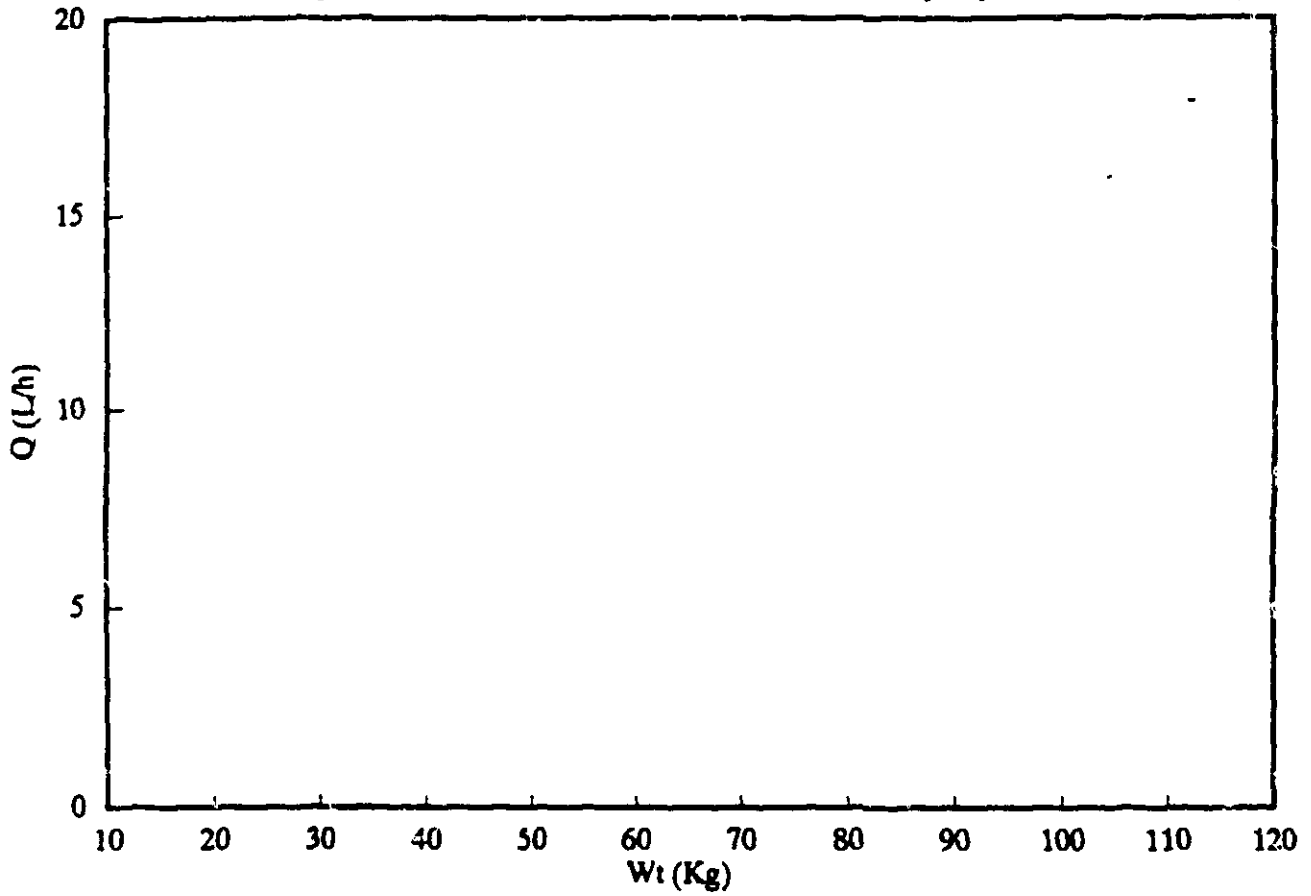


Fig. 38

Vol. of Peripheral Compartment Vs. Weight

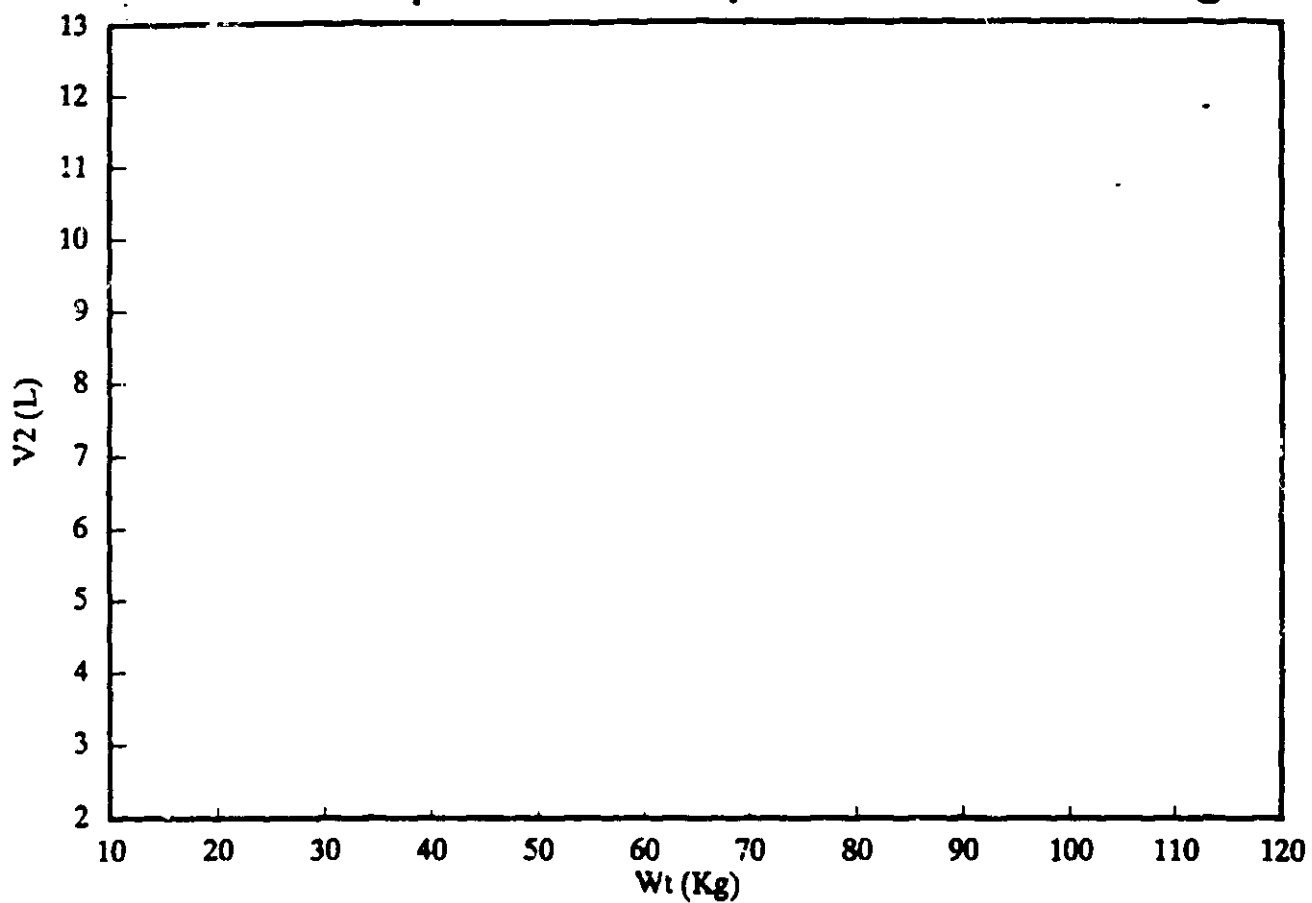


Fig. 39

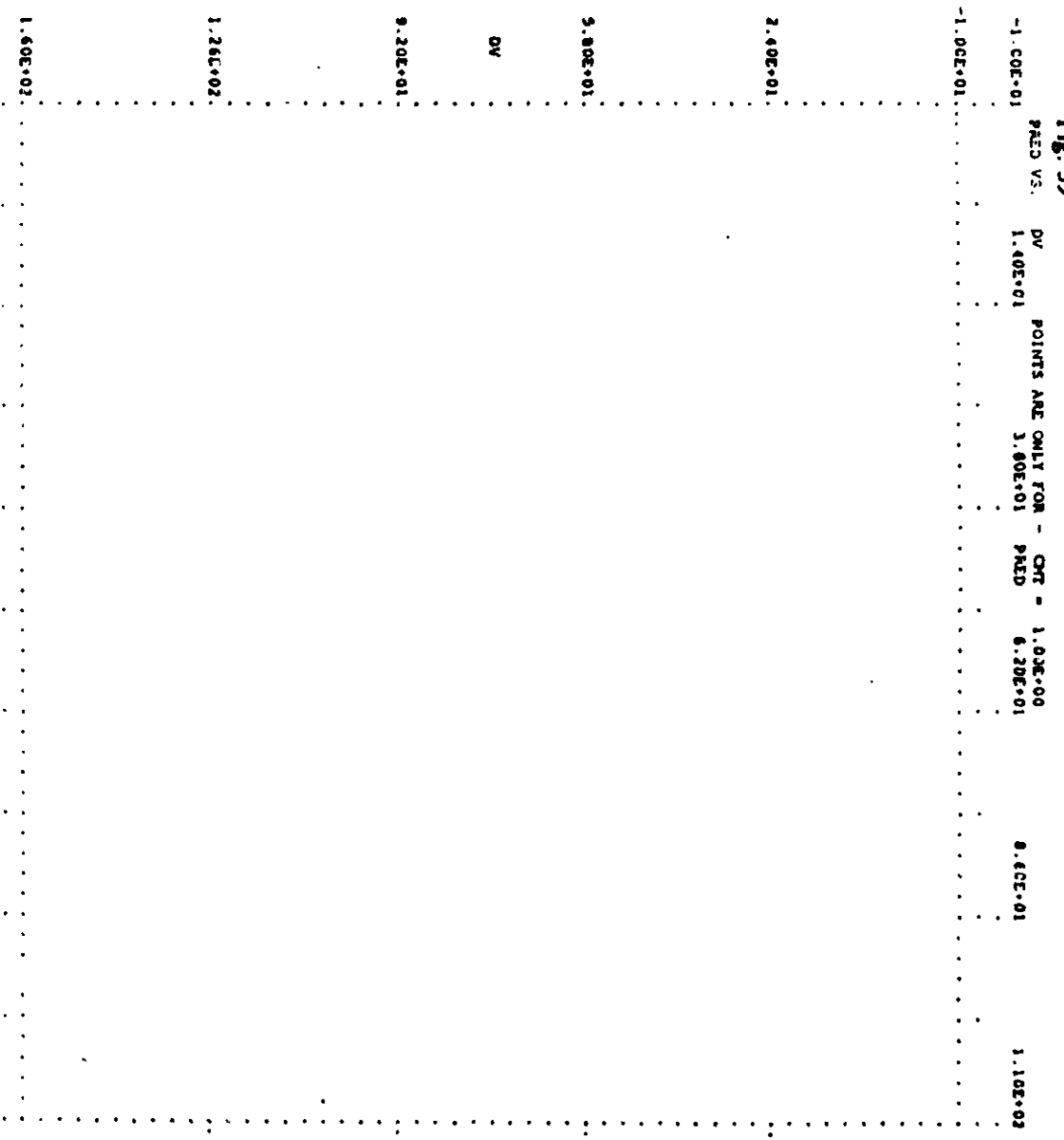


Fig. 40 Total Body Clearance Vs. CRCL

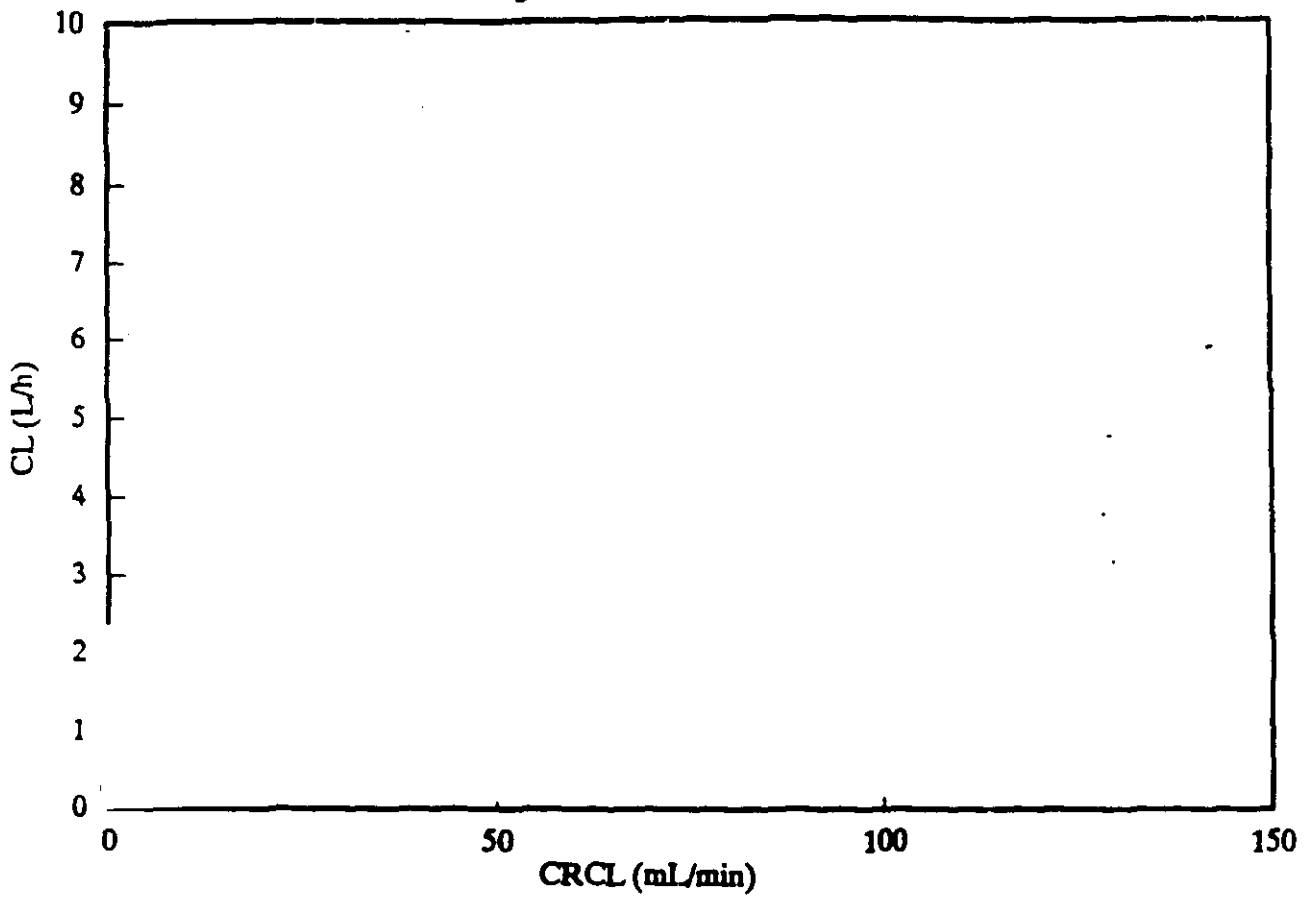


Fig. 41 Total Body Clearance Vs. CRCL

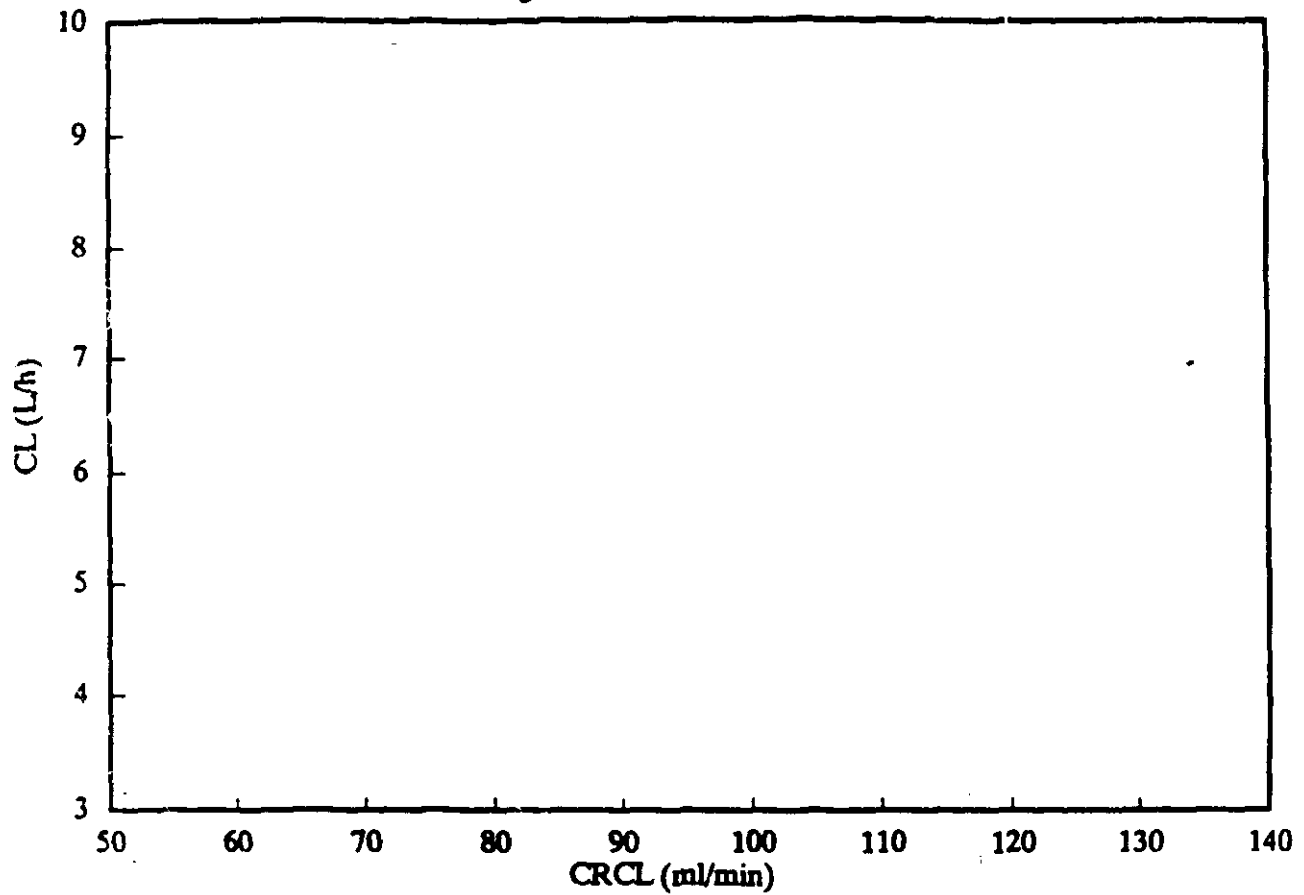
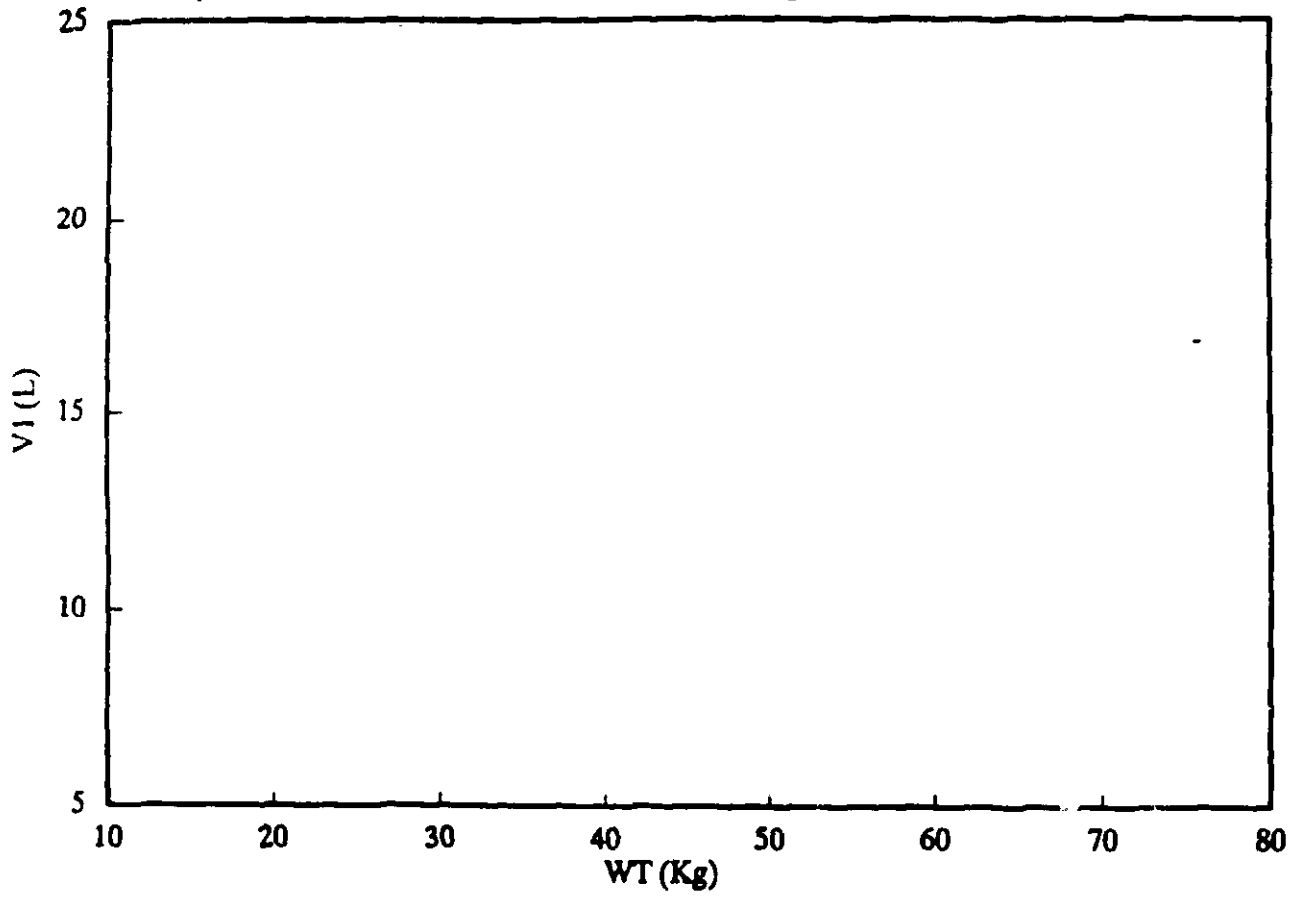


Fig. 4.2

V1 Vs Weight



Felton 4/13/94

CLINICAL PHARMACOLOGY (page 2)

The average plasma concentrations of cefepime observed in healthy adult male volunteers at various times following single 30-minute infusions (IV) of Maxipime® 500 mg, 1 g and 2 g are summarized in Table 1. Elimination of cefepime is principally via renal excretion with an average (1 SD) half-life of 2.0 (± 0.3) hours and total body clearance of 120.0 (± 8.0) mL/min in healthy volunteers. Cefepime pharmacokinetics are dose independent over the range 250 mg to 2 g. There is no evidence of accumulation in healthy adult volunteers receiving doses up to 2 g IV every 8 hours for a period of 9 days. There is moderate intersubject variability in cefepime pharmacokinetics (Table 1).

unapproved

ABSORPTION

Cefepime is rapidly and completely absorbed after IM administration. The average plasma concentrations in healthy adult volunteers at various times following a single intramuscular (IM) injection of Maxipime® 500 mg are summarized in Table 1. The relative bioavailability is 100%. (EXAM)

TABLE 1				
Average Plasma Concentrations (ug/mL) of Cefepime and Derived Pharmacokinetic Parameters.				
Parameter	Maxipime® Dose			
	500 mg IV	1 g IV	2 g IV	500 mg IM
0.5 hr	38.2	78.7	163.1	8.2
1.0 hr	21.6	44.5	85.8	12.5
2.0 hr	11.6	24.3	44.8	12.0
4.0 hr	5.0	10.5	19.2	6.9
8.0 hr	1.4	2.4	3.9	1.9
12.0 hr	0.2	0.6	1.1	0.7
C _{MAX} , ug/mL	34.0(5.7)	67.9(7.7)	125.7(21.7)	13.9(3.4)
T _{MAX} , hr	0.5(0.0)	0.5(0.0)	0.5(0.1)	1.4(0.9)
AUC, hr*ug/mL	60.7(11.0)	138.0(17.0)	245.0(35.0)	60.0(8.0)
N	17	14	7	6

() 1 SD.

DISTRIBUTION

The average steady state volume of distribution of cefepime is 18.0 ($\pm$ 2.0) L. The serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum. Cefepime is excreted in human milk. The nursing infant dose would be approximately 0.5 mg/day (see **PRECAUTIONS**).

Concentrations of cefepime achieved in specific tissues and body fluids are listed in Table 2.

Tissue or Fluid	Dose/Route	# of Patients	Average Time of Sample Post-Dose (hr)	Average Concentration
Urine	500 mg IV	8	0-4	292 ug/mL
	1 g IV	12	0-4	926 ug/mL
	2 g IV	12	0-4	3120 ug/mL
Blister Fluid	2 g IV	6	1.5	81.4 ug/mL
Bronchial Mucosa	2 g IV	20	4.8	24.1 ug/g
Sputum	2 g IV	5	4.0	7.4 ug/mL

*Need Serum
Cefepime*

15x

METABOLISM

Cefepime is metabolized to N-methylpyrrolidine (NMP) which is rapidly converted to the N-oxide (NMP-N-oxide).

EXCRETION

Urinary recovery of unchanged cefepime accounts for approximately 90% of the administered dose. Less than 1% of the administered dose is recovered from urine as NMP, 6.8% as NMP-N-oxide, and 2.5% as an epimer of cefepime. Because renal excretion is a significant pathway of elimination, dosing adjustment in patients with mild to moderate renal dysfunction is necessary (see **DOSAGE AND ADMINISTRATION**). In patients with severe renal dysfunction or undergoing hemodialysis, dosing must be modified (see **DOSAGE AND ADMINISTRATION**).

SPECIAL POPULATIONS

GERIATRIC: Cefepime pharmacokinetics have been investigated in elderly (65 years of age and older) men and women whose creatinine clearance was 74.0 ($\pm$ 15.0) mL/min. There appeared to be a decrease in cefepime total body clearance as a function of creatinine clearance. Therefore, dosage administration of cefepime in the elderly should be adjusted as appropriate if the patient's creatinine clearance is 60 mL/min or less (see **DOSAGE AND ADMINISTRATION**).

CYSTIC FIBROSIS: The pharmacokinetics of cefepime have been investigated in cystic fibrosis patients. The pharmacokinetics in this patient group is not different from the population average parameters. Therefore, it is not necessary to alter the dosage of cefepime in this patient population.

RENAL INSUFFICIENCY: Cefepime pharmacokinetics have been investigated in patients with renal insufficiency. The average half-life in severely impaired patients requiring dialysis therapy is 13.5 ($\pm$ 2.7) hours for hemodialysis or 19.0 ($\pm$ 2.0) hours for continuous peritoneal dialysis. Cefepime total body clearance decreased proportionally with creatinine clearance in patients with abnormal renal function, which serves as the basis for dosage adjustment recommendations in this group of patients (see **DOSAGE AND ADMINISTRATION**).

HEPATIC INSUFFICIENCY: The pharmacokinetics of cefepime have been investigated in patients with impaired hepatic function who received a 1 g dose. Since the pharmacokinetics were not altered, a dosage adjustment is not required for patients with hepatic dysfunction.

GERIATRIC USE (page 16)

2 nd paragraph

In elderly patients, dosage and administration of cefepime should be adjusted as appropriate for patients with creatinine clearance of 60 mL/min or less.

DOSAGE AND ADMINISTRATION (page 7)

TABLE 7

Creatinine Clearance (mL/min)	Normal Recommended Dosing Schedule		
	500 mg q12h	1 g q12h	2 g q12h
>60	Usual dose, no adjustment necessary .		
30-60	500 mg q24h	1 g q24h	2 g q24h
11-30	500 mg q24h	500 mg q24h	1 g q24h
<=10	250 mg q24h	250 mg q24h	500 mg q24h

Corres

memos

NDA 50-679 -

Hugh McIlhenny, Ph.D.
Director
Worldwide Regulatory Affairs
Bristol-Myers Squibb Co.
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

APR 27 1993

Dear Dr. McIlhenny

Please refer to your New Drug Application (NDA) dated June 30, 1992, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for cefepime hydrochloride injection.

We also refer to a telephone conversation held on April 26, 1993, between you and Mr. Carmen DeBellis of the Division of Anti-Infective Drug Products. During this conversation a mutual agreement was reached to extend the review clock for this NDA 150 days from April 28, 1993 to September 25, 1993.

Therefore the new due date will be September 25, 1993.

If you have question concerning this NDA, please contact Mr. Carmen DeBellis, of the Project Management Staff at 301-443-6797.

Sincerely yours,

Lillian Gavrilovich, M.D.
Deputy Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CC:

Orig NDA
50-679
HFD-520
HFD-82
HFD-473
HFD-730
HFD-500
HFD-520/SMO/Albrecht
HFD-520/MO/Sherman
HFD-638

Concurrence:

HFD-520/SCSO/Bona

~~HFD-520/CSO/DeBellis~~
EXTENSION

4/27/93
/s/ [signature]

MEMORANDUM OF A TELEPHONE CONVERSATION

Date: March 25, 1993

Between:

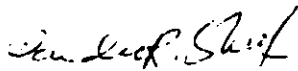
Mr. Hugh McIhenny, Dr. Kessler and Dr. Fung-Tomc
Bristol-Myers Squibb Co
Ph. 203-284-7879

And: Pandu Soprey
Microbiologist, HFD-520

Subject: NDA 50-679, Cefepime
Microbiology Section of the Labelling

1. The proposed text of the label included in the NDA was discussed.
2. Inclusion of and limits for *Neisseria gonorrhoeae* and *Haemophilus influenzae* as quality control organisms was discussed.

The applicants agreed that the proposed label included in the NDA need to be changed and the applicant intend to submit a modified package label during June-July, 93.


Pandur R. Soprey

4/16/93

cc:
Orig. NDA #50-679
HFD-473
HFD-635
HFD-502
HFD-520
HFD-520/Micro/Soprey
HFD-520/MO/Sherman
HFD-520/Pharm/Mainigi
HFD-520/Chem/Roy
HFD-520/CSO/DeBellas
HFD-520/Smicro/Asheldon B 4/24/93
HFD-520/DepDir/Lgavrilovich

NDA 50-679-

Ms. Elizabeth A. Garofalo
Chemistry, Manufacturing & Controls
Worldwide Regulatory Affairs
Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 4755
Syracuse, New York 13221-4755

DEC 24 1992

Dear Ms. Garofalo:

Reference is made to your supplemental New Drug Application (NDA), and to your amendment dated December 22, 1992, received by the Food and Drug Administration (FDA) on December 23, 1992, for cefepime hydrochloride for injection.

We consider your submission a major amendment under 21 CFR 314.60 and have determined that 120 additional days will be required for its review.

The new due date is April 28, 1993.

If questions arise concerning this NDA, please contact Mr. Carmen DeBellas, of the Project Management Staff, on (301) 443-6797.

Sincerely,

Lillian Gavrilovich, M.D.
Deputy Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Pharmacokinetics of Cefepime Dihydrochloride Arginine in Subjects with Renal Impairment

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Received 18 November 1991/Accepted 8 September 1992

In this study, the safety, tolerance, and pharmacokinetics of a single 1-g intravenous dose of cefepime (BMY-28142) were investigated. Twenty-three volunteers with various degrees of renal function were assigned to four trial groups according to glomerular filtration rate (GFR). Group IV consisted of five patients with end-stage renal disease undergoing treatment with hemodialysis. Cefepime concentrations in samples from plasma, urine, and infusion solutions were assayed with high-pressure liquid chromatography. The volume of distribution corresponded to the assumed extracellular fluid volume and did not differ significantly between the four groups. The area under the concentration-time curve increased as renal function decreased; in group II (GFR, 31 to 80 ml/min $\times$ 1.73 m²; n = 6), it was already three times higher than in group I (GFR, $\geq$ 80 ml/min $\times$ 1.73 m²; n = 5). Mean residence time was 2.4, 6.8, 11.4, and 31.6 h for the four groups, respectively. Total clearance decreased (97.2, 34.6, 19.8, and 6.3 ml/min $\times$ 1.73 m²) with decreasing renal function, and a linear relationship between total plasma clearance and GFR was found with the regression equation $y = 0.92x - 2.0$ ($r = 0.991$). Renal clearance was linearly correlated to GFR with the regression equation $y = 0.87x - 6.1$ ($r = 0.989$), indicating that renal elimination is mainly by glomerular filtration. During hemodialysis, the extraction ratios were between 0.40 and 0.65. Dialysis clearance varied between 69.9 and 94.6 ml/min $\times$ 1.73 m².

CC:
RA
LS
C. O. B.
S. L. A. M.

Cefepime (aminothiazolemethoxyamino cephalosporin) is a new parenteral beta-lactam antibiotic. It has a broad spectrum including activity against *Pseudomonas aeruginosa* and members of the family *Enterobacteriaceae* and retained potency against *Staphylococcus aureus* and other gram-positive organisms (5, 7, 9, 11, 17, 18). It is active against clinical isolates resistant to ceftazidime and other beta-lactams (9, 17). Cefepime is extremely stable to hydrolysis by β -lactamases (15) and penetrates well into the cerebrospinal fluid in animal models (10, 15, 16). The activity

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of the Medical Faculty, University of Lund, and by the Swedish Medical Products Agency. All subjects gave written informed consent prior to the study.

Antibiotic. Cefepime (BMY-28142) was provided by Bristol-Myers Squibb International Corporation (Wallingford, Conn.) as a dry-fill, sterile powder in vials containing 1 g of cefepime arginine dihydrochloride for reconstitution and

TABLE 1. Subject characteristics for the four study groups^a

Group (n)	No. of patients		Age (yrs) ^b	Wt (kg) ^b	BSA (m ²) ^b	Serum creatinine (μ mol/liter) ^b	GFR (ml/min $\times$ 1.73 m ²) ^b
	Female	Male					
I (5)	2	3	30.6 $\pm$ 5.0	74.9 $\pm$ 12.1	1.94 $\pm$ 0.24	77.5 $\pm$ 17.5	107 $\pm$ 4.1
II (6)	1	5	52.7 $\pm$ 8.2	76.0 $\pm$ 7.9	1.90 $\pm$ 0.16	169.3 $\pm$ 34.2	42.5 $\pm$ 9.9
III (7)	3	4	46.1 $\pm$ 16.8	67.6 $\pm$ 12.2	1.81 $\pm$ 0.23	352.7 $\pm$ 181.0	22.0 $\pm$ 5.8
IV (5)	3	2	41.2 $\pm$ 7.9	66.4 $\pm$ 17.3	1.77 $\pm$ 0.23	872.4 $\pm$ 212.4	ND ^c

^a Kruskal-Wallis test results: age, $P = 0.021$; weight, $P > 0.1$; BSA, $P > 0.1$; Serum creatinine, $P < 0.001$; GFR, $P < 0.001$.

^b Mean $\pm$ standard deviation.

^c ND, not determined.

against both gram-positive and gram-negative organisms provides the possibility of empirical treatment of severe infections. Since, in patients with severe infections, renal dysfunction is common, this study was undertaken to investigate the influence of renal impairment on the pharmacokinetics of cefepime.

(This work was presented in part at the 7th International Congress of Chemotherapy, Berlin, Germany, June 1991.)

intravenous administration. To each vial, 2.8 ml of sterile water for injection was added, giving a total volume of 4.2 ml. From two reconstituted-drug vials, 8 ml of the clear solution was withdrawn and added to 32 ml of physiological saline for injection. Exactly 20 ml of this solution was given intravenously for 5 min to each subject with a constant-rate infusion pump. The excess solution was used to fill the infusion lines and to save an aliquot for drug assay.

Volunteers. Twenty-three volunteers over 18 years of age were included in the study. Their body weights were between 50 and 110 kg, and they were in an acceptable clinical

* Corresponding author.

TABLE 2. Demographic data for the subjects in group IV^a

Subject	Sex ^a	Diagnosis	Yrs on dialysis	Time of cefepime administration relative to hemodialysis
19	F	Thrombotic thrombocytopenic purpura	4.5	Before
21	M	Nephrosclerosis and chronic glomerulonephritis	11	Before
22	F	Mesangioproliferative glomerulonephritis	3	Before
28	F	Chronic pyelonephritis (nephrectomy)	10	During
30	M	Chronic nephropathy	3	During

^a F, female; M, male.

condition according to physical and laboratory examinations. Subjects were divided into four different groups on the basis of actual glomerular filtration rate (GFR) measured by iohexol clearance determination (13). Table 1 shows the characteristics of the four groups of subjects with regard to age, sex, weight, and renal function. Table 2 describes the demographic data for the subjects in group IV.

In group I, two subjects received only half the intended dose because of a miscalculation which occurred when the vials were prepared for infusion. In group II, one subject could not accurately collect urine and his urine-based data were excluded.

Exclusion criteria were pregnancy, hepatic disease, blood donation within a month prior to the investigation, known hypersensitivity to cephalosporins or penicillins, human immunodeficiency virus or hepatitis B surface antigen positivity, drug allergy, drug or alcohol abuse, and fluctuating or rapidly deteriorating renal function.

Study design. The study was an open, single-dose study with 1 g of cefepime administered intravenously for 5 min with a constant-rate infusion pump. Multiple blood samples were taken from the contralateral cubital vein predose and at 0.17, 0.34, 0.50, 0.75, 1.0, 1.5, 2, 4, 6, 8, 10, and 12 h after the start of infusion in group I. In group II, blood samples were collected as described above, with additional samples at 16, 20, and 24 h. In group III, blood samples were collected as in group II, with additional samples at 36 and 48 h after the start of infusion. In group IV, three patients were dosed 24 h before the start of hemodialysis; blood samples were collected at 0.17, 0.50, and 1 h and then every 2 h up to the start of dialysis and also at the beginning of dialysis, 0.50 h after the beginning of dialysis, and every hour thereafter. The other two patients in group IV received their dose at the start of dialysis and were monitored during dialysis with samples collected at 0.50, 1, 1.5, 2, 3, and 4 h. All patients in group

IV were monitored for 2.5 h after the end of dialysis. The specific data for the dialysis procedure are shown in Tables 3 and 4. During dialysis, blood samples were taken from both the efferent and the afferent lines of the dialysis machine. Samples were centrifuged at 4°C within 60 min of collection, and plasma was separated and immediately frozen at -70°C.

Urine was collected quantitatively predose and at 0 to 2, 2 to 4, 4 to 8, and 8 to 12 h after the start of infusion in groups I, II, and III, with additional samples taken at 12 to 24 h in groups II and III and at 24 to 36 h and 36 to 48 h in group III. The volume of each urine portion was recorded, and aliquots were mixed with 2 parts of 0.2 M sodium acetate buffer, pH 4.25, and frozen at -70°C.

Laboratory evaluation. Hematological, clinical chemical, and urinary tests were conducted predose, 8 h postdose, and at the end of the study period. GFR was measured by iohexol clearance determination (13) on the day of the study except in group IV. The iohexol dose was given immediately after the cefepime infusion.

Clinical examination. Electrocardiograms were obtained before dose administration. Physical examinations were done before and after the trial. Body temperature, blood pressure, and pulse and respiratory rates were monitored from the start of infusion and throughout the study period. Caffeine, nicotine, and alcohol were not allowed during the observation period. Subjects had a light breakfast before the start of the study and were allowed to drink freely. They were requested to report any side effects, and all observed adverse reactions were noted.

Assay procedure. Plasma and urine samples were assayed for concentrations of cefepime by high-pressure liquid chromatography using a modified version of the procedure of Barbhaiya et al. (2). A Waters ALC/GPC 204 liquid chromatograph was used with a Waters 712 WISP automatic sample injector, a Waters 450 tunable absorbance detector set at 280 nm, and a Waters data module recorder. The stationary phase consisted of a 5- μ m Nucleosil C₁₈ (Macherey-Nagel, Düren, Germany) slurry packed in stainless-steel columns (20 cm by 4 mm [inside diameter]). For plasma assays, the mobile phase was a mixture of 5 mM octanesulfonic acid in water and acetonitrile (90:10 [vol/vol]) with a flow rate of 1.0 ml/min. Cefepime for preparation of plasma standards was weighed precisely, dissolved in distilled water to a stock standard of 1 mg/ml, and stored at -70°C. Working standards were prepared in pooled human plasma at concentrations ranging from 1.0 to 20 mg/liter. Three milliliters of methylene chloride was mixed with 1.5 ml of acetonitrile and 5% (wt/vol) trichloroacetic acid in a glass test tube. During vortexing, 1.0 ml of plasma sample was added. This mixture was centrifuged at 2,000 $\times$ g for 10 min, and 10 μ l of the aqueous phase was injected for chromatography. For the urine assay, cefepime was weighed precisely and dissolved in distilled water to a stock standard of 10

TABLE 3. Dialysis procedures for group IV^a

Subject	Dialysis machine	Dialyzer	Blood flow (ml/min)	Membrane pressure (mm Hg) ^b	Membrane size (m ²)	Dialysis duration (h)
19	Gambro AK 100	Gambro GFS 12+	230	170	1.30	4
21	Gambro AK 100	Gambro F 6	200	125	1.25	5
22	Gambro AK 10	Gambro GFE 15	230	170	1.50	5
28	Gambro AK 10	Gambro GFE 18	210	120	1.80	4
30	Fresenius Bic + FCM	Gambro GFE 18	225	80	1.80	4

^a Dialysate flow for all patients was 500 ml/min.

^b 1 mm Hg = 133.322 Pa.

TABLE 4. Performance of the Cuprophane hollow-fiber dialyzers used^a

Dialyzer	Thickness (mm)	In vitro clearance (ml/min) of ^b			Ultrafiltration coefficient (ml/mm Hg/hr)
		Creatinine	Urea	B ₁₂	
Alwall GFE 15	8	162	182	62	6.4
Alwall GFE 18	8	170	190	70	8.3
Alwall GFS 12+	8	156	180	64	6.8
Fresenius F 6	40	162	183	56	5.5

^a Inside diameter for each was 300 µm.

^b Perfusion flow, 200 ml/min; B₁₂, vitamin B₁₂.

^c 1 mm Hg = 133.322 Pa.

mg/ml, and the solution was kept at -70°C. Working standards were prepared in pooled human urine at concentrations ranging from 10 to 1,000 mg/liter. One part of the standard solution was mixed with two parts of 0.2 M sodium acetate buffer, pH 4.25. The stationary phase, flow rate, detection wavelength, and injected volume were the same as for plasma. The mobile phase was a mixture of methanol, tetrahydrofuran, and 10 mM sodium dodecyl sulfate (90:15:150 [vol/vol]).

Control samples of known concentrations in pooled human plasma and pooled human urine, treated and stored in exactly the same manner as the study samples, were assayed in each series of analyses.

Pharmacokinetic analysis. Noncompartmental methods were used for calculation of pharmacokinetic variables (8). The maximum concentration of cefepime in serum (C_{max}) was defined as the concentration 5 min after the end of the cefepime infusion. The extraction ratio for cefepime during dialysis was calculated according to the formula $(C_{in} - C_{out})/C_{in}$, where C_{in} and C_{out} are the concentrations in plasma entering and leaving the dialyzer, respectively.

The clearance of cefepime during dialysis (CL_D) was calculated as $Q_p \times [(C_{in} - C_{out})/C_{in}]$, where Q_p is the plasma flow through the dialyzer, determined from the known blood flow (Q_B) and the packed-erythrocyte volume (H) according to the formula $Q_p(1 - H)$.

The area under the concentration-time curve (AUC) was calculated according to the log-trapezoidal rule and extrapolated to infinity by dividing the last measured concentration by the terminal elimination rate constant. All clearance values were corrected to a 1.73-m² body surface area (BSA) since the volunteers had BSAs of between 1.40 and 2.17 m². For the same reason, the volume of distribution at steady state (V_{SS}) was given in liters per kilogram of body weight.

Statistical moment analyses were performed, and the volumes of distribution were adjusted for infusion time. Nonrenal clearance (CL_{NR}) was calculated as the difference between total clearance (CL_T) and renal clearance (CL_R).

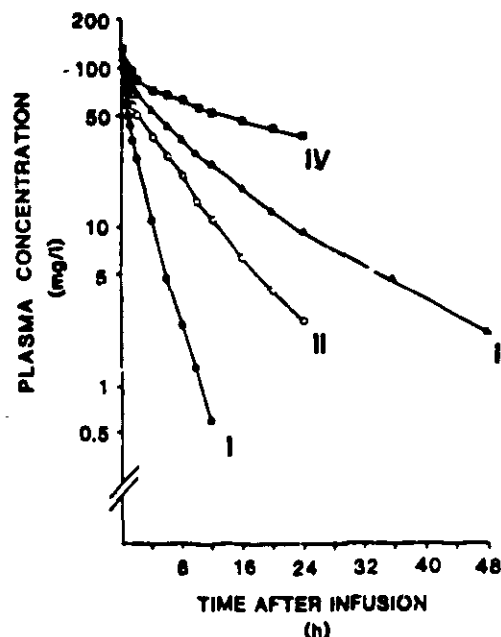


FIG. 1. Mean plasma concentration-versus-time curves for the four groups (I, healthy volunteers; II, moderate renal impairment; III, severe renal impairment; IV, end-stage renal disease) after a 1-g intravenous infusion of cefepime.

RESULTS

The mean plasma concentration-versus-time curves are shown in Fig. 1, in which the decrease in elimination with increasing renal impairment is obvious. The mean pharmacokinetic variables derived from plasma and urine data are shown in Tables 5 and 6. The V_{SS} corresponded approximately to the assumed extracellular volume and did not differ significantly among the four groups. An increase in C_{max} with progressive renal dysfunction was seen. A progressively higher AUC was noted as renal function declined. The terminal elimination half-life and the mean residence time increased with declining GFR.

The relationship between CL_T and GFR, shown in Fig. 2, was linear with the regression equation $y = 0.92x - 2.0$ ($r = 0.991$). CL_R was linearly correlated to GFR ($y = 0.87x - 6.1$) ($r = 0.989$) (Fig. 3), and CL_{NR} accounted for approximately 10% of the elimination of cefepime in group I. In subjects with reduced renal function, CL_{NR} was slightly lower. In subjects with end-stage renal disease, CL_T corresponded to CL_{NR} since their renal function was virtually nonexistent.

The coefficients of variation for control plasma samples of 30 and 2 mg/liter were 4.7 and 3.8%, respectively.

TABLE 5. Plasma data-derived pharmacokinetic parameters of cefepime after a 1-g intravenous infusion^a

Group (n)	Dose (mg)	C_{max} (mg/liter)	k_e (h ⁻¹)	$t_{1/2}$ (h)	MRT (h)	AUC (mg · h/liter)	CL_T (ml/min × 1.73 m ²)	V_{SS} (liters/kg)
I (5)	1,039 ± 26 ^b	102.9 ± 22.6 ^b	0.386 ± 0.0182	1.80	2.39 ± 0.09	153 ± 30 ^b	97.2 ± 7.8	0.21 ± 0.03
II (5)	1,037 ± 122	114.9 ± 15.3	0.147 ± 0.0312	4.70	6.75 ± 1.56	482 ± 142	34.6 ± 9.6	0.20 ± 0.03
III (7)	1,021 ± 40	117.7 ± 21.6	0.092 ± 0.0242	7.55	11.43 ± 3.68	897 ± 257	19.8 ± 6.3	0.20 ± 0.02
IV (3)	997 ± 91	130.4 ± 23.4	0.033 ± 0.0258	21.13	31.56 ± 6.11	2,659 ± 361	6.3 ± 2.3	0.18 ± 0.06

^a All values except $t_{1/2}$ (half-life) are means ± standard deviations. k_e , terminal elimination rate constant; MRT, mean residence time.

^b Two subjects were excluded after being given half the intended dose by mistake.

TABLE 6. Urine data-derived pharmacokinetic parameters of cefepime after a 1-g intravenous infusion*

Group (n)	CL _R (ml/min × 1.73 m ²)	CL _{NR} (ml/min × 1.73 m ²)	Recovery (0-12 h)	
			mg	%
I (5)	86.2 ± 8.1	11.0 ± 4.2	904.9 ± 69.9	87.7 ± 4.2
II (5)	31.9 ± 11.9	2.7 ± 2.1	822.1 ± 200.5	77.6 ± 12.7
III (7)	12.8 ± 5.6	7.0 ± 3.7	469.4 ± 142.4	45.8 ± 13.3

* Values are means ± standard deviations.

Urinary recoveries of the administered dose of cefepime up to 12 h postdose are shown in Table 6. The recovery in urine up to 24 h in group II was 89.6%, and the recovery up to 48 h in group III was 62.7%. The coefficients of variation for urine samples of 200 and 1,000 mg/liter were 5.2 and 4.7%, respectively.

During hemodialysis, the extraction ratio in the dialyzer was between 0.40 and 0.65. CL_D varied between 69.9 and 94.6 ml/(min × 1.73 m²), with a mean of 83.9 ml/(min × 1.73 m²).

Cefepime was well tolerated. Three subjects complained of mild to moderate headache, which in one instance was judged as probably related to the study drug. One subject reported a penicillin taste beginning 30 min after infusion and lasting 1 h; this was judged a drug-related reaction. Laboratory screening showed no drug-related abnormalities.

DISCUSSION

The pharmacokinetic data from this study confirm earlier published reports on patients with renal impairment (3, 4) and respiratory tract infections (12) and on healthy volunteers (1, 4, 14). Since we administered the drug as an intravenous injection for 5 min, C_{max} was higher in our group of healthy volunteers. The increase in C_{max} with decreasing renal function was probably due to reduced renal elimination rate. The lower CL_T values in this study are explained by the correction for BSA. There was no difference among V_{ss} values for the four groups. The AUC increased as renal

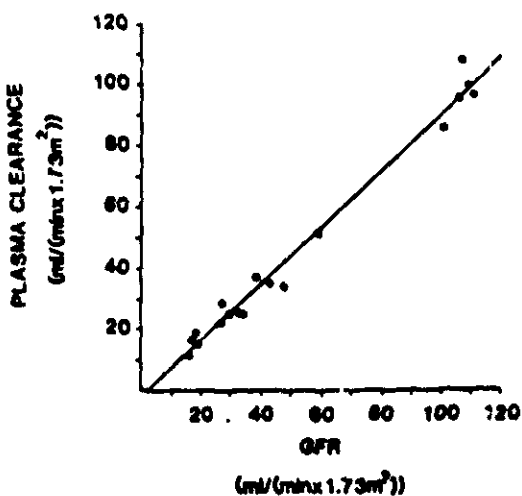


FIG. 2. Correlation between CL_T of cefepime and GFR. The correlation has the equation $y = 0.92x - 2.0$, with a correlation coefficient of 0.991.

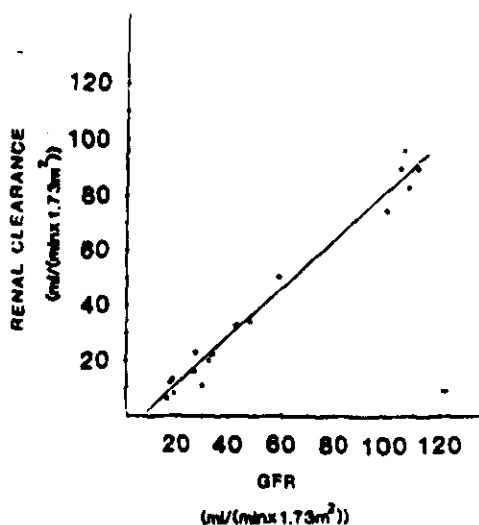


FIG. 3. Correlation between CL_R of cefepime and GFR. The correlation has the equation $y = 0.87x - 6.1$, with a correlation coefficient of 0.989.

function decreased and was already three times higher at GFR between 30 and 80 ml/min (group II) than in healthy volunteers (group I).

As GFR declined, there was a proportional reduction of CL_T and a corresponding proportional reduction of CL_R. The correlation between CL_R and GFR indicates that renal elimination was mainly by glomerular filtration. CL_{NR} accounted for approximately 10% of the elimination of cefepime in healthy volunteers, which is comparable to data reported earlier (1-4). The metabolic clearance of cefepime is assumed to take place in the liver by hydrolysis to *N*-methylpyrrolidine, an alicyclic tertiary amine, and further oxidation to *N*-methylpyrrolidine-*N*-oxide (6). The three patients with end-stage renal disease who were dosed 24 h before the start of dialysis had an average CL_T of 6.3 ml/(min × 1.73 m²), which, since the patients were anuric, corresponded to the CL_{NR} and was not different from the CL_{NR} values for the other three groups. Thus, no evidence of compensation by increased metabolic clearance was found in patients with renal insufficiency.

The data obtained in this investigation, with a linearity between GFR and CL_T, indicate that it is advisable to base dosing recommendations on renal function. Our data support the recommendation of the manufacturer for a dose reduction of cefepime for patients with severe renal insufficiency. A proposed dosing schedule for cefepime is presented in Table 7.

Hemodialysis effectively cleared cefepime from the circulation. CL_D averaged 83.9 ml/(min × 1.73 m²), which is

TABLE 7. Suggested dosages for patients with renal impairment

Creatinine clearance (ml/min)	Dose (mg)	Interval (h)
>30	1,000	12
<30	500	24
<10	250	24*

* Supplementary dose after hemodialysis.

comparable to the CL_T for the healthy volunteers in group I. The half-life during dialysis was 1.94 h, which is close to the half-life of 1.80 h obtained for healthy subjects. A supplementary dose of 250 mg is recommended after hemodialysis.

ACKNOWLEDGMENTS

Financial support was given by the Medical Faculty, University of Lund, and Bristol-Myers Squibb International Corporation.

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Consult # 168 (HFD-520)

MAXIPIME

Cefepime Hydrochloride Injection

A review revealed one sound alike name: Amoxapine. Despite the difference in dosage forms (injection vs tablet) the real sound-alike similarity between the names was thought to be a concern.

The first two syllables, maxi, are cause for concern. Maxi carries the connotation of maximum and implies a maximum strength, dosage spectrum or effectiveness, potency, clinical coverage, etc. While this is a broad spectrum antibiotic, so are all cephalosporins; therefore, we do not believe maximum is appropriate. It appears this product has no attributes which are reasonably, maximum.

Accordingly, the Committee believes the name Maxipime may be considered misleading [201.10(e)(3)].

CDER Labeling and Nomenclature Committee

D. J. Johnson, Chair

10/4/02

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**Bristol-Myers Squibb
Pharmaceutical Research Institute**

5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

June 30, 1992

Carl Peck, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Central Documents Room
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, MD 20852

Dear Dr. Peck:

Reference: NDA # 50-679; Cefepime Hydrochloride for Injection

Pursuant to 21CFR 314.50, we are submitting complete archival and review copies of a New Drug Application for Cefepime Hydrochloride for Injection. Cefepime hydrochloride is a semi-synthetic broad spectrum cephalosporin antibiotic intended for intramuscular or intravenous administration when constituted from a sterile dry mixture with L-arginine. It will be supplied in vials equivalent to 500 mg, 1 g and 2 g of cefepime.

Investigational studies in humans were conducted with cefepime under IND with a sodium chloride formulation, and under IND with the cefepime hydrochloride L-arginine blend proposed for commercial use.

The clinical efficacy and safety of cefepime have been evaluated in extensive comparative and non-comparative trials in both North America and Europe that enrolled a total of 6275 patients at the time of data cutoff for this submission; 4423 patients were assigned to cefepime treatment. Cefepime was determined to be effective single agent therapy against the principal gram-positive and gram-negative bacterial pathogens which cause the following types of moderate, severe and very severe, life-threatening infections in hospitalized patients:

- Pneumonia (nosocomial and community-acquired)
- Bronchitis
- Complicated urinary tract infections (including pyelonephritis)
- Uncomplicated urinary tract infections
- Skin and skin-structure infections
- Complicated intra-abdominal infections (including peritonitis and biliary tract infections)
- Bacterial septicemia



A Bristol-Myers Squibb Company

Cefepime has also been used successfully in combination with other antibiotics such as vancomycin in the empiric treatment of potentially very severe or life-threatening febrile episodes in neutropenic patients.

Cefepime can be distinguished from currently available cephalosporins as a fourth-generation cephalosporin based on certain microbiological properties, which include good potency against a broad range of important pathogens including *S. aureus* and *P. aeruginosa*, unique activity against *Enterobacter*, and a low rate of emergence of antibiotic-resistant strains in *in vitro* and *in vivo* models.

Adverse events associated with cefepime during clinical studies were those usually reported for cephalosporin antibiotics. Cefepime has a safety profile comparable to that of ceftazidime, a drug known to be well tolerated. When administered intramuscularly, cefepime is better tolerated than ceftriaxone at the site of injection. The results of extensive toxicology studies in animal models support the safe use of cefepime in humans.

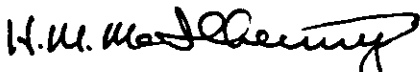
The format and content of this submission, contained in 343 volumes, are based on the requirements as set forth in 21CFR 314.50 under paragraphs (a) through (f), and follow published guidelines for the information to be provided within each technical section. An introductory reviewer guide is attached to this letter to facilitate an understanding of the organization of the NDA.

The analysis and presentation of the data from clinical trials have been the subject of ongoing discussions with the reviewing division throughout the course of development of the cefepime program, and reflect our agreements on how best to fulfill current divisional policy standards for the review and approval of antimicrobial drugs.

As also agreed in meetings with the reviewing division, a computer-assisted NDA will accompany this Application in support of the medical review. This is based on a successful demonstration of the systems to be utilized as presented to the Agency on April 28, 1992. Arrangements will be made soon after this submission with the reviewing Medical Officer for installation of the electronic data systems.

We very much look forward to the continuation of our effective interaction with the Division. Please contact the undersigned with any questions that may arise during the review phase of this Application.

Sincerely,



Hugh M. McIlhenny, Ph.D., Director
Worldwide Regulatory Affairs

Memo of Teleconference

NDA 50-679

Date: July 21, 1994

Drug Name: Maxipime (cefepime)

Objective: Information

Attendees

Applicant:	Dr. Hugh McIlhenny	Director Regulatory Affairs
	Dr. Anthony Santipolo	Vice President Worldwide Regulatory Affairs

Food and Drug Administration:

Dr. Murray Lumpkin	Director of Review Management
Mr. Carmen DeBellis	Project Management

Dr. Lumpkin initiated the call in order to answer the concerns of the applicant about their NDA.

He explained that the NDA review is completed and there were comments and concerns discussed at a divisional meeting last evening which may be in the action letter.

He explained that he would be out of town on Friday and the action letter would issue the following Monday or Tuesday. He then mentioned the letter would contain the following approvable indications: Uncomplicated Urinary Tract Infections, Complicated Urinary Tract Infections (pyelonephritis), with concurrent
Skin and Skin Structure Infections, and Pneumonia

He also informed the applicant that they would not be approved for _____ because of the small number of evaluable patients.

He stated that he understood that pseudomonas was very important to the applicant, but the Agency had some concerns about approving the organism. When you look at the pharmacokinetics parameters for treating pseudomonas at recommended doses because of the half-life the peak is under the MIC after four hours. Another dose is not given until 8 hours later. In the clinical trials the cure rate eradication of pseudomonas came out to be 50-60. These low numbers did not allow for clinical approval as well as statistical. There was a significant clinical difference with ceftazidime.

The clinical review will be supplied to you. Before we sit down and discuss the labeling, read the review and see our analysis. If you find any discrepancies we can discuss them. You real do need to see Dr. Sherman's data base before we discuss the NDA.

Drs. McIlhenny and Santipolo both agreed they would take a look at the review when they received their copy.


Carmen DeBellis

Orig NDA
HFD-520
HFD-520/SMO/Albrecht
HFD-520/MO/
HFD-520/CSO/Debellis
Meeting Minutes

Memorandum to the File

NDA 50-679

Maxipime

Teleconference

Bristol Myers Squibb

Subject: Clarification of Deficiencies on NDA 50-679

Date: January 26, 1994

Bristol Myers Squibb:

Robert Simon	Worldwide Regulatory Affairs
Michael Burnett	Worldwide Regulatory Affairs
Elizabeth Garofalo	Worldwide Regulatory Affairs
John Woolever	Analytical Research & Development
Joseph Ticome	Worldwide Technical Services
Sheeram Agharkar	Pharmaceutics Research & Development
Robert Carpenter	Product Quality Control
Michael Goldstein	Technical Regulatory Support
James McNiff	Technical Regulatory Support
Linda Subird	Technical Regulatory Support

Food and Drug Administration:

Suva Roy	Reviewing Chemist
Wilson DeCamp	Supervisory Chemist
Carmen DeBellas	Project Manager

The following issues were discussed. Agreements from the applicant follow each issue.

Issue #1 We recommend that you add a total organic residual solvent limit of % in the regulatory specifications for cefepime HCl drug substance.

Agreement Understood that the acetone limit should be reduced, at present % is acceptable. This method will only test for acetone and no other solvents. Reports for other solvents were done by different, more sensitive methods. They agreed to test for other solvents.

Issue #2 Please include assay of 10 individual vials as described in USP <905> for potency and content uniformity in method GM0044. This product is a physical mixture of L-arginine and cefepime HCl.

Agreement The content uniformity will be done by USP <905> method which requires assay and not weight variation, at release.

Issue #3 & #4 We recommend, the assay five individual vials for NMP assay, method SM 1690-04. The replicates are needed to assure the reliability of the assay data.

Your argument against multiple testing of each method assuring stability study misses the point. The replicates are necessary to assure the reliability of the stability data. Please include potency and impurities assay from at least 5 individual vials in the marketed product stability protocols.

Agreement It was agreed that the NMP assay and multiple testing for stability will have replicate measurements to assure reliability of the data. Singlet measurement of NMP will be fine if measurement is under %, but if not then triplicate measurement should be done. The same should be done for stability except the acceptable range should not exceed %. NMP will fail long before product is subpotent.

Issue #5 The impurity BMY-33648 will show up on assay of the drug product. We recommend, that a specification for the impurity be included in the drug product specification for completeness. The specification should be the same as the drug substance at %.

Agreement BMY-33648 impurity is process-related, not degradation related. This impurity is unlikely to be observed in the product analysis because of the long retention time. The addition of a spec would for this impurity would require development and validation of a new method, must be met for the bulk to meet GMP's. Specs for BMY-33648 will not be needed.

Issue #6 Please include stability studies of constituted product with I.M. and I.V. diluents identified in the labeling at 12, 24 and 36 months. This is needed to assure that the marketed product continues to remain within the specifications at the end of the dilution utility period claimed in the labeling.

- Agreement The stability studies of constituted product should be conducted to show that the product meets the label claim; Bristol Myers Squibb have lots on stability that are studied for reconstitution through 36 months, They will submit additional data.
- Issue #7 A request was made to submit stability data on the drug substance that was being shipped in polyethylene bags.
- Agreement The information given in the NDA was supportive data but the packaging they use for the drug substance is and has always been glass. The non sterile crude is shipped in polyethylene bags in fiber drums. Bristol-Myers Squibb will be providing additional data if they have any.

The meeting ended with Bristol-Myers Squibb pledging to respond as quickly as possible.

Carmen DeBellus
Carmen DeBellus
Project Manager

Orig NDA
50-679
HFD-520
HFD-520/Chem/Roy *2/1/94*
HFD-520/SCSO/DeBellus *1/2/94*

Concurrence:
HFD-520/SChem/DeCamp

**PROJECT MANAGEMENT STAFF TELECONFERENCE
MEMORANDUM**

NDA 50-679

APPLICANT - BRISTOL-MYERS SQUIBB
5 RESEARCH PARKWAY P.O. BOX 5100
WALLINGFORD, CONNECTICUT 06492-7660
(203) 284-7879

REPRESENTATIVES:

Richard DeRegis, Ph.D., Clinical Research
and Development
Hugh Mac Illenny, Ph.D., Regulatory Affairs

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS:

Linda Sherman, M.D., Medical Officer
Carmen DeBellas, R.Ph., Project Manager

GENERIC NAME: Cefepime Hydrochloride Injection
TRADE NAME: MAXEPIME^R

DATE: December 9, 1992

The discussion concerns the recording of the progress of discharged patients. The recording of signs and symptoms is very important. Dr. Sherman stated the applicant should use a page from the case report forms and adverse reaction page from the protocol.

The signs and symptoms required to be monitored:

Fever	frequency	chills	pain
malaise	cough	lethargy	hypotension
rigor	exudate	dysuria	erythema
urgency	tachycardia	edema	petechiae
diaphoresis	purpura	Lymphadenopathy	urgency
frequency	pain (burning)		

Also, leave a few blanks for handwritten comments on the case report forms for protocol #160. These case report forms should be used for hospitalized patients as well as patients on home treatment. Remember the patients on this protocol need to be sepsis patients by definition.

NDA 50-679

Page 2

Adverse Reactions should be done in the same fashion as the other case report forms. The adverse reaction section should contain some of the following information:

Was the ADR drug related or not?

What method of treatment was used, if any?

Were there any sequelae?

Was the patient hospitalized or did a death occur?

These can be done on two pages and attached to the patient diary. The information can be obtained by a nurse.

Dr. Sherman expressed concern about who would be entering the data on the outpatient forms. She would prefer an investigation monitor (physician) or a home healthcare nurse. Another concern was that if the patient truly had sepsis, why would they be leaving the hospital so early in the study. The applicant should be sure they are enrolling the right patients.

In Summary:

The use of outpatients is acceptable as long as the data is captured correctly. The recorder of the data needs to be a qualified person (nurse or physician) and the data must be taken down precisely. The patient must be followed closely (no more than 2-3 weeks without a physician evaluation). The patient needs to be followed by the appropriate personnel to ensure evaluability.

Carmen DeBellas
Carmen DeBellas, R. Ph.

Linda Sherman MD
Linda Sherman, Medical Officer

CC: Orig NDA
50-679

HFD-520
HFD-520/MO/Sherman
HFD-520/CSO/DeBellas

MEMORANDUM OF A TELEPHONE CONVERSATION

November 12, 1992

Between: David Burnett and Elizabeth Garafalo
Bristol-Myers Squibb
(203)-284-7979

And: Suva B. Roy, Ph.D. *SBR*
Review chemist, HFD-520

Subject: NDA 50-679 - Cefepime hydrochloride

Dr. Burnett and Dr. Elizabeth Garafalo called to enquire how to handle the following amendments to their NDA.

- They intend to add a new source of 3I/AC. HCl intermediate to their NDA. Their Syracuse facility do not have enough capacity for the intermediate. The new source is BMS facility at Germany.
- They also indicated that they have additional admixture stability data.

I said that they could send the amendments now if they wanted.

They asked if that will delay the approval.

I responded that these appear to be major chemistry amendments and we might need a 180 day extension.

Dr. Burnett said that it may not be problem.

- Dr. Burnett also asked when and where he should send the methods validation kits.

I told him that I have instructed the inspector at San Juan, Puerto Rico to pick up the method validation kits during inspection.

Dr. Burnett said that the San Juan facility may not have enough impurity and related substances samples.

I requested him to forward the methods validation kits to our Detroit District Laboratory, Michigan, attention Dr. Betty Williams and to the Division of Research and Testing, Washington DC, attention Dr. Joseph Graham. I also gave him the full mailing addresses.

I took this opportunity to ask the following :

- Identify the pages where the sterility testing of the sterile bulk Cefepime HCl and the sterile mixture with L-arginine are described. I indicated that the reviewing microbiologist could not find the above information.

Dr. Burnett responded that they will get back to us with the information.

I suggested that they respond to Carmen Debellas with the information.

- Whether their Latina, Italy facility will be ready for inspection in mid-January as discussed earlier. I also asked Dr. Burnett to confirm this in writing.

Dr. Burnett responded that he will double check and confirm in writing the expected date when the Latina facility will be ready for inspection.

The conversation ended amicably.

cc : Orig. NDA 50-679
HFD-520/Division File
HFD-520/SBR
HFD-520/Sherman
HFD-520/Mainigi
HFD-520/Soprey
HFD-520/Debellas

NDA 50-679 -

**Memorandum to file
October 20, 1992
Teleconference**

Participants:

Ms. Pamela Ligato-Strode,	Bristol-Myers Squibb
Dr. Hugh McIlhenney,	Bristol-Myers Squibb
Ms. Carolyn Doyle,	Bristol-Myers Squibb
Dr. Mohan	Bristol-Myers Squibb
Dr. Ralph Harkins,	Division of Anti-Infectives (statistician)
Ms. Alaka Chackavaty	Division of Anti-Infectives (statistician)
Mr. Carmen DeBellis	Division of Anti-Infectives

Topics: Generation of Tables

The statisticians are looking for patient line listing containing all the patients enrolled and their outcome. They should also contain safety data, clinical ADR's, Laboratory ADR's, data for clinical and microbiologic cures (some cures in micro are presumptive). Basically, the need is for baseline and demographic data.

Bristol-Myers Squibb commented that such a section with the baseline line listing is not present because of the volume of material. The data are in multiple appendices. If the statisticians require a format, they can generate one. This is easily done for a single data item. A problem exists when there are multiple items to summarize on one line (example: symptoms).

Dr. Harkins said there may also be a problem in working with the current data listings if there are more than one isolate found per patient.

Bristol-Myers Squibb- The data are organized as follows: Most information is in the patient profile, (Volumes 1-42) which Dr. Sherman has. The laboratory data is in a different section on a separate page.

Dr. Harkins stated if this could be done electronically, the sorting would be easier. The applicant stated the SAS information comes from 20 sets which is difficult to sort. They may be able to merge SAS data sets and pull out what is needed.

NDA 50-679

Page 2

Conclusion:

The applicant will send one indications data to statistics to see if the format is acceptable.

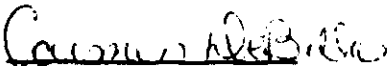
The applicant will send an example of 10 patients on hard copy, a data base on a diskette and patient profiles.

The applicant was not sure if the data will fit on a single disk. The Agency can handle cartridges but not magnetic tape.

The Summary lab file may have to be used since the lab data consists of one test/one patient/day.

The applicant will also try to give a dictionary of codes for the important data.

The applicant said examples will be submitted as soon as possible.



Carmen Debellas 11/5/92
Project Manager



Linda Sherman, M.D.
Medical Officer

CC: Orig NDA
50-679

HFD-520

HFD-520/Mo/Sherman 3/10/93

HFD-520/CSO/Debellas

Anti-Infective
Drug Products
Ac mtg Slides
9/24/93

***Anti-Infective Drug Products
Advisory Committee Meeting***

***The Infected Patient with SIRS and Positive Blood Culture(s),
a UNIQUE subset?***

Friday Morning, September 24, 1993

-
-
**ADVISORY COMMITTEE MEETING
SPEECH FOR 9/24/93**

Thank you, Dr. Beam. Good morning, Ladies and Gentlemen.

The position with regard to the terms "sepsis or septicemia" has been under discussion in the Division for some time. The debate has paralleled those that have appeared in the medical literature. Some of the issues are semantic and others may have clinical implications.

This morning's presentation will be a continuation of the formal presentation and discussion which took place in the July Advisory Committee Meeting. In general, the July's meeting centered around sicker patients who would be defined as having "severe sepsis and/or shock." These are patients who would likely benefit from traditional medical therapy and adjunctive therapies such as immunomodulators. The patient population that we would like to concentrate our discussion on today are those patients with objective evidence of infection, with concurrent bacteremia, with a systemic inflammatory response (or SIRS) and without organ dysfunction, hypoperfusion or hypotension.

The outline for today is as follows (Slide 1).

In order to clarify how I will be using the terms in my presentation, I will briefly review some "old" and "new" terminology. (Slides 2) Historically, the Division has granted indications designated as "bacteremia" and "septicemia" based on the study of infected patients with one or two positive blood culture(s), respectively. A search of the PDR indicates that roughly 32 anti-infective drugs have these terms in the indication and usage section of the label. In the July Draft of the Points to Consider Document, the Division proposed the term "sepsis" to be used for those patients identified with an infection, concurrent bacteremia, SIRS and no organ dysfunction. Because the term "sepsis" in the Consensus group definitions does not require the presence of a positive blood culture; the Division, in an effort to reduce further confusion, has tentatively adopted the term to identify these patients as having "bacteremic sepsis." As a review, the definitions from the Consensus group are abbreviated on the following slide. (Slide 3) It should be noted that bloodstream invasion by microorganisms is not a criterion for any Consensus Group definitions of sepsis, severe sepsis or septic shock.

At the last meeting, (Slide 4) Dr. Lumpkin, in his Points to Consider document, proposed that two "claims or indications" could be identified based on definitions proposed by the Consensus Group i.e. "sepsis-bacteremic sepsis" and "severe sepsis/septic shock."

For "sepsis/bacteremic sepsis," the document suggests that two independent, statistically valid, adequate and well controlled studies would be required to test the efficacy of a new broad spectrum antimicrobial drug. To enter these studies, patients must meet the definition of SIRS and have at least two positive blood cultures. Although implied, a statement with regard to an identifiable focus of infection was not included in the document. The primary endpoint of effectiveness would be cure of infection (i.e. implied survival); a secondary endpoint would be sterilization of blood cultures.

The second claim would require the study of adjunctive therapies for the treatment of "severe sepsis/septic shock." For this indication, two independent, statistically adequate and well controlled trials would be necessary to establish efficacy of the adjunctive therapy beyond traditional antibiotic therapy and other supportive measures. The primary efficacy endpoints would be mortality or morbidity/mortality. Patients to be included in these trials would meet the Consensus definition for SIRS, have objective evidence of infection and shock, perfusion abnormalities and/or end organ

dysfunction. A scoring system that is predictive of the individual's risk for death, such as the APACHE III, could be used as an entry criterion to calculate risk-adjusted mortality in these studies.

Dr. Bone delivered a very fine, detailed dissertation about progress being made to further our understanding of the concepts of severe sepsis and shock. He presented the concept that the body responds to an insult, such as trauma or infection, with a systemic inflammatory response. This response is the result of the release of chemical mediators. Dr. Bone has found that there is a correlation between these mediators of inflammation and the incidence of multi-organ failure and mortality. He has conducted several studies in order to elucidate more understanding of the epidemiology of SIRS. SIRS is a very sensitive criterion and includes both patients with an inflammatory response due to infection and patients that are not infected. In a study of 191 patients with severe sepsis, a mortality rate of 26% was determined. Bacteremia was present in 45% of these patients. Of note, the outcome of the non-bacteremic and bacteremic patients was identical. This study suggested, as have others conducted by Dr. Bone, that "until we develop the means to rapidly ascertain the organism(s) causing sepsis, new therapies may be more effective if directed against the common pathway underlying all forms of SIRS, rather than against a component of a single class of organism."

Dr. William Knaus made the second scientific presentation. Dr. Knaus stated that "sepsis" is a very complex disease. At entry into any "sepsis" study, every patient presents with multiple risk factors, all of which may impact final outcome. To demonstrate this, Dr. Knaus identified 1200 patients with severe sepsis from a database of 60,000. Each patient was scored based on multiple pre-defined, physiological variables such as blood pressure, pH, hematocrit etc. Based on the stratification according to risk factors, predictions of low, intermediate or high risk mortality were made. This model was applied to a Phase III trial of IL-1ra. The mortality rate of the placebo group in this Phase III trial correlated well with the 1200 patients cited previously. When the study data were examined, it was demonstrated that the mortality rate of low risk individuals did not change with study drug. But the projected mortality of the high risk group was altered by the test product. Using the mathematical model, potential benefits of the study drug could be demonstrated. Another interesting point from this data base was that the data were re-examined with regard to the presence or absence of infection. The finding was that a patient's outcome was determined by his initial risk assessment and not his initial disease. In other words, if a patient was in the 24% mortality risk group, whether as a result of ARDS or gram negative sepsis, the benefit from IL-1ra was the same. In sum, Dr. Knaus has developed a tool that may be helpful in assessing the impact of adjunctive therapy in the treatment of severe illness. It should also be noted that this is a summary of Dr. Knaus' presentation; it does not represent the interpretation of the Agency.

Dr. Santopaulo of Bristol Myers-Squibb made a final presentation with regard to the semantics of sepsis/sepsis syndrome/shock and the labelling aspect of a new anti-infective drug product. Recognizing that in the past the terms for bacteremia and sepsis were ill-defined, Dr. Santopaulo proposed a labelling statement for bacteremia. The proposal would read as follows: "Drug X is indicated for the treatment of bacteremia associated with indication A." In addition, it was suggested that the label for sepsis be as follows: "Drug X is indicated for the treatment of patients exhibiting the clinical and laboratory criteria of bacteremic sepsis." Each of these definitions would be annotated. For example, in the case of bacteremic sepsis, it would be stated that patients with SIRS and bacteremia were studied.

At the conclusion of the formal presentations, one consultant noted that much of the morning's discussion centered around the concept of "severe sepsis." Although "sepsis" had been defined by the Consensus group, it had not been studied with regard to risk assessment as had "severe sepsis" -

and septic shock. --"Sepsis" (i.e. infection without organ dysfunction) data for use as a surrogate marker is not valid, because it has not been examined in the same manner. Dr. Dellinger made the following strong statement: "If we were looking at labelling or doing a study to see if an antibacterial product was effective with a specific type of infection, location, organism; to me the most important thing would be documentation that it was an infection based on our current knowledge and the fact that it was infection without severe sepsis. I do not know how infection with sepsis versus just infection differentiates any(thing) further than just infection without severe sepsis." He further added that if infection with SIRS and infection without SIRS responded differently, it would be appropriate to make that distinction in the label. However, this point has not been well studied.

The following conclusions were determined by the Committee at the conclusion of the last meeting:

- 1) To require a third criterion to the definition of SIRS in order to make a more clinically relevant "sepsis" population was considered counter-productive. The efforts of the Consensus Committee was to minimize the confusion of terminology.
- 2) It was determined that a pair of blood cultures taken from separate sites was most meaningful. The positivity of the blood culture leads to increased specificity of the diagnosis.
- 3) It was suggested that adjunctive therapies be studied in both the "sepsis/bacteremic sepsis" and the "severe sepsis" populations. Until more is known, it would be inappropriate to exclude the "sepsis/bacteremic sepsis" group.
- 4) Twenty-eight day mortality should be used as an endpoint of study in trials of severe sepsis.
- 5) Using risk assessments as an entry criterion may exclude some patients worthy of study.

To reiterate, in July, the Committee and the consultants agreed that patients classified as severe sepsis/septic shock represented an identifiable subset of patients who could be enrolled and studied for a response to therapy. In contrast, discussion of the subpopulation the Division proposes to call "bacteremic sepsis" was limited and no preliminary conclusions were reached.

The dilemma, if you will, for the Division is to answer the question: "Do patients with infection, SIRS and bacteremia represent a definable medical entity that would have clinical relevance and therapeutic implications?" In other words, is there another subpopulation of patients that could be defined between those with localized infection and those with severe sepsis?

The progression or pathogenesis of infectious diseases can often be thought of as a continuum. (Slide 5) Some patients begin with a focal infection and recover; while others progress to more extensive systemic involvement including organ dysfunction and death. What makes some patients' infections progress and while others resolve is not known. Certainly prompt medical care including supportive care and appropriate antimicrobial therapy can effect change. However, disease progression is multifactorial; the factors to identify those patients' whose diseases worsen despite apparent appropriate treatment is currently not possible.

The problem that the Division faces is defining transition points on the line of continuum for the purpose of study and approval of indications. The danger is setting up arbitrary endpoints that have no clinical relevance. Can we define borders on this line of continuum? Would this be a meaningful exercise? Can we develop criteria that will assist in the identification of those patients who have not yet crossed over "the line of no return?" and further differentiate those patients that are likely to cross over and those that are not?

We tried to look at these questions using the database from a recently submitted NDA for a parenteral drug product. The NDA had included a request for the indication of bacteremia/septicemia (using the previous Divisional terminology, i.e. infected patients with one or two positive blood cultures,

respectively). The patient population for this indication was pooled from multiple protocols; no individual protocol was specifically written for this indication. In the past, to be evaluable for bacteremia/septicemia, a patient had to have signs and symptoms of a primary infection, the presence of bacteria within the bloodstream demonstrated by two positive blood cultures, received a full course of study drug therapy, and a clinical and microbiological (i.e. blood culture) evaluation at the test-of-cure visit.

In keeping with the evolving definitions of sepsis, severe sepsis and shock, the Division, with the extensive assistance and cooperation of the applicant, evaluated the patient information from this NDA in a new light. In order to answer the question whether a valid subset of patients exists that would warrant a separate indication and therapeutic recommendations, one has to examine patients designated as having "bacteremia-septicemia" and then compare them with an individual indication to try to isolate what feature or features would yield a specific definition. There are several ways that the data can be sliced. (Slide 6) For example, someone might decide to look at dose duration as a measure of severity of illness. The selection of parameters has to be done carefully. For example, in some instances, looking at the duration of therapy is a subjective, investigator dependent parameter.

In this new analysis, we chose to focus on the importance of viable bacteria in the bloodstream and its impact on the incidence of SIRS and on mortality outcome. Were patients with a specific indication and bacteremia more likely to die? We looked retrospectively at these two indications, i.e. all patients suspected of having bacteremia/septicemia and all patients diagnosed with pneumonia.

The following slides illustrate the results of this analysis. (Slide 7) 654 patients were originally classified as having septicemia-bacteremia by their investigator. SIRS was evaluated for each of these patients using the 2/4 Bone criteria. Some modifications of the SIRS criteria were necessary based on the data available. Heart rate was determined by pulse. Respiratory rates were not recorded; therefore, descriptions of tachypnea and dyspnea were accepted. Although white blood cell counts were recorded; the number of juvenile granulocytes were not. This probably was significant in the elderly or renally impaired patients who often do not mount a significant white count, but usually have increased number of bands with infection. Temperature was recorded. For this study, all parameters were assessed on the same day, at entry. Some patients did not have all four of the parameters recorded (HR, WBC, T or RR) and therefore, they could not have SIRS assessed. Only 10% of patients fell into this category, however. 589 or 90% of patients with the designation of bacteremia/septicemia could be assessed. All patients had at least one blood culture taken and all patients were diagnosed by the investigator as having "septicemia/bacteremia." 217 patients had two positive cultures, 292 had one culture positive and 145 had no culture positive. It is important to remember that the number of positive cultures is a function of the number of cultures that were obtained. The results demonstrate that the percentage of patients with SIRS i.e. 80%, 84% and 85% for 0, 1, 2 positive blood cultures are essentially equivalent. Statistically, there is no difference in the incidence of SIRS in the three blood culture groupings. This might suggest that the clinician has used a yet undefined criterion to identify his septicemia patient; therefore the incidence of SIRS in these three populations is equivalent. Or, stated in another way, if you have an infection; not necessarily a positive blood culture, you are more likely to have SIRS than not.

(Slide 8) Similarly, for the 589 patients in whom SIRS was assessable, 28 day mortality was evaluated. Twenty-eight day mortality was defined as the number of patients who died within 28 days after receiving the first dose of test drug. Twenty-eight day mortality was a useful endpoint to assess "severe sepsis" and "shock." In the illness without organ compromise such as "bacteremic sepsis," mortality may or may not be meaningful. However, it was examined, because it was an objective measure of outcome.

In this slide, there are the mortality results based on the three blood culture groupings. There are no statistical differences in the mortality rates between the "0" positive blood culture group and the one or two positive blood culture groups. (However, there is a statistical difference in mortality when one and two positive blood culture patients are compared.) Within a blood culture group, there is essentially no differences in mortality rates between SIRS negative and SIRS positive persons. The conclusions that I draw from this table are 1) that the overall death rate for each blood culture subgroup was approximately the same, and 2) that the overall death rates are lower than those expected for patients with "severe sepsis" and (3) that there is an unidentified criterion other than blood culture that the clinician has used to identify the "sepsis" patient.

At the last Advisory Committee meeting, various members raised the question as to whether a patient with pneumonia, SIRS and a positive blood culture is different from a patient with pneumonia, SIRS and a negative blood culture.

The next few slides examine an individual indication, pneumonia, to determine if there are differences among patient populations based on the presence of SIRS and a positive blood culture. (Slide 9) Three groups are defined on the basis of blood culture information. It should be noted that the procurement for blood cultures in most protocols was encouraged, but was optional. Patients are again grouped according to number of blood cultures that were positive either 0, 1 or 2. Fifty percent of patients in the category labelled "0 blood culture" were blood culture negative and 50% the investigator felt were unlikely to have a positive blood culture and therefore no blood culture was obtained. Fifty patients had two positive blood cultures, 102 had one positive blood culture and 1358 patients had either a negative or no blood culture. Again approximately, 10% of patients could not have SIRS assessed. In the case of patients enrolled with pneumonia, there is a definite trend observed in patients with SIRS. There is a statistically significant difference between patients with two positive blood cultures (98% SIRS+) and patients with no or unknown blood culture result (84%) and the incidence of SIRS.

With respect to mortality (Slides 10 & 11), there are no differences among the three subgroups. Although the absolute percentages appear higher in the blood culture positive groups, they are not statistically significant. The apparent discrepancy is a function of sample size. Mortality rates within a subgroup for SIRS+ and SIRS- individuals were also not significantly different. The mortality rates for the European population were higher than those of the US. This also correlated with higher percentage of SIRS found in European patients. Although patients that are moribund are usually excluded from pneumonia protocols, several enrolled European patients had illnesses best classified as severe sepsis. In sum, (1) a positive blood culture and infectious pneumonia was directly correlated with the presence of SIRS, (2) mortality rates were not dependent on blood culture positivity (3) the higher mortality risk observed in Europe was a reflection of the severity of illness in the enrolled population and (4) the mortality rates for pneumonia were not different from those rates found in patients with "bacteremic sepsis."

Although the actual values are not being presented to you at this time, because the final review has not been completed within the Division; another point of comparison is the clinical outcome for the two indications. The preliminary cure rate for the "bacteremia/septicemia" indication was essentially identical to the cure rate for patients in the pneumonia indication. Furthermore, the rate of clinical cure for patients with pneumonia with a positive blood culture or patients with pneumonia without a positive blood culture was also essentially the same.

Let me summarize what I believe has been suggested by the presentation of this data thusfar (Slide 12)

"SEPSIS"

1. SIRS and mortality rates for those patients with "BACTEREMIC SEPSIS" are independent of blood culture positivity.
2. SIRS is related to Blood culture positivity in patients with PNEUMONIA. However, mortality, as an outcome, is unrelated to the presence of a positive blood culture in these patients.
3. The clinical outcome (preliminary cure rates) in patients with BACTEREMIC SEPSIS and patients with PNEUMONIA with or without a positive blood culture are essentially the same.

This foregoing discussion is perhaps the prototype of analysis that may be undertaken in order to determine whether bacteremic patients with infection and SIRS have different therapeutic requirements. However, in this particular dataset; there are many pitfalls and it would be unwise to read too much into these results. (Slide 13) The data is, at best an approximation, because it was not designed to answer the questions that we have raised. It was hampered by the lack of available information. Data for the SIRS criteria were incomplete and were estimated using the aforementioned data points. (see Slide 13) Blood cultures were optional for most patients; this inadvertently and perhaps inaccurately dilutes the database. Patients with positive blood cultures were potentially evaluable for two indications, the primary infection and bacteremia/septicemia. However, the final evaluation was not different nor were the therapeutic measures guided by the presence or absence of bacteremia. Finally, and most importantly, the dataset reflects the experience of only a single applicant.

As stated earlier, one of the objectives for today is to determine if patients with infection, SIRS and bacteremia constitute a separate subset of patients that will require a separate indication and therapeutic management considerations. If so, what are the necessary criteria that define it. It is interesting to note that the clinicians in the NDA were able to isolate this population intuitively. This is presumably why patients with negative blood cultures and the diagnosis of "septicemia-bacteremia" had the same mortality and SIRS rates as those patients that had positive blood cultures.

A prospective study potentially could be created to answer these questions, but it would have to be very carefully designed and executed.

In sum, the Division is trying to provide meaningful statements to prescribing physicians with regard to VALID indications and the implications for therapeutic management. (Slide 14) There are several OLD drugs with labels such as the example listed in this slide which are non-specific and not helpful to the physician in the selection of a dosing regimen appropriate for his patient.

Uncomplicated infections -

use 1 gram every 12 hours

Moderate to severe infections -

use 1-2 grams every 8 hours

Infections commonly needing antibiotics in higher dosage (e.g., septicemia) -

use 2 grams every 6-8 hours

Life threatening infections -

use 2 grams every 4 hours

Range 2-12 grams/day.

Current labelling recommendations are more disease specific. These state the disease entity and the appropriate dosage for the disease.

"SEPS-5"

If it can be concluded that infected patients with and without bacteremia can achieve the same outcome with equivalent therapy, then two entities should not be artificially identified in the label. On the other hand, if two distinct entities can be delineated then it is appropriate to place them in the label.

With this background, the Division would be grateful for guidance from the Committee with regard to the questions posed in the handout. (Slide 15)

Thank you.

STATED OBJECTIVES

1. Review of the Terminology
2. Summary of July's Discussion Points
3. The "Points to Consider" Draft
4. A Recent Submission for "Bacteremia/Septicemia"
5. Selecting a Meaningful Patient Subpopulation
6. Discussion of the Questions:

Consider the population of patients with a defined infection, SIRS, bacteremia and without organ dysfunction, hypoperfusion or hypotension.

- a. Are these Patients a *Valid* Subpopulation?
- b. Do they require different therapeutic recommendations?
- c. Is a separate *Indication* useful to prescribing physicians?
- d. If so, is the indication best referred to as "*bacteremic sepsis*?"

DIVISIONAL TERMINOLOGY

PREVIOUS USAGE:

Bacteremia -

An identified Infection with at least 1 positive blood culture

Septicemia -

An identified Infection with at least 2 positive blood cultures

Bacterial Septicemia -

Synonym for septicemia

SUGGESTED TERMS:

Sepsis -

Suggested new term in the Points to Consider Draft for patients with infection, SIRS, positive blood cultures and no organ dysfunction

Bacteremic Sepsis -

More descriptive term for patients listed for "sepsis" above

Severe Sepsis/Septic Shock -

Patients with infection, SIRS and evidence of shock, perfusion abnormalities and/or end organ dysfunction

CONSENSUS GROUP TERMINOLOGY

Infection: The invasion of normally sterile host tissue by microorganisms

Bacteremia: The presence of viable bacteria in the blood

Systemic Inflammatory Response Syndrome (SIRS):
The response to a variety of clinical insults manifested by two or more of the following:

- Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or $\text{PaCO}_2 <32$ torr
- WBC $>12,000$ or $<4,000$ cells/ mm^3 or $>10\%$ bands

Sepsis: The systemic response to infection. Two of four SIRS criteria fulfilled as a response to infection.

Severe Sepsis: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension.

Septic Shock: Sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include lactic acidosis, oliguria, or an acute alteration in mental status.

Critical Care Medicine (1992; 20: 864-874).

POINTS TO CONSIDER

SEPSIS/BACTEREMIC SEPSIS:

Two adequate and well controlled trials

Primary efficacy endpoint = clinical CURE (survival)

Secondary efficacy endpoint = negative blood cultures

Inclusion criteria: SIRS, blood culture positive,
Men and women

Exclusion criteria: No shock or perfusion
abnormalities

SEPTIC SHOCK/SEVERE SEPSIS:

Two adequate and well controlled trials

Primary efficacy endpoint = MORTALITY $\pm$ Morbidity

Inclusion criteria: SIRS, objective infection, shock,
organ dysfunction, perfusion
abnormalities $\pm$ severity score
Men and women

DISEASE CONTINUUM

Well -	
Localized Infection -	
Localized Infection & Bacteremia -	Do these Patients Warrant Different Therapeutic Management?
Localized Infection & SIRS -	
Localized Infection & SIRS & Bacteremia -	Do these?
Infection, SIRS & Organ Dysfunction, Hypoperfusion &/or Hypotension -	
Infection, SIRS & Organ Dysfunction, Hypotension Unresponsive to Fluids, Pressors	
Death -	

DISTRIBUTION OF SIRS AMONG PATIENTS DIAGNOSED WITH "BACTEREMIA/SEPTICEMIA"

US & EUROPE

ENROLLED, N = 654
SIRS ASSESSABLE, N = 589

SIRS	"0" BC * n = 145	1 POS BC n = 292	2 POS BC n = 217
UNDET	18	28	19
NO	26 (20%)	42 (16%)	30 (15%)
YES	101 (80%)	222 (84%)	168 (85%)

* Most patients had a negative blood culture.
A few were classified as undetermined i.e. possibly a blood culture positive out of the pre-treatment window.

**28 DAY MORTALITY AMONG PATIENTS
DIAGNOSED WITH "BACTEREMIA/SEPTICEMIA"**

US & EUROPE

SIRS ASSESSABLE, N = 589

28 DAY DEATHS	"0" BC * n = 127	1 POS BC n = 264	2 POS BC n = 198
SIRS +	11/101 (11%)	13/222 (6%)	22/168 (13%)
SIRS -	2/26 (8%)	5/42 (12%)	5/30 (17%)
ALL	13/127 (10%)	18/264 (7%)	27/198 (14%)

* Most patients had a negative blood culture.
A few were classified as undetermined i.e. possibly a blood culture positive out of the pre-treatment window.

**28 DAY MORTALITY AMONG PATIENTS
DIAGNOSED WITH PNEUMONIA
IN PATIENTS WHERE SIRS COULD BE ASSESSED**

**US ONLY
N = 941**

28 DAY DEATHS	"0" BC* n = 844	1 POS BC n = 61	2 POS BC n = 36
SIRS +	50/699 (7%)	4/55 (7%)	4/35 (11%)
SIRS -	7/145 (5%)	1/6 (17%)	0/1 (0%)
ALL	57/844 (7%)	5/61 (8%)	4/36 (11%)

* "0" BC includes patients whose cultures were negative as well as patients who did not have a blood culture drawn

**28 DAY MORTALITY AMONG PATIENTS
DIAGNOSED WITH PNEUMONIA
IN PATIENTS WHERE SIRS COULD BE ASSESSED**

**EUROPE ONLY
N = 430**

28 DAY DEATHS	"0" BC* n = 385	1 POS BC n = 33	2 POS BC n = 12
SIRS +	33/339 (10%)	7/32 (22%)	2/12 (17%)
SIRS -	4/46 (9%)	0/1 (1%)	0/0 (0%)
ALL	37/385 (10%)	7/33 (21%)	2/12 (17%)

* "0" BC includes patients whose cultures were negative as well as patients who did not have a blood culture drawn

UNDERSTANDING THE DATA PRESENTED

1. A Retrospective look is an APPROXIMATION.
2. The original design of this database was to collect information for the "bacteremia/septicemia" indication. It was not meant to assess "SIRS" or the new "BACTEREMIC SEPSIS" definition.
6. SIRS was evaluated using the following approximations:
 - a) Pulse was used for "heart rate"
 - b) Respiratory rate was taken from the symptom score designated as "tachypnea" and "dyspnea"
 - c) WBC count was the absolute number of WBCs, no value for bands was available
 - d) temperature at entry
3. Blood cultures were OPTIONAL for most of the primary indications. This inadvertently dilutes the database.
4. A patient with a positive blood culture could potentially be evaluable for BOTH the PRIMARY INFECTION and "SEPTICEMIA."
5. The outcome assessment for BOTH indications was the clinical observation at the "test of cure" visit.
4. There was no evidence that therapeutic management (i.e. adjusting dosage) was guided by the presence or absence of a positive blood culture.
3. The data presented is a LIMITED look from a SINGLE sponsor.

**DISTRIBUTION OF SIRS AMONG PATIENTS
DIAGNOSED WITH PNEUMONIA**

US & EUROPE

N = 1510

SIRS	"0" BC* n = 1358	1 POS BC n = 102	2 POS BC n = 50
UNDET	129	8	2
NO	191 (16%)	7 (7%)	1 (2%)
YES	1038 (84%)	87 (93%)	47 (98%)

* "0" BC includes patients whose cultures were negative as well as patients who did not have a blood culture drawn

28 DAY MORTALITY AMONG PATIENTS
DIAGNOSED WITH PNEUMONIA
IN PATIENTS WHERE SIRS COULD BE ASSESSED

US & EUROPE
N = 1371

28 DAY DEATHS	"0" BC* n = 1229	1 POS BC n = 94	2 POS BC n = 48
SIRS +	83/1038 (8%)	11/87 (13%)	6/47 (13%)
SIRS -	11/191 (6%)	1/7 (14%)	0/1 (0%)
ALL	94/1229 (8%)	12/94 (13%)	6/48 (13%)

* "0" BC includes patients whose cultures were negative as well as patients who did not have a blood culture drawn

LIST OF POSSIBLE PARAMETERS - TO "SLICE" THE DATA

1. DEMOGRAPHICS - Age, Sex
2. DIAGNOSIS - UTI, SST, B&J, LRTI
3. DURATION OF TREATMENT
4. DOSE OF DRUG
5. SEVERITY SCORE
6. SIRS - WBC, RR, HR, Temp
7. BLOOD CULTURE DATA
8. EVALUABILITY
9. CLINICAL OUTCOME
10. 28 DAY MORTALITY

OLD LABELLING FORMAT

Uncomplicated infections -

use 1 gram every 12 hours

Moderate to severe infections -

use 1-2 grams every 8 hours

Infections commonly needing antibiotics in higher dosage (e.g., septicemia) -

use 2 grams every 6-8 hours

Life threatening infections -

use 2 grams every 4 hours

(Range = 2 to 12 grams administered/day)

CURRENT LABELLING

Urinary tract infection -

use 2 grams every 6 hours

QUESTIONS:

1. *Are infected patients with evidence of SIRS and concurrent bacteremia but without organ dysfunction, hypoperfusion, or hypotension a clinically different group of patients than other similarly infected patients without concurrent bacteremia?*
2. *If the answer to #1 is presently unknown, should an analysis of similarly infected patients both with and without concurrent bacteremia be undertaken? If so, what parameters would be meaningful in such an analysis?*
3. *If the answer to #1 is yes, are these clinical differences such that different therapeutic approaches are warranted?*
4. *If the answer to #1 is yes, are these clinical differences such that physicians would be helped by information included in a separate indication section in drug product labelling called "bacteremic sepsis."*

SUMMARY

1. SIRS and mortality rates for those patients with "BACTEREMIC SEPSIS" are independent of blood culture positivity.
2. SIRS is related to Blood culture positivity in patients with PNEUMONIA. However, mortality, as an outcome, is unrelated to the presence of a positive blood culture in these patients.
3. The clinical outcome (cure rates) in patients with BACTEREMIC SEPSIS and patients with PNEUMONIA with or without a positive blood culture are essentially the same.

END

MD

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