CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-222

MICROBIOLOGY REVIEW

Division of Anti-Infective Drug Products
Clinical Microbiological Review # 1

NDA # 21-222 **Date Completed:June 26, 2001**

Applicant

TAP Holdings inc.
2355 Waukegan Road
Deerfield, Illinois. 60015

Chem/Ther. Type: Broad spectrum cephalosporin (Cephem)

Submission Reviewed: Original NDA

Indications applied for: Oral treatment of Acute Bacterial Exacerbation of Chronic Bronchitis, [redacted] Pharyngitis/Tonsillitis and, Uncomplicated Skin and Skin Structure Infections.

Product Name:

Proprietary: Spectracef

Non-proprietary: Cefditoren Pivoxil:

Code number: 4010300

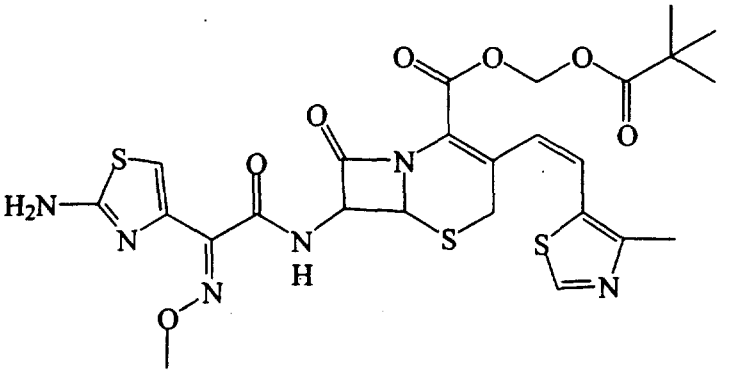
Chemical name:

(6R,7R)-2,2-DIMETHYLPROPIONYLOXYMETHYL 7-((Z)-2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINOACETAMIDO)-3-((Z)-2-(4-METHYLTHIAZOL-5-YL) ETHENYL)-8-OXO-5-THIA-1-AZABICYCLO(4.2.0)OCT-2-ENE-2-CARBOXYLATE

Mol weight: 620

Mol Formula: $C_{25}H_{28}N_6O_7S_3$

Structural formula:



Dosage form: 200 Mg Tablets BID

Route of administration: Oral

Pharmacological Category: Antiinfective

Dispensed: Rx

Initial Submission Dates

Received by CDER: 12/29/99
Received by Reviewer: 01/04/00
Review Completed: 1/06/12

Related Documents:

[redacted]

Remarks:

- **The analysis of the pharmacokinetics and pharmacodynamics of this antibiotic will be conducted with the primary emphasis on MIC $_{90}$ susceptibility endpoints.**
- **Since the drug is 88% serum bound and a cephem, antibiotic susceptibility breakpoints will be related to clinical results and isolates and/or, unbound drug.**
- **Cefditoren has a relatively short T1/2, 1-2h and the % bioavailability is low, 16% with a 25% variation.**
- **The *in vitro* antimicrobial spectrum includes gram positive and negative bacteria.**
- **Cefditoren binds to penicillin binding proteins and resists β-lactamase**
- **The numbers of strains used in the applicant's analysis are small and a broad geographic and genetic distribution is not included.**
- **Scattergrams of MIC versus zone size is lacking in numbers and spectrum i.e. the applicant has included 251 isolates but 500-2,000 is the NCCLS standard. Only gram positives bacteria including the 6 organisms targeted for clinical indications and *Neisseria* were included in the scattergram, gram-negative bacteria were not.**
- **In the text, references were numbered but they were not numbered in the reference volumes making it difficult and time consuming to find the original text and documents.**
- **Clinical results including cure and eradication for infections caused by *S. aureus* and *H. influenzae* do not correlated with MICs.**
- **Neither the applicant's proposed pharmacodynamics nor clinical results support breakpoints of 2, 4, and 8ug/ml.**

Conclusion: The microbiological portion of the NDA submission is lacking information to support several microbiology items in the draft package insert. The lack of support will be reflected by recommended changes to the applicant's

proposed package insert. The recommended microbiology section of the PI is given in Ceditoren review # 2.

Table of Contents:

INTRODUCTION:

Cefditoren pivoxyl is a cephem antibiotic under development and clinical evaluation in the United States by Tap Holdings inc. It is being proposed by the applicant for usage in the oral treatment of: Acute Bacterial Exacerbation of Chronic Bronchitis, [redacted] Pharyngitis/Tonsillitis and, Uncomplicated Skin and Skin Structure Infections. It is being targeted for the eradication of 6 species of bacteria: S. *aureus, S. pneumonia, H. influenzae, H. parainfluenzae, S. pyogenes, and M. catarrhalis.* Cefditoren has consistent activity versus gram positive and variable activity versus gram negative bacteria and is active in animal models of infectious disease. Cefditoren is 88% serum bound, to Human Serum Albumen, and has a half-life of 1-2 hours in man.

PRECLINICAL EFFICACY

In vitro

Mechanism(s) of Action.

Cefditoren acts similarly to other β-lactam antibiotics by binding to Penicillin Binding Proteins (PBPs) in the cytoplasmic membrane and preventing cell wall

formation in susceptible organisms resulting in cidal activity. The protein binding site was determined by the ability of Cefditoren to displace bound radioactive penicillin G. Specific sites of binding were PBP 1, 2, 3, and weakly to PBP 4 of S. aureus; PBPs 1, 2, and 4 of *S. pneumoniae*; PBPs-3, 1a and 1b of *E. coli* and *P. aeruginosa*; and to PBP 4, and 5 of *H. influenzae*. Bacterial killing was studied in time kill studies and as a low MBC/MIC ratio. In time kill studies, 4 to eight times the MIC of Cefditoren was needed to obtain 99.9% kill for strains of *S. aureus, S. pyogenes, S. pneumoniae, H. influenzae, M. catarrhalis, E. coli, and K. pneumoniae*. Cidal activity was shown by observing a tube dilution MBC/MIC ratio of 2 or less when 10 isolates each of *S. pneumoniae, Group A Streptococcus, S. aureus (MSSA), H. influenzae and M. catarrhalis* were tested.

Antimicrobial Spectrum of Activity.

With the exception of *S. pneumoniae* and *M. catarrhalis,* few isolates of each genus and species were tested and the geographic distribution was narrow. Several statements by the FDA including the January 1993 NDA holders letter strongly recommend 100 or more isolates representing broad geographic distribution be tested to establish the antimicrobial activity of a test antibiotic versus a given genus and species of microorganism. Information concerning requirements for the submission of Microbiological data and needed data were conveyed to the applicant at and following the pre-NDA meeting of August 26, 1999 including the NDA Holder's letter and the draft guidance for the format of microbiological data, version #70.

With the above limitations, Cefditoren exhibited *in vitro* activity against gram-positive organisms:

(See the applicant's tables which follow)

1. Active versus Methicillin susceptible *S. aureus*
2. Active versus Methicillin susceptible *S. epidermidis*
3. Active versus *S. pyogenes and other β- and α-hemolytic streptococci*
4. Active versus *S. pneumoniae*
5. Inactive versus methicillin resistant *Staphylococcus aureus* (MRSA) and *E. faecalis*.

Table 3.6.3a ***In Vitro*** **Antibacterial Activity of Cefditoren and Other Cephalosporin Antibiotics against *S. aureus* Clinical Isolates; US Studies**

Organism	No. of Isolates	Compound	MIC (µg/mL) MIC_{50}	MIC_{90}	Range	Ref
S. aureus Methicillin-susceptible	21	Cefditoren	0.5	1		1
		Cefotaxime	1	2		
		Cefaclor	2	4		
S. aureus Methicillin-susceptible	18	Cefditoren	0.5	1		3
		Cefotaxime	2	8		
		Ceftazidime	8	16		
		Cefixime	>32	>32		
S. aureus Methicillin-resistant	20	Cefditoren	16	>32		3
		Cefotaxime	4	64		
		Ceftazidime	16	>128		
S. aureus Methicillin-resistant	9	Cefditoren	>64			1
		Cefotaxime	>64			
		Cefaclor	>64			

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Table 3.6.3c *In Vitro* Antibacterial Activity of Cefditoren and Other Cephalosporin Antibiotics against *S. pneumoniae* Clinical Isolates: US Studies

Organism	No. of Isolates	Compound	MIC (µg/mL) MIC$_{50}$	MIC$_{90}$	Range	Ref
S. pneumoniae	17	Cefditoren	≤0.06	0.12		3
		Cefotaxime	≤0.06	0.12		
		Ceftazidime	0.6	0.25		
		Cefixime	0.25	0.5		
S. pneumoniae Penicillin-Susceptible	336	Cefditoren	≤0.008	0.015		2,6
		Cefadroxil	≤1	2		
		Cefaclor	0.25	0.5		
		Cefprozil	≤0.12	≤0.12		
		Cefuroxime	≤0.12	≤0.12		
		Cefixime	0.25	0.5		
		Cefpodoxime	≤0.03	0.06		
S. pneumoniae Penicillin-Susceptible	75	Cefditoren	≤0.06	≤0.06		9
		Cefdinir	≤0.06	0.125		
		Cefuroxime	≤0.06	0.125		
		Cefpodoxime	≤0.06	0.125		
		Cefprozil	≤0.06	0.125		
		Cefaclor	0.25	0.5		
		Cefixime	0.125	0.5		
		Ceftriaxone	0.03	0.125		
S. pneumoniae Penicillin-Susceptible	10	Cefditoren	0.015	0.015		1
		Cefotaxime	0.015	0.03		
		Cefaclor	0.5	1		
S. pneumoniae Penicillin-Intermediate	108	Cefditoren	0.12	0.5		2,6
		Cefadroxil	16	>16		
		Cefaclor	8	64		
		Cefprozil	1	4		
		Cefuroxime	1	4		
		Cefixime	>4	>4		
		Cefpodoxime	0.5	2		
S. pneumoniae Penicillin-Intermediate	55	Cefditoren	0.125	0.5		9
		Cefdinir	0.25	2.0		
		Cefuroxime	1.0	4.0		
		Cefpodoxime	0.25	2.0		
		Cefprozil	0.5	4.0		
		Cefaclor	2.0	>16.0		
		Cefixime	4.0	>16.0		
		Ceftriaxone	0.25	1.0		
S. pneumoniae Penicillin-Intermediate	10	Cefditoren	0.12	1		1
		Cefotaxime	0.12	1		
		Cefaclor	2	64		
S. pneumoniae Penicillin-Resistant	73	Cefditoren	0.5	1.0		9
		Cefdinir	4.0	8.0		
		Cefuroxime	4.0	4.0		
		Cefpodoxime	2.0	4.0		
		Cefprozil	4.0	16.0		
		Cefaclor	>16.0	>16.0		
		Cefixime	>16.0	>16.0		
		Ceftriaxone	2.0	2.0		

Table 3.6.3c ***In Vitro*** **Antibacterial Activity of Cefditoren and Other Cephalosporin Antibiotics against *S. pneumoniae* Clinical Isolates; US Studies (continued)**

Organism	No. of Isolates	Compound	MIC (μg/mL) MIC_{50}	MIC (μg/mL) MIC_{90}	MIC (μg/mL) Range	Ref
S. pneumoniae Penicillin-Resistant	56	Cefditoren	0.5	2		2,6
		Cefadroxil	>16	>16		
		Cefaclor	64	>64		
		Cefprozil	8	>16		
		Cefuroxime	4	16		
		Cefixime	>4	>4		
		Cefpodoxime	>4	>4		
S. pneumoniae Penicillin-Resistant	15	Cefditoren	1	2		1
		Cefotaxime	1	4		
		Cefaclor	>64	>64		

Table 3.6.3d ***In Vitro*** **Antibacterial Activity of Cefditoren and Other Cephalosporin Antibiotics against *S. pyogenes* Clinical Isolates; US Studies**

Organism	No. of Isolates	Compound	MIC (μg/mL) MIC_{50}	MIC (μg/mL) MIC_{90}	MIC (μg/mL) Range	Ref
S. pyogenes	25	Cefditoren	≤0.015	0.03		3
		Cefotaxime	0.015	0.06		
		Ceftazidime	0.25	0.5		
		Cefixime	0.12	0.25		
S. pyogenes	20	Cefditoren	0.008	0.015		1
		Cefotaxime	0.015	0.015		
		Cefaclor	0.12	0.25		

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Table 3.6.3e ***In Vitro*** **Antibacterial Activity of Cefditoren and Other Cephalosporin Antibiotics against *Streptococcus* spp. Clinical Isolates; US Studies**

Organism	No. of Isolates	Compound	MIC (µg/mL) MIC_{50}	MIC (µg/mL) MIC_{90}	MIC (µg/mL) Range	Ref
S. agalactiae (Group B)	15	Cefditoren	≤0.015	0.03		3
		Cefotaxime	0.015	0.06		
		Ceftazidime	0.25	0.5		
		Cefixime	0.12	0.25		
S. agalactiae (Group B)	20	Cefditoren	0.03	0.06		1
		Cefotaxime	0.06	0.06		
		Cefaclor	0.5	1		
Streptococcus Group C	11	Cefditoren	≤0.015	0.03		3
		Cefotaxime	0.015	0.03		
		Ceftazidime	0.25	0.25		
		Cefixime	0.12	0.25		
Streptococcus Group C	10	Cefditoren	0.015	0.12		1
		Cefotaxime	0.03	0.12		
		Cefaclor	0.25	2		
Streptococcus Group G	10	Cefditoren	≤0.015	0.03		3
		Cefotaxime	0.015	0.03		
		Ceftazidime	0.25	0.5		
		Cefixime	0.03	0.15		
Streptococcus Group G	10	Cefditoren	0.015	0.015		1
		Cefotaxime	0.015	0.03		
		Cefaclor	0.25	0.25		
Streptococcus Viridans group	10	Cefditoren	0.5	4		3
		Cefotaxime	0.25	4		
Streptococcus bovis (Group D)	10	Cefditoren	0.25	0.5		3
		Cefotaxime	0.12	0.5		
		Ceftazidime	0.25	1		
		Cefixime	0.5	1		
Enterococcus faecalis (Group D)	20	Cefditoren	8	8		3
		Cefotaxime	128	>128		
		Ceftazidime	>128	>128		
		Cefixime	>32	>32		
E. faecalis (Group D)	20	Cefditoren	>64	>64		1
		Cefotaxime	>64	>64		
		Cefaclor	>64	>64		
S. faecalis (Group D)	10	Cefditoren	>32	>32		3
E. faecium (Group D)	20	Cefditoren	>64	>64		1
		Cefotaxime	>64	>64		
		Cefaclor	>64	>64		

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Variable *in vitro* activity was noted against Gram-negative bacteria (based on small numbers). H. influenzae and M. catarrhalis can be included in the list of organisms proven for clinical indications since large numbers were included. For the other listed genera and species of gram negative bacteria, less than 100 isolates were examined for each genus and species therefore, they can not be included in list two of the package insert.

(See the applicant's tables that follow)

1. Active versus *H. influenzae and M. catarrhalis*, β-lactamase positive (but with less activity versus the gram-negative strains) and negative strains.
2. Active versus *E. coli, Shigella spp. Klebsiella pneumonia, Klebsiella oxytoca, Proteus vulgaris,* and *Proteus mirabilis.*
3. Did not inhibit *Pseudomonas aeruginosa*
4. Had weak and or variable activity against *Citrobacter freundii, Enterobacter cloacae,* and anaerobes such as *Bacteroides spp., Bacteroides fragilis, and Clostridium difficile.*

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Table 3.6.3f ***In Vitro*** **Antibacterial Activity of Cefditoren and Other Cephalosporin Antibiotics against *H. influenzae* Clinical Isolates; US Studies**

Organism	No. of Isolates	Compound	MIC (μg/mL) MIC_{50}	MIC (μg/mL) MIC_{90}	MIC (μg/mL) Range	Ref
H. influenzae Ampicillin-resistant	13	Cefditoren	≤0.015	0.06		3
		Cefotaxime	0.015	0.12		
		Ceftazidime	0.12	1		
		Cefixime	0.12	0.25		
H. influenzae type b	25	Cefditoren	≤0.008	≤0.008		4
		Cefaclor	1	4		
		Cefixime	≤0.03	≤0.03		
		Cefpodoxime	≤0.03	0.06		
		Cefprozil	1	4		
		Cefuroxime	≤0.25	0.5		
		Cefotaxime	≤0.03	≤0.03		
		Ceftriaxone	≤0.03	≤0.03		
H. influenzae β-lactamase-positive	173	Cefditoren	≤0.008	0.015		2,6
		Cefadroxil	>16	>16		
		Cefaclor	4	64		
		Cefprozil	4	>16		
		Cefuroxime	0.5	2		
		Cefixime	≤0.03	≤0.03		
		Cefpodoxime	≤0.03	0.12		
H. influenzae β-lactamase-positive	15	Cefditoren	0.015	0.03		1
		Cefotaxime	0.015	0.06		
		Cefaclor	2	8		
H. influenzae β-lactamase negative	326	Cefditoren	≤0.008	0.015		2,6
		Cefadroxil	>16	>16		
		Cefaclor	2	8		
		Cefprozil	2	8		
		Cefuroxime	0.5	4		
		Cefixime	≤0.03	≤0.03		
		Cefpodoxime	≤0.03	0.12		
H. influenzae β-lactamase negative	5	Cefditoren	0.008			1
		Cefotaxime	0.008			
		Cefaclor	1			
H. influenzae BLNAR	5	Cefditoren	0.5			1
		Cefotaxime	0.25			
		Cefaclor	8			
H. influenzae unTypeable	154	Cefditoren	≤0.008	≤0.008		4,5
		Cefaclor	2	16		
		Cefixime	≤0.03	≤0.03		
		Cefpodoxime	0.06	0.12		
		Cefprozil	2	16		
		Cefuroxime	0.5	2		
		Cefotaxime	≤0.03	≤0.03		
		Ceftriaxone	≤0.03	≤0.03		

BLNAR: β-lactamase negative ampicillin-resistant

Table 3.6.3g ***In Vitro*** **Antibacterial Activity of Cefditoren and Other Cephalosporin Antibiotics against *H. parainfluenzae* Clinical Isolates; US Studies**

Organism	No. of Isolates	Compound	MIC (µg/mL) MIC_{50}	MIC_{90}	Range	Ref
H. parainfluenzae	21	Cefditoren	≤0.008	0.015		4,5
		Cefaclor	2	8		
		Cefixime	≤0.03	0.06		
		Cefpodoxime	0.06	0.5		
		Cefprozil	2	8		
		Cefuroxime	0.5	2		
		Cefotaxime	≤0.03	≤0.03		
		Ceftriaxone	≤0.03	≤0.03		

Table 3.6.3h ***In Vitro*** **Antibacterial Activity of Cefditoren and Other Cephalosporin Antibiotics against *M. catarrhalis* Clinical Isolates; US Studies**

Organism	No. of Isolates	Compound	MIC (µg/mL) MIC_{50}	MIC_{90}	Range	Ref
M. catarrhalis Ampicillin-resistant	11	Cefditoren	0.03	0.25		3
		Cefotaxime	0.03	0.06		
		Cefixime	0.03	0.25		
M. catarrhalis	250	Cefditoren	0.12	0.5		2,6
		Cefadroxil	2	4		
		Cefaclor	0.5	1		
		Cefprozil	1	4		
		Cefuroxime	1	2		
		Cefixime	0.25	0.25		
		Cefpodoxime	0.5	1		
M. catarrhalis	50	Cefditoren	0.12	0.25		4,5
		Cefaclor	1	2		
		Cefixime	0.25	0.25		
		Cefpodoxime	1	1		
		Cefprozil	2	8		
		Cefuroxime	1	2		
		Cefotaxime	0.5	0.5		
		Ceftriaxone	0.5	0.5		
M. catarrhalis β-lactamase-positive	15	Cefditoren	0.06	0.5		1
		Cefotaxime	0.12	0.5		
		Cefaclor	2	4		
M. catarrhalis β-lactamase-negative	5	Cefditoren	0.015			1
		Cefotaxime	0.06			
		Cefaclor	0.25			

Table 3.6.3i ***In Vitro*** **Antibacterial Activity of Cefditoren and Other Cephalosporin Antibiotics against** ***Enterobacteriaceae*** **and** ***Pseudomonas aeruginosa*** **Clinical Isolates; US Studies**

Organism	No. of Isolates	Compound	MIC (μg/mL) MIC_{50}	MIC_{90}	Range	Ref
Citrobacter diversus Ampicillin-resistant	10	Cefditoren	0.5	1		3
		Cefotaxime	0.06	0.12		
		Ceftazidime	0.12	0.25		
		Cefixime	0.5	1		
Citrobacter freundii Ampicillin-resistant	25	Cefditoren	2	>32		3
		Cefotaxime	2	128		
		Ceftazidime	1	>128		
		Cefixime	2	>32		
E. coli Ampicillin-resistant	20	Cefditoren	0.25	0.5		3
		Cefotaxime	0.06	0.12		
		Ceftazidime	0.25	0.5		
		Cefixime	0.12	2		
Enterobacter aerogenes Ampicillin-resistant	10	Cefditoren	1	32		3
		Cefotaxime	0.12	32		
		Ceftazidime	0.25	32		
		Cefixime	1	32		
Enterobacter cloacae Ampicillin-resistant	24	Cefditoren	1	>32		3
		Cefotaxime	1	64		
		Ceftazidime	2	>128		
		Cefixime	2	>32		
Klebsiella pneumoniae Ampicillin-resistant	20	Cefditoren	0.25	2		3
		Cefotaxime	0.06	0.12		
		Ceftazidime	0.25	1		
		Cefixime	0.06	0.5		
Klebsiella oxytoca Ampicillin-resistant	10	Cefditoren	0.25	0.5		3
		Cefotaxime	0.03	0.12		
		Ceftazidime	0.25	0.5		
		Cefixime	0.12	0.25		
Morganella morganii Ampicillin-resistant	15	Cefditoren	0.12	1		3
		Cefotaxime	0.03	1		
		Ceftazidime	0.12	4		
		Cefixime	2	4		
Proteus mirabilis	15	Cefditoren	0.12	1		3
		Cefotaxime	0.015	0.03		
		Ceftazidime	0.06	0.12		
		Cefixime	0.03	0.03		
Proteus vulgaris Ampicillin-resistant	10	Cefditoren	0.25	2		3
		Cefotaxime	0.25	2		
		Ceftazidime	≤0.06	0.25		
		Cefixime	0.015	2		

Table 3.6.3k ***In Vitro*** **Antibacterial Activity of Cefditoren and Other Cephalosporin Antibiotics against Other Bacterial Clinical Isolates; US Studies**

Organism	No. of Isolates	Compound	MIC (µg/mL) MIC_{50}	MIC (µg/mL) MIC_{90}	MIC (µg/mL) Range	Ref
N. gonorrhoeae Ampicillin-resistant	11	Cefditoren	≤0.015	≤0.015		3
		Cefotaxime	0.008	0.03		
		Ceftazidime	0.03	0.06		
		Cefixime	0.03	0.25		
S. haemolyticus	10	Cefditoren	64	>64		1
		Cefotaxime	>64	>64		
		Cefaclor	>64	>64		
Listeria monocytogenes	17	Cefditoren	4	32		3
		Cefotaxime	16	16		
		Ceftazidime	>128	>128		
		Cefixime	>32	>32		

Table 3.6.3j ***In Vitro*** **Antibacterial Activity of Cefditoren and Other Cephalosporin Antibiotics against Anaerobic Bacterial Clinical Isolates; US Studies**

Organism	No. of Isolates	Compound	MIC (µg/mL) MIC_{50}	MIC (µg/mL) MIC_{90}	MIC (µg/mL) Range	Ref
Bacteroides spp.	20	Cefditoren	4	32		3
		Cefotaxime	32	>32		
		Ceftazidime	>32	>32		
		Cefixime	>32	>32		
Clostridium spp.	18	Cefditoren	1	8		3
		Cefotaxime	1	8		
		Cefixime	2	8		

Table 3.6.3i ***In Vitro*** **Antibacterial Activity of Cefditoren and Other Cephalosporin Antibiotics against *Enterobacteriaceae* and *Pseudomonas aeruginosa* Clinical Isolates; US Studies (continued)**

Organism	No. of Isolates	Compound	MIC (μg/mL.) MIC_{50}	MIC_{90}	Range	Ref
Providencia rettgeri Ampicillin-resistant	10	Cefditoren	0.5	2		3
		Cefotaxime	0.06	2		
		Ceftazidime	0.25	2		
		Cefixime	0.03	1		
Providencia stuartii Ampicillin-resistant	15	Cefditoren	0.5	4		3
		Cefotaxime	0.06	1		
		Ceftazidime	0.5	1		
		Cefixime	0.03	0.5		
Salmonella spp. Ampicillin-resistant	20	Cefditoren	0.25	1		3
		Cefotaxime	0.12	0.5		
		Ceftazidime	0.5	4		
		Cefixime	0.25	0.5		
Shigella spp. Ampicillin-resistant	20	Cefditoren	0.25	1		3
		Cefotaxime	0.03	0.12		
		Ceftazidime	0.25	2		
		Cefixime	0.25	0.5		
Serratia marcescens Ampicillin-resistant	25	Cefditoren	1	16		3
		Cefotaxime	1	4		
		Ceftazidime	0.25	1		
		Cefixime	2	>32		
Pseudomonas aeruginosa Ampicillin-resistant	15	Cefditoren	64	>128		3
		Cefotaxime	128	>128		
		Ceftazidime	4	32		
		Cefixime	>32	>32		
Acinetobacter anitratus Ampicillin-resistant	8	Cefditoren	16	16		3
		Cefotaxime	16	32		
		Ceftazidime	8	32		
		Cefixime	>32	>32		

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Mechanism(s) of Resistance Studies

Organisms resistant to Cefditoren were not obtained in serial passage studies using strains of *S. pneumoniae*. Subculturing two Gram-positive and four Gram-negative bacteria on antibiotic containing agar plates after exposure to ¼ their MIC to cefditoren did not result in the development of cefditoren resistant bacteria. Organisms resistant to other cephem antibiotics were not examined for cross-resistance to cefditoren. Cefditoren had MIC_{90s} of 0.5 and 1.0 ug/ml against penicillin intermediate (55 isolates) and resistant *S. pneumoniae* (73 isolates) and an MIC_{90} of 0.15 against erythromycin resistant *S. pneumoniae* (37 isolates)

Post Antibiotic effects:

A 1-1.5 hr effect on the growth of organisms was seen using S. *aureus*. This was the only result presented on PAE.

Epidemiological Studies (Published Literature).

In vitro: Was not presented in a proper format, only literature references are provided. Information concerning requirements for the submission of Microbiological data and needed data were conveyed to the applicant at and following the pre-NDA meeting of August 26, 1999 including the NDA Holder's letter and the draft guidance for the format of microbiological data, version #70.

Pharmacokinetics/Bioavailability (Human and animal).

Because of poor oral absorption, an inactive pivoxil ester was synthesized and is used clinically for oral administration. Following adsorption in man, the Cefditoren pivoxil ester is hydrolyzed to the active form, cefditoren, by esterases. The absolute bioavailability in adults using the 200-mg tablet is 14%. Maximum plasma concentrations averaged 1.82 µg/mL in fasted patients and 2.67 µg/mL in patients fed a fatty meal following a 200-mg dose. The coefficient of variation for T_{max} was high, 36%. Plasma elimination is rapid with the $T_{1/2}$ ranging from one to two hours. Binding of cefditoren to plasma proteins is high, averaging 88% from *in vitro* determinations. Saturation of binding sites did not occur at 100 µg/ml where binding remained at 87%. Since the effect of serum on antiinfectives is unpredictable, it is important to study MICs in the presence of 50% human serum, serum can raise or lower MICs-lowering MICs for Geftriaxone that is also strongly serum bound but raising MICs for other antibiotics. For cefditoren, MICs were raised approximately 8 fold when MICs were conducted in the presence of 50% serum. Distribution of Cefditoren in the tissues does not appear to be

extensive, with concentrations in the tonsils [redacted] being 10 to 35% that of serum and 56% in non-inflammatory blister fluid and 40% in inflammatory blister fluid. These findings are relevant when evaluating the suitability of cefditoren for the treatment of [redacted] tonsilitis/pharyngitis and skin infections and, for the determination of breakpoints. Pharmacokinetics following administration of 3 and 6 mg/kg doses to children, were similar to that seen for the 200 and 400 mg doses in adults.

End-of-Text Table 4. Time-Above-MIC Data for Unbound Cefditoren from 84 Subjects Who Participated in Five Phase I Studies and Received 400 mg Cefditoren Pivoxil (continued)

	Percentage of Time in Dose Interval that Unbound Cefditoren Plasma Concentrations Exceed MIC (µg/mL)						
	2	1	0.5	0.25	0.12	0.015	0.008
All Subjects							
Mean	0	0	2.5	22.5	36.4	78.6	90.3
SD	0	0	4.7	8.0	7.9	11.5	9.1
%CV	-	-	187	35	22	15	10
Median	0	0	0	23	36	78	92
Minimum	[redacted]						
Maximum							
N	84	84	84	84	84	84	84
Male Subjects							
Mean	0	0	1.8	20.8	34.9	76.6	89.2
SD	0	0	4.1	8.0	7.5	11.3	9.1
%CV	-	-	230	39	22	15	10
Median	0	0	0	21	35	75	91
Minimum	[redacted]						
Maximum							
N	46	46	46	46	46	46	46
Female Subjects							
Mean	0	0	3.4	24.6	38.2	81.0	91.7
SD	0	0	5.2	7.5	8.1	11.5	8.9
%CV	-	-	155	31	21	14	10
Median	0	0	0	24	38	82	93
Minimum	[redacted]						
Maximum							
N	38	38	38	38	38	38	38

Pharmacodynamics: see Table 4: (a dose of 400 Mg, dosing at 200 mg would give lower blood levels. Thus, the T>MIC would be less than for the 400-mg dose.)

For cephem antibiotics, *invivo* activity is related to unbound antibiotic. For cephalosporins and penicillins, animal and human correlations have indicated that *invivo* antibiotic activity is related to time above the MIC_{90} with 40% usually considered to be the minimum time needed. As seen in the above table for studies of the pharmacokinetics and pharmacodynamics of cefditoren, time above MIC values for unbound drug exceeded 36.4% only against organisms with MICs of 0.12 µg/ml or less (for cephem antibiotics and cefditoren is a

cephem, activity is related to unbound drug). Thus on a PK/PD basis, breakpoints can not be justified above 0.12 ug/ml. Clinical results of sufficient numbers and consistency can lead to higher breakpoints than justified by PK/PD findings. The applicant's proposed breakpoints of 2 (S), 4(I), and 8(R) ug/ml are higher than justified by the PK/PD results and will therefore also be examined using clinical findings.

Animal Prophylactic and Therapeutic Studies.

As shown in Table 3.6.4h, Cefditoren pivoxil was active orally in systemic infectious models in mice using various gram positive and gram negative bacteria. It appears that most of the studies were conducted in Japan with some findings being expressed in terms of MG/KG which is more common in the US and others in terms of Mg/mouse which is commonly written by Japanese authors. Cefditoren was comparable in activity to the other tested antibiotics including cefpodoxime proxetil, cefteram pivoxil, cefaclor, cefixime cefotiam and cefdinir. Although low ED_{50} values are curative for the mice, Cefditoren MICs versus the test organisms are low and do not give added evidence for the applicant's proposed breakpoints.

Table 3.6.4h Activity of Cefditoren in Systemic Infection Models in Mice[24,26,29,32,33]

Organism	MIC (μg/mL)	ED_{50} (mg/mouse)
S. aureus (3 strains; 2 β-lac+)	0.20-0.78	0.15-0.55
S. pneumoniae (4 strains)	0.012-0.032	0.02-0.10
S. pyogenes (1 strain)	≤0.006	0.009
K. pneumoniae (5 strains; 1 β-lac+)	0.10-0.25	0.12-2.0
S. marcescens (2 strains)	0.78	0.14-0.22
E. coli (6 strains; 2 β-lac+)	0.01-0.78	0.03-1.6
P. vulgaris (1 strain; β-lac+)	0.20	4.0
P. mirabilis (2 strains)	0.10-0.20	0.09-0.16

As shown in the following table, Cefditoren pivoxil displayed activity in several infectious models in mice including burn, abscess, pulmonary in normal animals, pulmonary in leukopenic animals and urinary tract infection. Organisms studied included, *S. aureus, K. pneumoniae and E. coli.* Although ED_{50} values are curative for the mice, Cefditoren MICs versus the test organisms are low and pharmacokinetic/dynamic parameters in the animal models were not discussed. Therefore the relation of these animal findings to potential human clinical efficacy are not known.

Table 3.6.4i Effects of Cefditoren in Other Infection Models in Mice[22,35,36]			
Model	Organism	MIC (μg/mL)	Activity
Burn	*S. aureus* (2 strains)	0.78-1.56	1-5 mg/mouse (BID x 1 day)
Subcutaneous Abscess	*S. aureus* (2 strains)	0.78-1.56	ED_{50}: 1.8-3.3 mg/kg (0.04-0.07 mg/mouse) BID x 1 day
Pulmonary Infection	*K. pneumoniae*	0.10	25-100 mg/kg (0.5-2 mg/mouse) BID x 1 day; QD x 1 day
Pulmonary Infection in Leukopenic Mice	*S. pneumoniae*	0.012	25 mg/kg (0.5 mg/mouse) QD x 4 days
Urinary Tract Infection	*E. coli*	0.39	0.5-2 mg/mouse BID x 3 days

Derivation of Provisional Breakpoints for use in Clinical Trials

NEED FOR CEFDITOREN BREAKPOINTS

In order to see if cefditoren breakpoints could be different than those of other cephalosporins, in *vitro* studies were conducted by the Clinical Microbiological Institute (CMI). They compared cefditoren susceptibility data for both the disk and MIC methods against two previously approved antimicrobial agents, the oral agent, cefaclor, and the parenteral agent, cefotaxime. Recent clinical isolates from the CMI collection were used (age of isolates not specified). Both MIC and zone sizes increase linearly when comparing zone versus zone and MIC versus MIC when comparing cefditoren individually to each of the other two antibiotics. Cefditoren was more active than the other two antibiotics in this in vitro test. However, when comparing serum binding, cefditoren is bound approximately 88% to serum while the figures are 70% for cefotaxime and 25% for cefaclor. Because of this binding, it is unlikely that these comparisons will have clinical validity. 251 isolates total were included in the analysis, see figures. 3.6.6a, b, c, and d. Because of the greater activity of cefditoren and the differences in PK, separate cefditoren breakpoints will need to be determined.

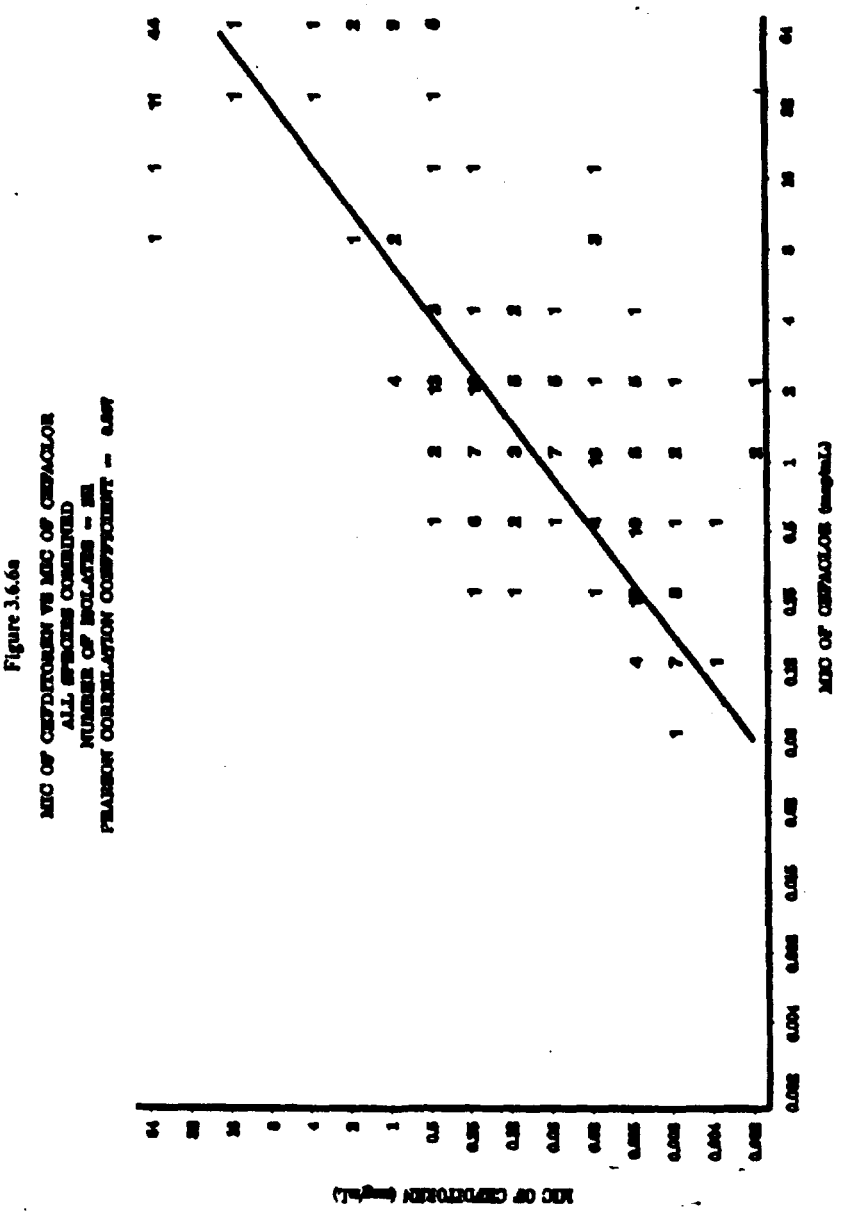


Figure 3.6.6a
MIC OF CEFDITOREN VS MIC OF CEFACLOR
ALL STRAINS COMBINED
NUMBER OF ISOLATES = 101
PEARSON CORRELATION COEFFICIENT = 0.697
MIC OF CEFACLOR (mg/mL)
MIC OF CEFDITOREN (mg/mL)

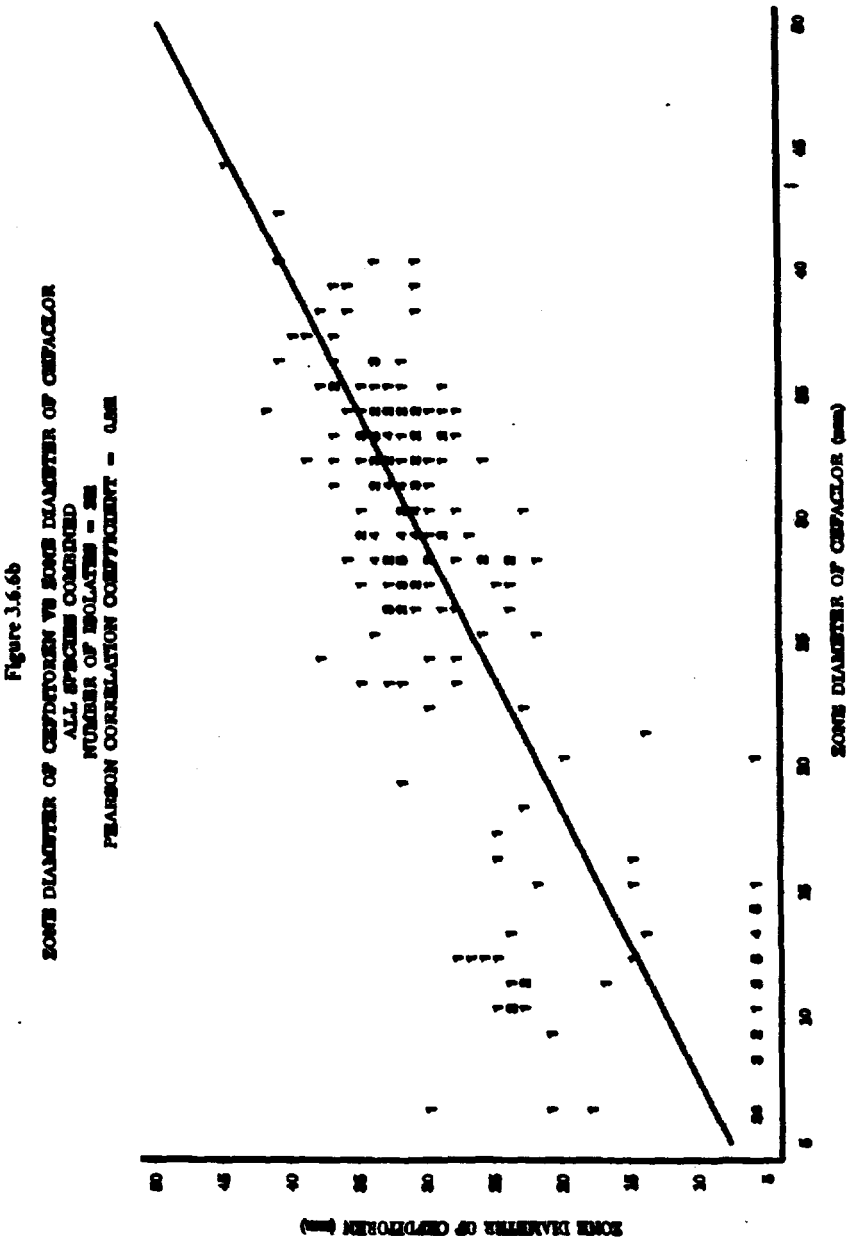

ZONE DIAMETER OF CEFDITOREN VS ZONE DIAMETER OF CEFACLOR
ALL SPECIES COMBINED
NUMBER OF ISOLATES = 288
PEARSON CORRELATION COEFFICIENT = -0.88
ZONE DIAMETER OF CEFACLOR (mm)
ZONE DIAMETER OF CEFDITOREN (mm)

Figure 3.6.6b

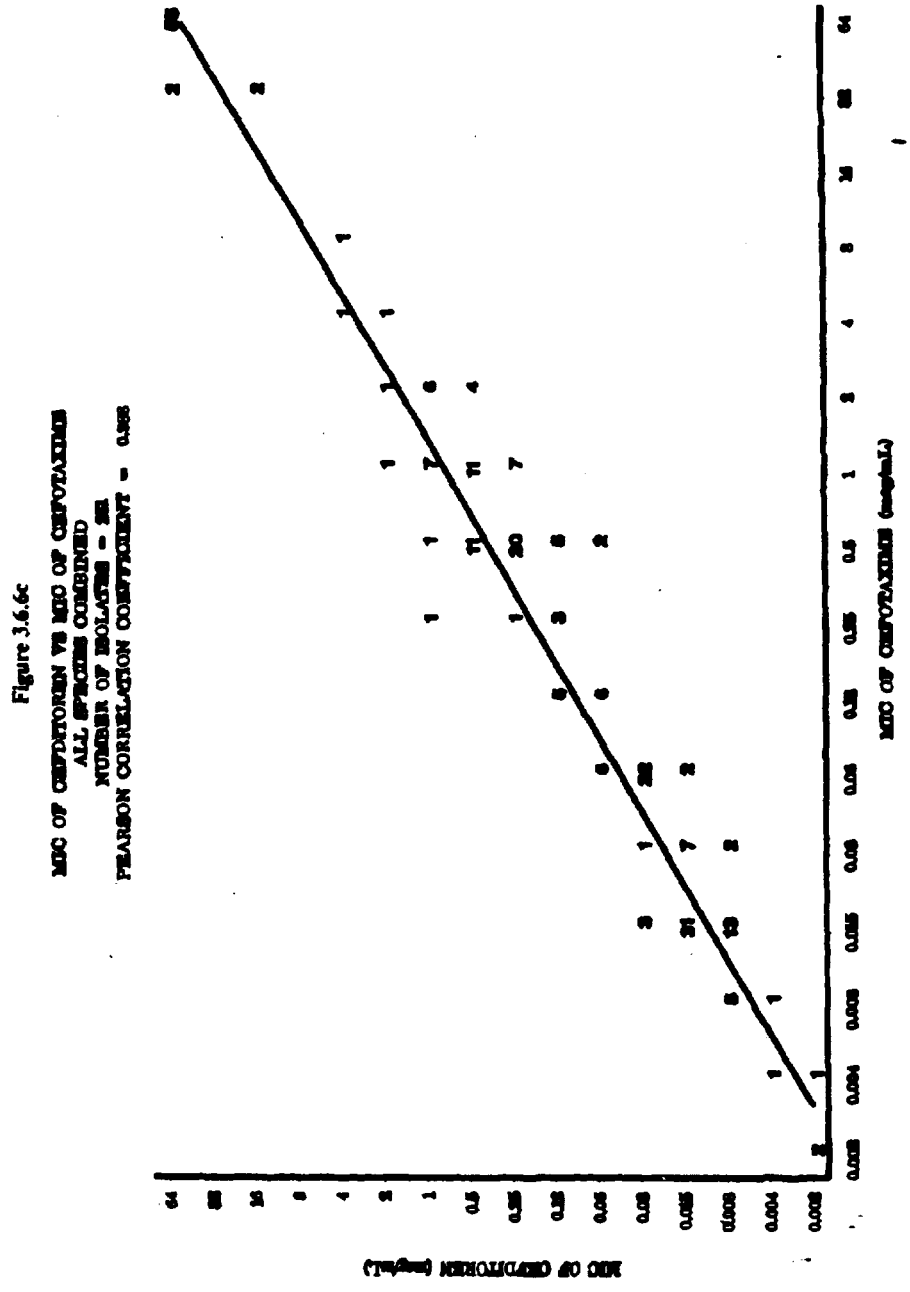


Figure 3.6.6c
MIC OF CEFDITOREN VS MIC OF CEFOTAXIME
ALL SPECIES COMBINED
NUMBER OF ISOLATES = 281
PEARSON CORRELATION COEFFICIENT = 0.955
MIC OF CEFOTAXIME (mcg/mL)
MIC OF CEFDITOREN (mcg/mL)

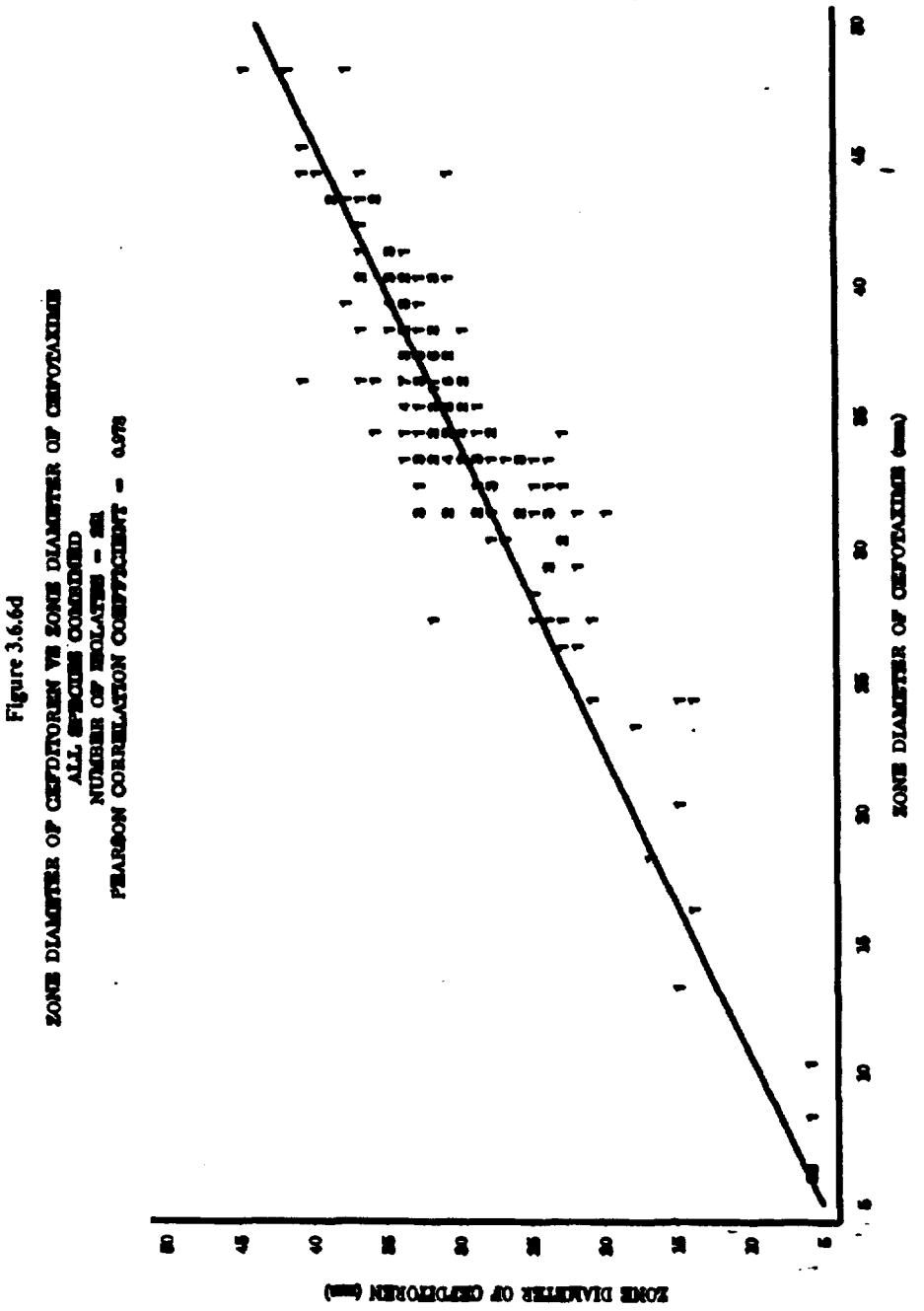

ZONE DIAMETER OF CEFDITOREN VS ZONE DIAMETER OF CEFOTAXIME
ALL SPECIES COMBINED
NUMBER OF ISOLATES = 251
PEARSON CORRELATION COEFFICIENT = 0.976
ZONE DIAMETER OF CEFOTAXIME (mm)
ZONE DIAMETER OF CEFDITOREN (mm)

Figure 3.6.6d

MIC and Disk diffusion Correlation Studies.

The frequency distributions on which the applicant based tentative breakpoints are shown in his reference one (1) that refers to Study CMI-97-31. In that study, a plot of MIC versus Zone diameter is shown for 251 strains from the CMI stock culture collection. Plots for individual genera and species were also presented.

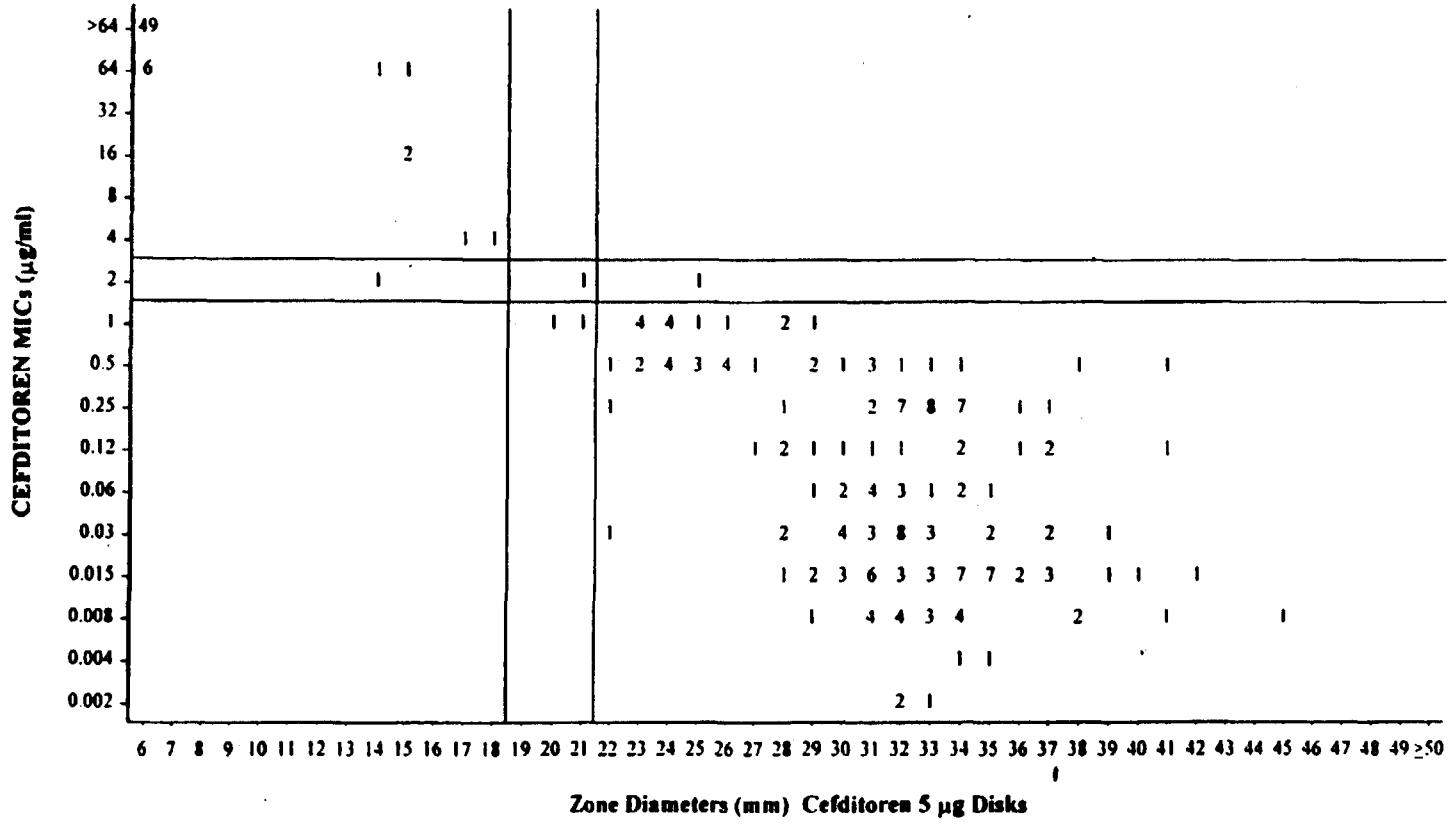
The isolates included, 10 *MRSA*, 10 *S. haemolyticus*, 10 *VR E. faecalis*, 10 *VR E. faecium*, 35 *S. pneumoniae*-10 susceptible, 10 intermediate and 15 resistant, 15 B-lactamase-positive M. catarrhalis, 5 *M. catarrhalis-B-lactamase negative, 15 B-lactamase positive H. influenzae* and 5 strains of *B-lactamase-negative ampicillin resistant (BLNAR) H. influenzae* 20 *S. epidermidis*, 20 *S. pyogenes*, 20 *S. agalactiae* and 10 *"C" streptococci.*

. This number of strains and composition of the data set is inadequate to establish the correlation between MIC and zone size, please refer to NCCLS document M23[1]. In the NCCLS document, 500 isolates are listed as the minimum number needed for this type of scattergram. The spectrum of organisms is also inadequate because members of the Enterobacteriaceae were not included amongst the organisms used in the scattergram. Therefore, zone diameter correlates can not be determined. The applicant will have to provide further evidence including more organisms and a broader spectrum of organisms to provide adequate evidence for his proposed breakpoints. Considering these limitations, the applicant made the following observations and proposed the following tentative MIC breakpoints:

Even though data requirements were not met, the TAP discussion and proposal is included as follows: The plot of zone diameter versus MIC was linear and tentative breakpoints of 1, 2 and 4 (4 minor errors) or 2, 4, and 8 (1 minor error) were proposed by TAP (table 3.6.6a) for the classification of sensitive, intermediate and resistant organisms respectively and 0.12, 0.25 and 0.5 for *S. pneumoniae*. A 5-mcg disc was used for the analysis. However a 10 and 30 mcg disc gave similar linear results with identical tentative breakpoints. Because of smaller zones of inhibition, the 5-mcg disc was chosen for development.

The MIC/zone diameter distribution used for the in vitro test development should be compared with those obtained from a large geographically diverse selection of recent clinical isolates of all clinically important organisms for the requested indications. This comparison was not conducted, adding to the difficulties of the evaluation.

Figure 1. CEFDITOREN MICs (µg/ml) vs ZONE DIAMETER (mm) 5 µg Disks
ALL SPECIES COMBINED



Frequency distributions and scattergrams were presented for the separate genera and species that constituted the 251 isolates in the all species combined scattergram. Since the numbers of organisms were small and they did not constitute a large number of organisms based on a wide geographic distribution, the distribution frequencies and scattergrams will not be included in this report.

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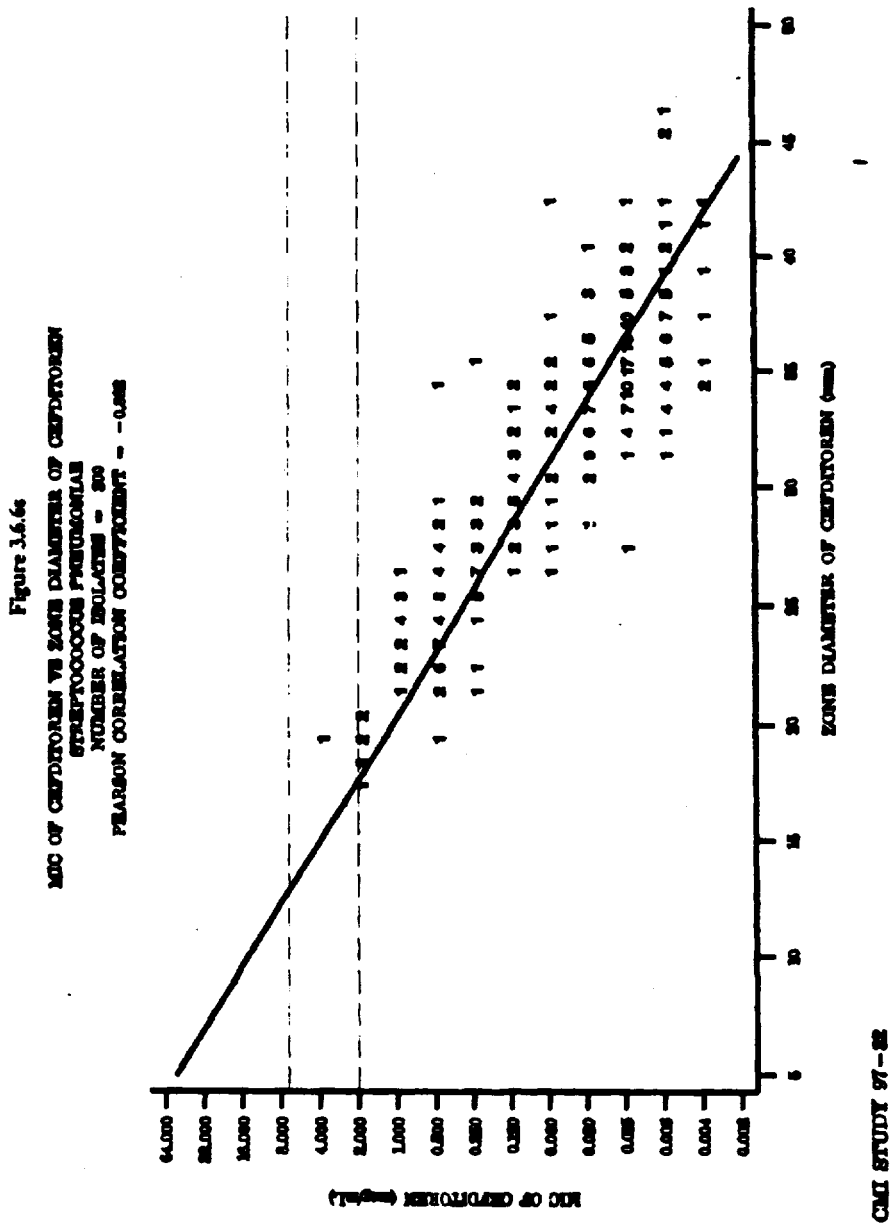

Separate scattergrams were presented for 300 strains of *S. pneumonia* (figure 3.6.6s) and 297 strains of *H. influenzae* (Figure 3.6.6t). Based on the applicant's

analysis, and provisional breakpoints in table 3.6.6b, there were no major errors for *S. pneumoniae* and 4 minor errors for *H. influenzae*.

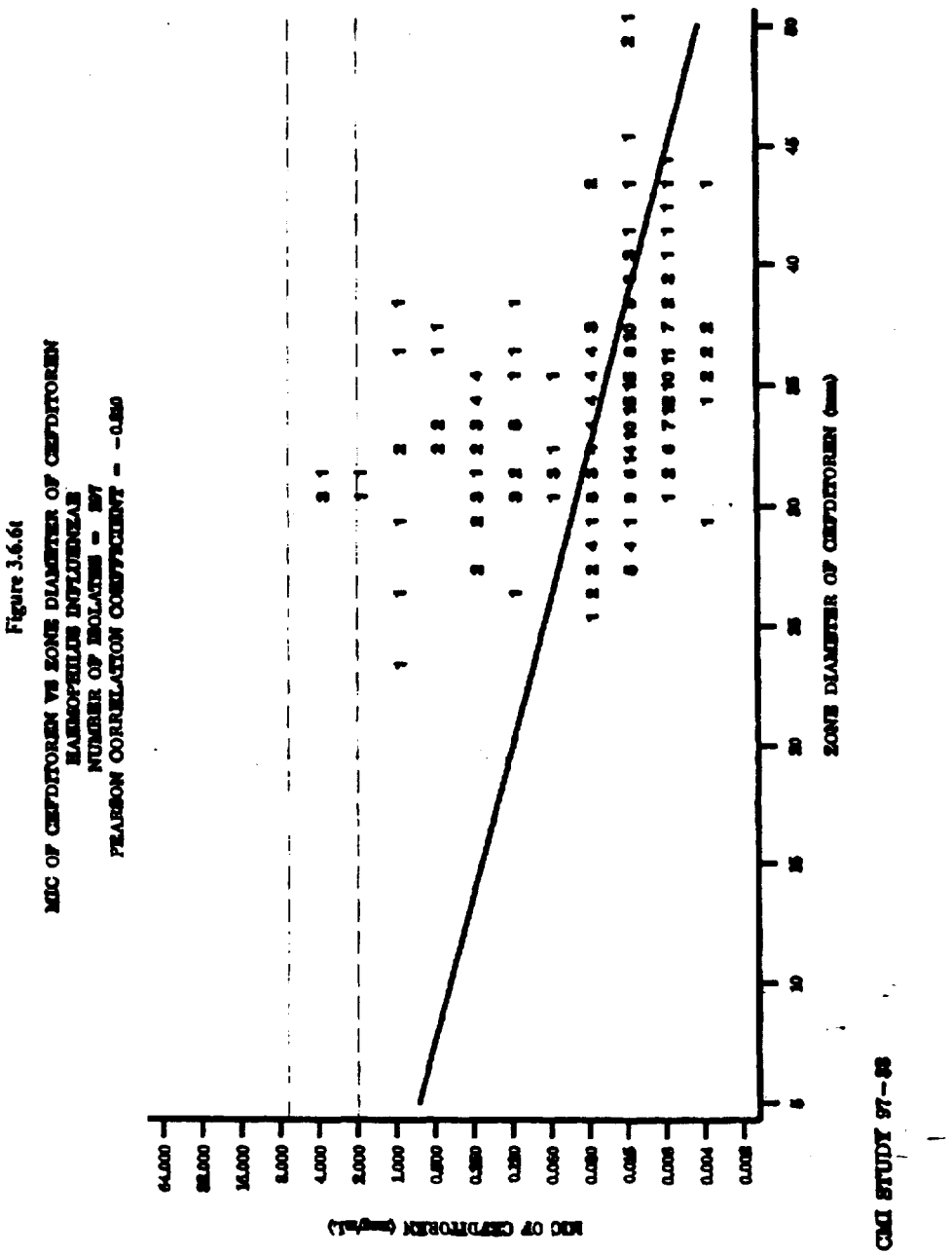

Figure 3.6.6i
MIC OF CEFDITOREN VS ZONE DIAMETER OF CEFDITOREN
HAEMOPHILUS INFLUENZAE
NUMBER OF ISOLATES = 297
PEARSON CORRELATION COEFFICIENT = -0.860

Bacteriological Efficacy

Correlation of Test Results with Outcome Statistics.

Cefditoren was compared with other antibiotics in clinical studies for efficacy versus 6 target pathogens: *S. pneumoniae, S. pyogenes, S. aureus, H. influenzae, H. parainfluenzae, and M. catarrhalis*. The organisms were compared in 7 clinical studies and the antibiotic comparators were clarithromycin, cefuroxime axetil, amoxicillin/clavulanate potassium, cefadroxil monohydrate, cefuroxime axetil, and Pen VK. The distribution of organisms and *in vitro* activity of cefditoren is shown in Table 3.6.7a and comparative *in vitro* activity in Table 3.6.7b. Based on the applicant's analysis of MIC 50 and 90 results, the *in vitro* activity of cefditoren was comparable or superior to the other tested agents against the clinical isolates. PK/PD parameters were not taken into account in the applicant's analysis making conclusions of superiority and clinical predictions questionable.

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Cefditoren Pivoxil
Application Summary – Microbiology Summary

Table 3.6.7a. *In vitro* Activity of Cefditoren for Pretreatment Clinical Study Isolates

Organism	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC Range (µg/mL)
H. influenzae				
All indications	348	0.015	0.030	
Sinusitis	60	0.015	0.060	
Bronchitis	288	0.015	0.030	
H. parainfluenzae				
All indications	814	0.030	0.060	
Sinusitis	14	0.030	0.060	
Bronchitis	800	0.030	0.060	
M. catarrhalis				
All indications	222	0.060	0.500	
Sinusitis	44	0.120	0.500	
Bronchitis	178	0.060	0.500	
S. pneumoniae				
All indications	198	0.015	0.500	
Sinusitis	73	0.015	0.500	
Bronchitis	125	0.015	0.500	
S. pyogenes				
All indications	866	0.015	0.015	
Pharyngitis	799	0.015	0.015	
Skin	53	0.015	0.015	
S. aureus				
All indications	725	1.000	1.000	
Skin	525	1.000	1.000	
Sinusitis	83	1.000	8.000	
Bronchitis	117	1.000	1.000	

Table 3.6.7b. *In vitro* **Activity of Comparators Against Pretreatment Clinical Study Isolates**

		MIC 50/90 µg/mL (MIC Range)				
Organism	N	Penicillin	Amoxicillin/Clavulanate[a] or Amoxicillin[b]	Cefuroxime	Cefadroxil[c]	Clarithromycin
S. pneumoniae						
All indications	198	0.03/2		0.06/4	N/A	0.03/2
Bronchitis	125	0.03/2	0.03/2	0.06/4		0.03/2
S. pyogenes						
All indications	866	0.015/0.015		0.06/0.06	N/A	0.03/0.06
% susc[d]		97%		N/A		95%
Pharyngitis	799	0.15/0.015	0.03/0.03	0.06/0.06	N/A	0.03/0.06
Skin	57	0.15/0.015	0.03/0.03	0.06/0.06	0.25/0.25 (0.12-0.25)	0.03/0.5
S. aureus						
All indications	725	8/16		2/4	N/A	0.5/64
% susc[d]		13%			N/A	76%
Pharyngitis	177	8/16	4/32	2/2	N/A	0.5/64
Skin	525	4/16	4/32	2/2	4/8 (1-64)	0.5/64
H. influenzae						
All indications	348	0.5/16		1/2	N/A	8/16
Bronchitis	248	0.5/16	1/64	1/2		8/16
H. parainfluenzae						
All indications	814	1.0/4		0.5/1	N/A	8/16
Bronchitis	800	1.0/4	0.5/1	0.5/1		8/16
M. catarrhalis						
All indications	222	2/16		0.5/2	N/A	0.12/0.12
% susc[d]				96%		98%
Bronchitis	178	2/16	0.5/4	0.5/2		

a Comparator for the sinusitis study; amoxicillin/clavulanate activity was determined for sinusitis isolates only.
b Amoxicillin activity was determined for bronchitis, pharyngitis, and skin isolates only.
c Cefadroxil was a comparator in one skin and skin structure infection trial; its activity was determined for skin isolates only.
[d] % susceptibility based on NCCLS interpretive criteria M100-S7, 1997. *M. catarrhalis* interpretive criteria not available, *S. aureus* criteria were used. N/A no interpretive criteria available.

Microbiologic efficacy of Cefditoren at the test of cure visit, results for the 6 organisms are presented in the following text and the following 6 tables. Results of the 200 MG dose are in the left hand columns and the 400 MG dose in the right hand column. The applicant did not present results obtained from the comparator antibiotics concerning eradication rates, only comparative MICs.

Streptococcus pneumoniae:

A total of 198 pretreatment isolates were obtained. 135 in the combined 200-mg and 400-mg cefditoren dose groups. Results demonstrated overall eradication rates of 86% for all indications, [redacted] 92% for bronchitis when patients were treated with 200-mg doses of cefditoren. However, when treated with 400-mg of cefditoren, eradication rates were 78% for all indications, [redacted] and 86% for bronchitis. Results are shown in tables 3.6.7c and 3.6.7d. Near to the proposed breakpoints, 5/6 organisms having a cefditoren MIC of 0.125 µg/mL were eradicated, 4/10 having an MIC of 0.25 µg/ml were eradicated and 4/5 organisms having a cefditoren MIC of 0.5 ug/ml were eradicated. (Table 3.6.7c).

Table 3.6.7c. Microbiologic Response by Pretreatment Cefditoren MIC for *S. pneumoniae* at the Follow-Up Visit (Test-of-Cure)

Pretreatment Cefditoren MIC (µg/mL)	Cefditoren Pivoxil 200 mg Number of Isolates				Cefditoren Pivoxil 400 mg Number of Isolates			
	N	Eradication[a]	Persistence[a]	N/A[b]	N	Eradication[a]	Persistence[a]	N/A[b]
All Indications								
≤0.015	38	33 (97%)	1 (3%)	4	38	27 (79%)	7 (21%)	4
0.030	6	6 (100%)	0	0	5	4 (80%)	1 (20%)	0
0.060	4	0	4 (100%)	0	4	4 (100%)	0	0
0.120	3	2 (67%)	1 (33%)	0	3	3 (100%)	0	0
0.250	7	6 (86%)	1 (14%)	0	8	5 (71%)	2 (29%)	1
0.500	4	1 (50%)	1 (50%)	2	9	5 (63%)	3 (38%)	1
1.000	2	2 (100%)	0	0	3	2 (67%)	1 (33%)	0
2.000	0	0	0	0	0	0	0	0
4.000	1	1 (100%)	0	0	0	0	0	0
8.000	0	0	0	0	0	0	0	0
16.000	0	0	0	0	0	0	0	0
≥32.000	0	0	0	0	0	0	0	0
Total	65	51 (86%)	8 (14%)	6	70	50 (78%)	14 (22%)	6
[redacted]								
Bronchitis								
≤0.015	24	21 (100%)	0	3	21	15 (83%)	3 (17%)	3
0.030	5	5 (100%)	0	0	4	4 (100%)	0	0
0.060	2	0	2 (100%)	0	2	2 (100%)	0	0
0.120	2	1 (50%)	1 (50%)	0	1	1 (100%)	0	0
0.250	4	4 (100%)	0	0	7	5 (83%)	1 (17%)	1
0.500	2	0	0	2	4	3 (75%)	1 (25%)	0
1.000	1	1 (100%)	0	0	1	1 (100%)	0	0
2.000	0	0	0	0	0	0	0	0
4.000	1	1 (100%)	0	0	0	0	0	0
8.000	0	0	0	0	0	0	0	0
16.000	0	0	0	0	0	0	0	0
≥32.000	0	0	0	0	0	0	0	0
Total	41	33 (92%)	3 (8%)	5	40	31 (86%)	5 (14%)	4

a Eradication and presumed eradication are combined. Persistence and presumed persistence are combined. In the [redacted] the clinical response was used as the presumed microbiologic response for patients without a microbiologic response.

b Indeterminate or missing response; not included in eradication or persistence calculation.

Table 3.6.7d. Microbiologic Response by Pretreatment Cefditoren Zone of Inhibition for *S. pneumoniae* at the Follow-Up Visit (Test-of-Cure)

Pretreatment Zone Diameter Grouping (mm)	Cefditoren Pivoxil 200 mg Number of Isolates				Cefditoren Pivoxil 400 mg Number of Isolates			
	N	Eradication[a]	Persistence[a]	N/A[b]	N	Eradication[a]	Persistence[a]	N/A[b]
All Indications								
<20	1	1 (100%)	0	0	0	0	0	0
20-25	3	2 (100%)	0	1	6	5 (83%)	1 (17%)	0
26-30	11	7 (70%)	3 (30%)	1	12	7 (70%)	3 (30%)	2
31-35	12	9 (82%)	2 (18%)	1	10	8 (80%)	2 (20%)	0
36-40	11	8 (89%)	1 (11%)	2	25	19 (86%)	3 (14%)	3
>40	27	24 (92%)	2 (8%)	1	17	11 (69%)	5 (31%)	1
Total	65	51 (86%)	8 (14%)	6	70	50 (78%)	14 (22%)	6
[redacted]								
Bronchitis								
<20	1	1 (100%)	0	0	0	0	0	0
20-25	2	1 (100%)	0	1	3	3 (100%)	0	0
26-30	7	5 (83%)	1 (17%)	1	7	5 (83%)	1 (17%)	1
31-35	8	7 (88%)	1 (13%)	0	7	7 (100%)	0	0
36-40	6	4 (100%)	0	2	16	12 (86%)	2 (14%)	2
>40	17	15 (94%)	1 (6%)	1	7	4 (67%)	2 (33%)	1
Total	41	33 (92%)	3 (8%)	5	40	31 (86%)	5 (14%)	4

a Eradication and presumed eradication are combined. Persistence and presumed persistence are combined. In the [redacted] the clinical response was used as the presumed microbiologic response for patients without a microbiologic response.

b Indeterminate or missing response; not included in eradication or persistence calculation.

Streptococcus pyogenes

458 *S. pyogenes* isolates were obtained from patients treated with cefditoren. The patients were from 2 pharyngitis studies and 2 skin studies with the majority coming from the pharyngitis study. Cure rates were 100% when treated with 400mg and 89-100% when treated with 200 mg of cefditoren. The persistent organisms all had low MICs, 0.03 or less. Organisms with the highest MICs, 0.120 (3/3) or 0.250 (2/2) were all eradicated. Bacteria were not isolated near the applicants proposed breakpoints of 2ug/ml for susceptible.

Table 3.6.7e. Microbiologic Response by Pretreatment Cefditoren MIC for *S. pyogenes* at the Post-Therapy Visit (Test-of-Cure Visit for Pharyngitis)

Pretreatment Cefditoren MIC (µg/mL)	Cefditoren Pivoxil 200 mg Number of Isolates				Cefditoren Pivoxil 400 mg Number of Isolates			
	N	Eradication[a]	Persistence[a]	N/A[b]	N	Eradication[a]	Persistence[a]	N/A[b]
All Indications								
≤0.015	408	357 (93%)	26 (7%)	25	26	23 (100%)	0	3
0.030	8	7 (88%)	1 (13%)	0	1	1 (100%)	0	0
0.060	10	10 (100%)	0	0	0	0	0	0
0.120	3	3 (100%)	0	0	0	0	0	0
0.250	2	2 (100%)	0	0	0	0	0	0
0.500	0	0	0	0	0	0	0	0
1.000	0	0	0	0	0	0	0	0
2.000	0	0	0	0	0	0	0	0
4.000	0	0	0	0	0	0	0	0
8.000	0	0	0	0	0	0	0	0
16.000	0	0	0	0	0	0	0	0
≥32.000	0	0	0	0	0	0	0	0
Total	431	379 (93%)	27 (7%)	25	27	24 (100%)	0	3
Pharyngitis								
≤0.015	381	333 (93%)	26 (7%)	22				
0.030	7	6 (86%)	1 (14%)	0				
0.060	10	10 (100%)	0	0				
0.120	3	3 (100%)	0	0				
0.250	2	2 (100%)	0	0				
0.500	0	0	0	0				
1.000	0	0	0	0				
2.000	0	0	0	0				
4.000	0	0	0	0				
8.000	0	0	0	0				
16.000	0	0	0	0				
≥32.000	0	0	0	0				
Total	403	354 (93%)	27 (7%)	22				
Skin								
≤0.015	23	21 (100%)	0	2	18	15 (100%)	0	3
0.030	1	1 (100%)	0	0	1	1 (100%)	0	0
0.060	0	0	0	0	0	0	0	0
0.120	0	0	0	0	0	0	0	0
0.250	0	0	0	0	0	0	0	0
0.500	0	0	0	0	0	0	0	0
1.000	0	0	0	0	0	0	0	0
2.000	0	0	0	0	0	0	0	0
4.000	0	0	0	0	0	0	0	0
8.000	0	0	0	0	0	0	0	0
16.000	0	0	0	0	0	0	0	0
≥32.000	0	0	0	0	0	0	0	0
Total	24	22 (100%)	0	2	19	16 (100%)	0	3

a Eradication and presumed eradication are combined. Persistence and presumed persistence are combined.
b Indeterminate or missing response; not included in eradication or persistence calculation.

Table 3.6.7f. Microbiologic Response by Pretreatment Cefditoren MIC for *S. pyogenes* at the Follow-Up Visit (Test-of-Cure Visit for Skin)

Pretreatment Cefditoren MIC (µg/mL)	Cefditoren Pivoxil 200 mg Number of Isolates				Cefditoren Pivoxil 400 mg Number of Isolates			
	N	Eradication[a]	Persistence[a]	N/A[b]	N	Eradication[a]	Persistence[a]	N/A[b]
All Indications								
≤0.015	408	326 (89%)	39 (11%)	43	26	23 (100%)	0	3
0.030	8	6 (86%)	1 (14%)	1	1	1 (100%)	0	0
0.060	10	9 (100%)	0	1	0	0	0	0
0.120	3	3 (100%)	0	0	0	0	0	0
0.250	2	2 (100%)	0	0	0	0	0	0
0.500	0	0	0	0	0	0	0	0
1.000	0	0	0	0	0	0	0	0
2.000	0	0	0	0	0	0	0	0
4.000	0	0	0	0	0	0	0	0
8.000	0	0	0	0	0	0	0	0
16.000	0	0	0	0	0	0	0	0
≥32.000	0	0	0	0	0	0	0	0
Total	431	346 (90%)	40 (10%)	45	27	24 (100%)	0	3
Pharyngitis								
≤0.015	381	303 (89%)	38 (11%)	40				
0.030	7	5 (83%)	1 (17%)	1				
0.060	10	9 (100%)	0	1				
0.120	3	3 (100%)	0	0				
0.250	2	2 (100%)	0	0				
0.500	0	0	0	0				
1.000	0	0	0	0				
2.000	0	0	0	0				
4.000	0	0	0	0				
8.000	0	0	0	0				
16.000	0	0	0	0				
≥32.000	0	0	0	0				
Total	403	322 (89%)	39 (11%)	42				
Skin								
≤0.015	23	19 (95%)	1 (5%)	3	18	15 (100%)	0	3
0.030	1	1 (100%)	0	0	1	1 (100%)	0	0
0.060	0	0	0	0	0	0	0	0
0.120	0	0	0	0	0	0	0	0
0.250	0	0	0	0	0	0	0	0
0.500	0	0	0	0	0	0	0	0
1.000	0	0	0	0	0	0	0	0
2.000	0	0	0	0	0	0	0	0
4.000	0	0	0	0	0	0	0	0
8.000	0	0	0	0	0	0	0	0
16.000	0	0	0	0	0	0	0	0
≥32.000	0	0	0	0	0	0	0	0
Total	24	20 (95%)	1 (5%)	3	19	16 (100%)	0	3

a Eradication and presumed eradication are combined. Persistence and presumed persistence are combined.
b Indeterminate or missing response; not included in eradication or persistence calculation.

Staphylococcus aureus:

495 *S. aureus* strains were isolated from patients in the cefditoren dose groups from 5 clinical studies, [redacted] 2 bronchitis, and 2 skin. The eradication rate at the test of cure visit was 85% for the 200 and 400-mg dose groups. Isolates were eradicated, regardless of MIC, i.e., 6/8 organisms isolated from the 200 mg dose group and 11/12 isolated from patients treated with 400 mg of cefditoren and having cefditoren MICs greater than 32

ug/ml were eradicated! See table 3.6.7i and 3.6.7j-the left columns represent results from a 200 Mg dose and the right columns from a 400 Mg dose of cefditoren. Therefore it is difficult to determine breakpoints for *S. aureus.* It is of interest that in vitro, cefditoren is not active against MRSA strains. Results from the two skin and skin structure trials, 97-009 and 97-011, show that 26/27 MRSA strains were eradicated in the patients and the patients cured clinically. Therefore, it is possible that the organisms isolated were either not pathogens or cefditoren is active in humans against MRSA (cefditoren MIC_{90} >32 μg/mL) and high level cefditoren resistant strains. The applicant also presented genetic and biochemical arguments that eradication might represent decreased bioburden by cefditoren due to heterogeneous resistance of the *S. aureus* isolates. However proof of heterogeneous resistance in the applicant's clinical isolates, based on laboratory findings, was not presented.

Table 3.6.7i. Microbiologic Response by Pretreatment Cefditoren MIC for *S. aureus* at the Follow-Up Visit

Pretreatment (ug/mL)	N	Eradication[a]	Persistence[a]	N/A[b]	N	Eradication[a]	Persistence[a]	N/A[b]
All Indications								
≤0.015	0	0	0	0	0	0	0	0
0.030	0	0	0	0	0	0	0	0
0.060	0	0	0	0	0	0	0	0
0.120	0	0	0	0	1	1 (100%)	0	0
0.250	5	4 (100%)	0	1	1	1 (100%)	0	0
0.500	100	80 (83%)	16 (17%)	4	104	82 (87%)	12 (13%)	10
1.000	109	85 (87%)	13 (13%)	11	121	89 (82%)	19 (18%)	13
2.000	4	4 (100%)	0	0	3	2 (67%)	1 (33%)	0
4.000	4	3 (75%)	1 (25%)	0	6	4 (67%)	2 (33%)	0
8.000	6	5 (83%)	1 (17%)	0	6	5 (100%)	0	1
16.000	1	1 (100%)	0	0	2	2 (100%)	0	0
≥32.000	10	6 (75%)	2 (25%)	2	12	11 (92%)	1 (8%)	0
Total	239	188 (85%)	33 (15%)	18	256	197 (85%)	35 (15%)	24
Bronchitis								
≤0.015	0	0	0	0	0	0	0	0
0.030	0	0	0	0	0	0	0	0
0.060	0	0	0	0	0	0	0	0
0.120	0	0	0	0	0	0	0	0
0.250	1	0	0	1	0	0	0	0
0.500	19	16 (84%)	3 (16%)	0	21	16 (94%)	1 (6%)	4
1.000	16	13 (87%)	2 (13%)	1	18	11 (85%)	2 (15%)	5
2.000	0	0	0	0	0	0	0	0
4.000	1	1 (100%)	0	0	0	0	0	0
8.000	0	0	0	0	0	0	0	0
16.000	0	0	0	0	1	1 (100%)	0	0
>32.000	2	0	0	2	1	1 (100%)	0	0
Total	39	30 (86%)	5 (14%)	4	41	29 (91%)	3 (9%)	9
Skin								
≤0.015	0	0	0	0	0	0	0	0
0.030	0	0	0	0	0	0	0	0
0.060	0	0	0	0	0	0	0	0
0.120	0	0	0	0	1	1 (100%)	0	0
0.250	4	4 (100%)	0	0	1	1 (100%)	0	0
0.500	72	55 (81%)	13 (19%)	4	78	64 (89%)	8 (11%)	6
1.000	82	61 (85%)	11 (15%)	10	86	66 (85%)	12 (15%)	8
2.000	4	4 (100%)	0	0	2	1 (50%)	1 (50%)	0
4.000	2	1 (50%)	1 (50%)	0	4	3 (75%)	1 (25%)	0
8.000	5	5 (100%)	0	0	6	5 (100%)	0	1
16.000	0	0	0	0	1	1 (100%)	0	0
≥32.000	6	5 (83%)	1 (17%)	0	7	7 (100%)	0	0
Total	175	135 (84%)	26 (16%)	14	186	149 (87%)	22 (13%)	15

a Eradication and presumed eradication are combined. Persistence and presumed persistence are combined. In the sinusitis study, the clinical

Table 3.6.7j. Microbiologic Response by Pretreatment Cefditoren Zone of Inhibition for *S. aureus* at the Follow-Up Visit (Test-of-Cure)

Pretreatment Zone Diameter Grouping (mm)	Cefditoren Pivoxil 200 mg Number of Isolates				Cefditoren Pivoxil 400 mg Number of Isolates			
	N	Eradication[a]	Persistence[a]	N/A[b]	N	Eradication[a]	Persistence[a]	N/A[b]
All Indications								
<11	12	8 (80%)	2 (20%)	2	20	18 (95%)	1 (5%)	1
11-15	7	6 (86%)	1 (14%)	0	5	4 (80%)	1 (20%)	0
16-20	10	8 (89%)	1 (11%)	1	8	6 (86%)	1 (14%)	1
21-25	179	141 (85%)	24 (15%)	14	199	151 (84%)	29 (16%)	19
26-30	28	22 (81%)	5 (19%)	1	22	17 (89%)	2 (11%)	3
>30	3	3 (100%)	0	0	2	1 (50%)	1 (50%)	0
Total	239	188 (85%)	33 (15%)	18	256	197 (85%)	35 (15%)	24
[redacted]								
Bronchitis								
<11	2	0	0	2	1	1 (100%)	0	0
11-15	0	0	0	0	1	1 (100%)	0	0
16-20	2	2 (100%)	0	0	1	0	0	1
21-25	27	21 (84%)	4 (16%)	2	35	26 (93%)	2 (7%)	7
26-30	5	4 (80%)	1 (20%)	0	2	1 (100%)	0	1
>30	3	3 (100%)	0	0	1	0	1 (100%)	0
Total	39	30 (86%)	5 (14%)	4	41	29 (91%)	3 (9%)	9
Skin								
<11	7	6 (86%)	1 (14%)	0	15	14 (100%)	0	1
11-15	7	6 (86%)	1 (14%)	0	3	3 (100%)	0	0
16-20	6	5 (100%)	0	1	5	5 (100%)	0	0
21-25	136	104 (84%)	20 (16%)	12	143	111 (85%)	20 (15%)	12
26-30	19	14 (78%)	4 (22%)	1	19	15 (88%)	2 (12%)	2
>30	0	0	0	0	1	1 (100%)	0	0
Total	175	135 (84%)	26 (16%)	14	186	149 (87%)	22 (13%)	15

a Eradication and presumed eradication are combined. Persistence and presumed persistence are combined. In [redacted], the clinical response was used as the presumed microbiologic response for patients without a microbiologic response.

b Indeterminate or missing response; not included in eradication or persistence calculation.

HAEMOPHILUS INFLUENZAE:

234 *H. influenzae* strains were isolated from patients with bronchitis [redacted] dosed with Cefditoren. The organism eradication rate for all indications was 91% for the 200-mg dose and 85% for the 400-mg dose. Concerning MICs of isolates, only 4 isolates had an MIC of 1ug/ml or greater and 3 of those were eradicated. All other isolates had MICs of 0.060 ug/ml or less. Therefore there is insufficient clinical evidence to support the breakpoints proposed by the applicant.

Table 3.6.7k. Microbiologic Response by Pretreatment Cefditoren MIC for *H. influenzae* at the Follow-Up Visit (Test-of-Cure)

Pretreatment Cefditoren MIC (µg/mL)	Cefditoren Pivoxil 200 mg Number of Isolates				Cefditoren Pivoxil 400 mg Number of Isolates			
	N	Eradication[a]	Persistence	N/A[b]	N	Eradication	Persistence	N/A[b]
All Indications								
≤0.015	74	64 (93%)	5 (7%)	5	82	64 (86%)	10 (14%)	8
0.030	26	18 (90%)	2 (10%)	6	29	20 (83%)	4 (17%)	5
0.060	11	8 (80%)	2 (20%)	1	6	3 (60%)	2 (40%)	1
0.120	1	0	0	1	1	1 (100%)	0	0
0.250	0	0	0	0	0	0	0	0
0.500	0	0	0	0	0	0	0	0
1.000	1	1 (100%)	0	0	1	1 (100%)	0	0
2.000	0	0	0	0	1	1 (100%)	0	0
4.000	0	0	0	0	0	0	0	0
8.000	0	0	0	0	0	0	0	0
16.000	0	0	0	0	0	0	0	0
≥32.000	1	0	0	1	0	0	0	0
Total	114	91 (91%)	9 (9%)	14	120	90 (85%)	16 (15%)	14
[redacted]								
Bronchitis								
≤0.015	60	53 (96%)	2 (4%)	5	68	51 (85%)	9 (15%)	8
0.030	21	15 (88%)	2 (12%)	4	23	17 (89%)	2 (11%)	4
0.060	8	7 (100%)	0	1	5	2 (50%)	2 (50%)	1
0.120	1	0	0	1	1	1 (100%)	0	0
0.250	0	0	0	0	0	0	0	0
0.500	0	0	0	0	0	0	0	0
1.000	1	1 (100%)	0	0	1	1 (100%)	0	0
2.000	0	0	0	0	0	0	0	0
4.000	0	0	0	0	0	0	0	0
8.000	0	0	0	0	0	0	0	0
16.000	0	0	0	0	0	0	0	0
≥32.000	1	0	0	1	0	0	0	0
Total	92	76 (95%)	4 (5%)	12	98	72 (85%)	13 (15%)	13

a Eradication and presumed eradication are combined. Persistence and presumed persistence are combined. In the [redacted] study, the clinical response was used as the presumed microbiologic response for patients without a microbiologic response.
b Indeterminate or missing response; not included in eradication or persistence calculation.

Table 3.6.7l. Microbiologic Response by Pretreatment Cefditoren Zone of Inhibition for *H. influenzae* at the Follow-Up Visit (Test-of-Cure)

Pretreatment Zone Diameter Grouping (mm)	Cefditoren Pivoxil 200 mg Number of Isolates				Cefditoren Pivoxil 400 mg Number of Isolates			
	N	Eradication[a]	Persistence[a]	N/A[b]	N	Eradication[a]	Persistence[a]	N/A[b]
All Indications								
<20	2	1 (100%)	0	1	2	1 (50%)	1 (50%)	0
20-25	6	4 (80%)	1 (20%)	1	7	4 (80%)	1 (20%)	2
26-30	29	21 (84%)	4 (16%)	4	35	27 (87%)	4 (13%)	4
31-35	46	38 (97%)	1 (3%)	7	48	36 (88%)	5 (12%)	7
36-40	23	20 (91%)	2 (9%)	1	24	20 (87%)	3 (13%)	1
>40	11	10 (91%)	1 (9%)	0	10	6 (67%)	3 (13%)	1
Total	117	94 (91%)	9 (9%)	14	126	94 (85%)	17 (15%)	15
[redacted]								
BRONCHITIS								
<20	2	1 (100%)	0	1	2	1 (50%)	1 (50%)	0
20-25	5	4 (100%)	0	1	7	4 (80%)	1 (20%)	2
26-30	21	16 (84%)	3 (16%)	2	28	22 (92%)	2 (8%)	4
31-35	38	31 (100%)	0	7	38	28 (88%)	4 (13%)	6
36-40	19	17 (94%)	1 (6%)	1	20	16 (84%)	3 (16%)	1
>40	10	10 (100%)	0	0	9	5 (63%)	3 (38%)	1
Total	95	79 (95%)	4 (5%)	12	104	76 (84%)	14 (16%)	14

a Eradication and presumed eradication are combined. Persistence and presumed persistence are combined. In the [redacted] the clinical response was used as the presumed microbiologic response for patients without a microbiologic response.

b Indeterminate or missing response; not included in eradication or persistence calculation.

Haemophilus parainfluenzae:

516 *H. parainfluenzae* isolates were obtained from bronchitis patients [redacted] patients treated with cefditoren. The eradication rates were 76% for the 200 and 79% for the 400-mg cefditoren treatment groups. MICs ranged up to [redacted] µg/ml with the majority of strains having MICs of 0.120 µg/ml or less. The eradication rate did not appear to be related to zone size or MIC. Results are shown in tables 3.6.7m and 3.6.7n. Because of this lack of correlation, it is difficult to determine breakpoints for *H. parainfluenzae*.

Table 3.6.7m. Microbiologic Response by Pretreatment Cefditoren MIC for *H. parainfluenzae* at the Follow-Up Visit (Test-of-Cure)

Pretreatment Cefditoren MIC (µg/mL)	Cefditoren Pivoxil 200 mg Number of Isolates				Cefditoren Pivoxil 400 mg Number of Isolates			
	N	Eradication[a]	Persistence[a]	N/A[b]	N	Eradication[a]	Persistence[a]	N/A[b]
All Indications								
≤0.015	110	80 (77%)	24 (23%)	6	119	86 (77%)	25 (23%)	8
0.030	96	67 (77%)	20 (23%)	9	76	59 (84%)	11 (16%)	6
0.060	48	33 (73%)	12 (27%)	3	31	23 (79%)	6 (21%)	2
0.120	8	5 (63%)	3 (38%)	0	16	9 (60%)	6 (40%)	1
0.250	2	1 (50%)	1 (50%)	0	3	2 (67%)	1 (33%)	0
0.500	2	2 (100%)	0	0	2	2 (100%)	0	0
1.000	4	3 (75%)	1 (25%)	0	1	0	0	1
2.000	1	1 (100%)	0	0	4	4 (100%)	0	0
4.000	0	0	0	0	1	0	0	1
8.000	0	0	0	0	0	0	0	0
16.000	0	0	0	0	0	0	0	0
≥32.000	0	0	0	0	0	0	0	0
Total	271	192 (76%)	61 (24%)	18	253	185 (79%)	49 (21%)	19
Bronchitis								
≤0.015	107	77 (76%)	24 (24%)	6	119	86 (77%)	25 (23%)	8
0.030	95	66 (77%)	20 (23%)	9	74	58 (85%)	10 (15%)	6
0.060	47	32 (73%)	12 (27%)	3	30	22 (79%)	6 (21%)	2
0.120	8	5 (63%)	3 (38%)	0	16	9 (60%)	6 (40%)	1
0.250	2	1 (50%)	1 (50%)	0	3	2 (67%)	1 (33%)	0
0.500	2	2 (100%)	0	0	2	2 (100%)	0	0
1.000	4	3 (75%)	1 (25%)	0	1	0	0	1
2.000	1	1 (100%)	0	0	4	4 (100%)	0	0
4.000	0	0	0	0	1	0	0	1
8.000	0	0	0	0	0	0	0	0
16.000	0	0	0	0	0	0	0	0
≥32.000	0	0	0	0	0	0	0	0
Total	266	187 (75%)	61 (25%)	18	250	183 (79%)	48 (21%)	19

a Eradication and presumed eradication are combined. Persistence and presumed persistence are combined. In the study, the clinical response was used as the presumed microbiologic response for patients without a microbiologic response

b Indeterminate or missing response; not included in eradication or persistence calculation.

Table 3.6.7n. Microbiologic Response by Pretreatment Cefditoren Zone of Inhibition for *H. parainfluenzae* at the Follow-Up Visit (Test-of-Cure)

Pretreatment Zone Diameter Grouping (mm)	Cefditoren Pivoxil 200 mg Number of Isolates				Cefditoren Pivoxil 400 mg Number of Isolates			
	N	Eradication[a]	Persistence[a]	N/A[b]	N	Eradication[a]	Persistence[a]	N/A[b]
All Indications								
<20	8	6 (75%)	2 (25%)	0	7	6 (100%)	0	1
20-25	52	34 (72%)	13 (28%)	5	46	31 (74%)	11 (26%)	4
26-30	63	47 (80%)	12 (20%)	4	65	43 (72%)	17 (28%)	5
31-35	69	47 (73%)	17 (27%)	5	60	50 (88%)	7 (12%)	3
36-40	49	34 (76%)	11 (24%)	4	46	34 (83%)	7 (17%)	5
>40	24	19 (86%)	3 (14%)	2	22	16 (76%)	5 (24%)	1
Total	265	187 (76%)	58 (24%)	20	246	180 (79%)	47 (21%)	19
[redacted]								
Bronchitis								
<20	8	6 (75%)	2 (25%)	0	7	6 (100%)	0	1
20-25	52	34 (72%)	13 (28%)	5	45	30 (73%)	11 (27%)	4
26-30	62	46 (79%)	12 (21%)	4	65	43 (72%)	17 (28%)	5
31-35	66	44 (72%)	17 (28%)	5	59	49 (88%)	7 (13%)	3
36-40	48	33 (75%)	11 (25%)	4	45	34 (85%)	6 (15%)	5
>40	24	19 (86%)	3 (14%)	2	22	16 (76%)	5 (24%)	1
Total	260	182 (76%)	58 (24%)	20	243	178 (79%)	46 (21%)	19

a Eradication and presumed eradication are combined. Persistence and presumed persistence are combined. In [redacted], the clinical response was used as the presumed microbiologic response for patients without a microbiologic response.
b Indeterminate or missing response; not included in eradication or persistence calculation.

MORAXELLA CATARRHALIS:

146 *M. catarrhalis* isolates were obtained from bronchitis [redacted] patients treated with cefditoren. Eradication rates were 88% for organisms from the patients treated with 200 or 400-mg of cefditoren. MICs ranged as high as [redacted] and were distributed relatively evenly from less than [redacted] eradication rates fell at the higher MICs and smaller zone sizes.

Results are shown in tables 3.6.7o and 3.6.7p. Although breakpoints are usually not given for M. catarrhalis, 0.125 ug/ml appears to be a reasonable breakpoint for susceptible with the β-lactamase producers having an MIC_{90} of 0.5 µg/mL which appears to be above the logical breakpoint for susceptibility.

Table 3.6.7a. Microbiologic Response by Pretreatment Cefditoren MIC for *M. catarrhalis* at the Follow-Up Visit (Test-of-Cure)

Pretreatment Cefditoren MIC (µg/mL)	Cefditoren Pivoxil 200 mg Number of Isolates				Cefditoren Pivoxil 400 mg Number of Isolates			
	N	Eradication[a]	Persistence[a]	N/A[b]	N	Eradication[a]	Persistence[a]	N/A[b]
All Indications								
≤0.015	11	10 (91%)	1 (9%)	0	21	17 (94%)	1 (6%)	3
0.030	16	14 (93%)	1 (7%)	1	8	7 (100%)	0	1
0.060	10	9 (100%)	0	1	19	18 (100%)	0	1
0.120	8	8 (100%)	0	0	10	9 (100%)	0	1
0.250	6	3 (50%)	3 (50%)	0	4	3 (75%)	1 (25%)	0
0.500	11	7 (78%)	2 (22%)	2	20	14 (70%)	6 (30%)	0
1.000	0	0	0	0	1	0	1 (100%)	0
2.000	0	0	0	0	1	1 (100%)	0	0
4.000	0	0	0	0	0	0	0	0
8.000	0	0	0	0	0	0	0	0
16.000	0	0	0	0	0	0	0	0
≥32.000	0	0	0	0	0	0	0	0
Total	62	51 (88%)	7 (12%)	4	84	69 (88%)	9 (12%)	6
[redacted]								
Bronchitis								
≤0.015	9	8 (89%)	1 (11%)	0	16	13 (100%)	0	3
0.030	14	13 (100%)	0	1	7	6 (100%)	0	1
0.060	7	6 (100%)	0	1	16	15 (100%)	0	1
0.120	7	7 (100%)	0	0	8	7 (100%)	0	1
0.250	4	2 (50%)	2 (50%)	0	3	3 (100%)	0	0
0.500	8	6 (86%)	1 (14%)	1	13	10 (77%)	3 (23%)	0
1.000	0	0	0	0	0	0	0	0
2.000	0	0	0	0	1	1 (100%)	0	0
4.000	0	0	0	0	0	0	0	0
8.000	0	0	0	0	0	0	0	0
16.000	0	0	0	0	0	0	0	0
≥32.000	0	0	0	0	0	0	0	0
Total	49	42 (91%)	4 (9%)	3	64	55 (95%)	3 (5%)	6

a Eradication and presumed eradication are combined. Persistence and presumed persistence are combined. In the [redacted] study, the clinical response was used as the presumed microbiologic response for patients without a microbiologic response.

b Indeterminate or missing response; not included in eradication or persistence calculation.

Table 3.6.7p. Microbiologic Response by Pretreatment Cefditoren Zone of Inhibition for *M. catarrhalis* at the Follow-Up Visit (Test-of-Cure)

Pretreatment Zone Diameter Grouping (mm)		Cefditoren Pivoxil 200 mg Number of Isolates				Cefditoren Pivoxil 400 mg Number of Isolates		
	N	Eradication[a]	Persistence[a]	N/A[b]	N	Eradication[a]	Persistence[a]	N/A[b]
All Indications								
<20	1	0	0	1	1	1 (100%)	0	0
20-25	12	8 (73%)	3 (27%)	1	19	13 (68%)	6 (32%)	0
26-30	20	17 (85%)	3 (15%)	0	22	18 (90%)	2 (10%)	2
31-35	15	13 (100%)	0	2	22	19 (100%)	0	3
36-40	8	8 (100%)	0	0	12	10 (91%)	1 (9%)	1
>40	6	5 (83%)	1 (17%)	0	7	7 (100%)	0	0
Total	62	51 (88%)	7 (12%)	4	83	68 (88%)	9 (12%)	6
[redacted]								
Bronchitis								
<20	1	0	0	1	1	1 (100%)	0	0
20-25	8	7 (88%)	1 (13%)	0	11	9 (82%)	2 (18%)	0
26-30	16	14 (88%)	2 (13%)	0	20	17 (94%)	1 (6%)	2
31-35	12	10 (100%)	0	2	18	15 (100%)	0	3
36-40	8	8 (100%)	0	0	9	8 (100%)	0	1
>40	4	3 (75%)	1 (25%)	0	4	4 (100%)	0	0
Total	49	42 (91%)	4 (9%)	3	63	54 (95%)	3 (5%)	6

a Eradication and presumed eradication are combined. Persistence and presumed persistence are combined. In [redacted] the clinical response was used as the presumed microbiologic response for patients without a microbiologic response.

b Indeterminate or missing response: not included in eradication or persistence calculation.

Package insert discussion:

The proposed package insert discussion is based on the approved indications of Tonsillitis/pharyngitis and uncomplicated skin and skin-structure infections. Review number 2 has a description of the package insert which includes ABECB as an indication.

MIC-Disk Zone Correlation and breakpoints:

MIC versus disk zone diameter is plotted for each of the 6 target organisms. Straight-line plots were obtained with a minimum of major and minor errors. Interpretive criteria are indicated on the plots and the sponsor suggests that breakpoints be established as in Table 3.6.6a based on frequency distribution. In the applicant's discussion of breakpoints it is mentioned that the time above MIC ratio and concentration of unbound drug in serum suggest lower breakpoints, the applicant claims that results of clinical trials support the higher breakpoints for 200 and 400 mg dosing. Therefore, if the higher breakpoints are warranted, sufficient numbers of organisms isolated from patients and treated successfully or unsuccessfully, and organisms eradicated or not must be available from

the controlled human clinical trials. Concerning the pharmacokinetics, Cmax levels of 2.67 µg/mL were obtained from a 200-mg dose and 4.1 µg/mL from a 400-mg dose in fed patients high fat meals). However, the drug is 88% serum bound and the bioavailability averaged 14% from a 200mg dose in fasted patients and a relatively short T1/2 of 1-2h. Distribution in the tissues is not extensive with concentrations [redacted] 10 to 35% that of serum and 56% that of serum in non-inflammatory blister fluid and 40% in inflammatory blister fluid. In the applicant's reference 7, request no. 128-10-221, [1207]-01812-V2, Miyazaki, et al, it was reported that the effectiveness of cephems in systemic infections depends on the concentration of free drug (unbound drug). In that same report, data is presented demonstrating that MICs and bactericidal activity of cefditoren is correlated with the concentration of free drug in the prescence of 4% human serum albumen or 50% serum in that MICs and bactericidal activity required 8 times more drug in the prescence of HSA or 50% serum. In the applicant's end of text Table 4, Time-above-MIC Data for unbound Cefditoren from 84 subjects who participated in five phase I studies and received 400 mg Cefditoren pivoxil, the percentage in dose Interval that unbound cefditoren plasma concentrations exceeded MICs is shown. Only at an MIC of 0.12 did the time average 36% above the MIC 90 with a range of [redacted]

Therefore, as stated by the applicant, we used the results of clinical trials as the primary source of data for the setting of breakpoints and/or pharmacodynamics based on unbound drug. It should be noted that as of the drafting of this review, the approved indications for cefditoren were Pharyngitis/tonsillitis and uncomplicated skin and skin structure infections.

The applicant has placed the following table and statement in the draft package insert for list two of microorganisms. The presentation of this information is not allowed for drugs that do not have the indication for pathogens that are of public health significance. In addition, the format does not comply with the 1993 NDA Holders letter issued by the Center for Drug Evaluation and Research and will therefore not be included in the PI.

Study Number	*S. pneumoniae* Strains	Cefditoren MIC (µg/mL)	
		MIC_{50}	MIC_{90}
Study 1	Penicillin-intermediate N=108	0.12	0.5
	Penicillin-resistant N=56	0.5	2.0
Study 2	Penicillin-intermediate N=55	0.12	0.5
	Penicillin-resistant N=73	0.5	1.0

The following *in vitro* data are available, **but their clinical significance is unknown.**

Because cefditoren has greater *in vitro* activity against *Streptococcus pneumoniae* than does penicillin, the majority of *S. pneumoniae* strains with intermediate or resistant susceptibility to penicillin are fully susceptible to cefditoren. The following table summarizes *in vitro* activity of cefditoren for penicillin-intermediate and -resistant strains of *S. pneumoniae.*

The above statement is not acceptable for the following reasons:

1. Assuming that cefditoren has more *in vitro* activity than penicillin does not imply that the strains are either susceptible or fully susceptible to cefditoren (the phrase fully susceptible is not a defined term)
2. The cited references in the annotated package insert do not have data concerning the study where a direct comparison with penicillin is conducted.
3. Penicillin is a general term and the sponsor should refer to penicillin g, v or the penicillin used in the comparative studies.
4. These strains should be listed in the body of the listing with the other genera and species.
5. PRSP is considered a public health problem and is therefore not put in list two of package inserts

The applicant has requested that the following organisms be included in list two proceeded by the enclosed standard language: In all cases, very few isolates were examined. It is required that at least 100 isolates of each genera and species be studied and that the strains represent a broad geographic distribution within the United States. In the organisms proposed, only 10-45 isolates were studied, and they were from one reference source. The applicant should also pay careful attention to what organisms are considered common pathogens in the clinical indications requested as some of the listed organisms are not commonly considered pathogens for these indications.

Therefore, the listed bacteria should not be in the product Package insert. It should be noted that the proposed language from the applicant is unacceptable because the accepted level for sensitivity to cefditoren is ≤0.125 µg/ml which we will use to determine break points.

4 page(s) of revised draft labeling has been redacted from this portion of the review.

Joel Unowsky
Microbiology Reviewer

CONCURRENCE ONLY

1

SMicro/ATSheldon
RD#1 Initialed 10/20/00
RD#2 Initialed12/21/00
Final Initialed 6/26/01 ATS
DepDir/LGavrilovich

Cc: Original NDA # 21,222
HFD-520
HFD-520/DepDir/LGavrilovich
HFD-520/Micro/JUnowsky
HFD-520/MO/JMulinde
HFD-520/Pharm/KSeethaler
HFD-520/Chem/B.V.Shetty
HFD-520/CSO/BDuvallmiller

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[1] NCCLS Reference: Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters-Second Edition. Approved Standard NCCLS Document M23-A2, Vol. 21, No. 7, NCCLS, Wayne, Ps., May 2001

Division of Anti-Infective Drug Products
Clinical Microbiological Review # 2

NDA # 21-222
Amendments 021, 026
Supplement 032

Date Completed:July 9, 2001

Applicant

TAP Holdings inc.
2355 Waukegan Road
Deerfield, Illinois. 60015

Chem/Ther. Type: Broad spectrum cephalosporin (Cephem)

Submission Reviewed: Original NDA

Indications applied for: Oral treatment of Acute Bacterial Exacerbation of Chronic Bronchitis, [redacted] Pharyngitis/Tonsillitis and, Uncomplicated Skin and Skin Structure Infections.

Product Name:

Proprietary: Spectracef

Non-proprietary: Cefditoren Pivoxil:

Code number: 4010300

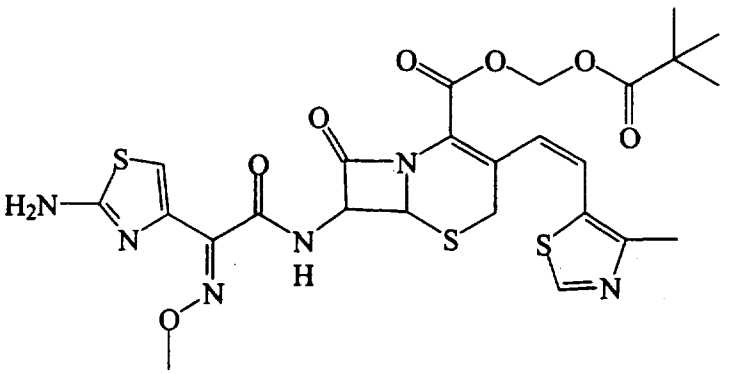
Chemical name:

(6R,7R)-2,2-DIMETHYLPROPIONYLOXYMETHYL 7-((Z)-2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINOACETAMIDO)-3-((Z)-2-(4-METHYLTHIAZOL-5-YL) ETHENYL)-8-OXO-5-THIA-1-AZABICYCLO(4.2.0)OCT-2-ENE-2-CARBOXYLATE

Mol weight: 620

Mol Formula: $C_{25}H_{28}N_6O_7S_3$

Structural formula:



Dosage form: 200 Mg Tablets BID

Route of administration: Oral

Pharmacological Category: Antiinfective

Dispensed: Rx

Initial Submission Date of NDA
Received by CDER: 12/29/99
Received by Reviewer: 01/04/00
Review Completed:

Amendment: 021
Received by CDER:9-27-00, 10-16-00
Received by Reviewer:10-3-00, 10-17-00
Review Completed:

Amendment: 026
Received by CDER: 10-16-00
Received by Reviewer: 10-20-00
Review Completed:

Supplement: 032
Received by CDER: 11-20-00
Received by Reviewer: 11-27-00
Review Completed:

Related Documents:

[redacted]

Remarks: (Based on supplements and amendment, the NDA was reviewed previously)

Data to support TAP's revised package insert was submitted as a supplement and two amendments. The data was evaluated and used in the determination of package insert recommendations. The package insert recommendation assumes approval of three indications, Pharyngitis/tonsillitis, mild skin and skin structure infection and, acute bacterial exacerbation of chronic bronchitis[redacted]Policy issues and distribution of the review are in the hands of the supervisory microbiologist, Dr. Albert Sheldon.

Conclusion: The FDA recommended microbiology section of the package insert and reasons for the recommendation are included. Evaluation of the microbiology of cefditoren is continued from the previous report. (NDA #21, 222, Microbiology Review #1)

INTRODUCTION:

Cefditoren pivoxil is a cephem antibiotic under development and clinical evaluation in the United States by Tap Holdings inc. It was originally proposed for usage in the oral treatment of: Acute Bacterial Exacerbation of Chronic Bronchitis, [redacted] Pharyngitis/Tonsillitis and, Uncomplicated Skin and Skin Structure Infections. Cefditoren is being targeted for the clinical eradication of 6 species of bacteria: S. *aureus, S. pneumonia, H. influenzae, H. parainfluenzae, S. pyogenes, and M. catarrhalis* in patients with the above indications. Cefditoren has consistent antibacterial activity versus gram positive and variable activity versus gram negative bacteria and is active in animal models of infectious disease. Cefditoren is 88% serum bound mainly to Human Serum Albumen, and has a short half-life of 1-2 hours in man. In the NDA microbiological review for 21, 222, FDA breakpoints were proposed based on pharmacokinetics, pharmacodynamics and clinical results of cures and organism eradication. Due to the small numbers of isolates tested for invitro activity and used in the comparison of MIC versus zone size (251), organisms were not listed for list two and zone size correlates could not be determined. The breakpoint proposed by the FDA for cefditoren is ≤ 0.125 µg/ml for sensitivity.

In order for organisms to be included in list two, the following three criteria must be met:

1. MICs of more than 100 recent clinical isolates representing a broad geographical distribution using NCCLS methods of analysis must be presented.

2. The MIC 90s must be no greater than the established susceptibility breakpoints-this takes into account, pharmacokinetics/dynamics as well as clinical results.

3. The organism must be considered to be a normal pathogen for the indication(s) under consideration.

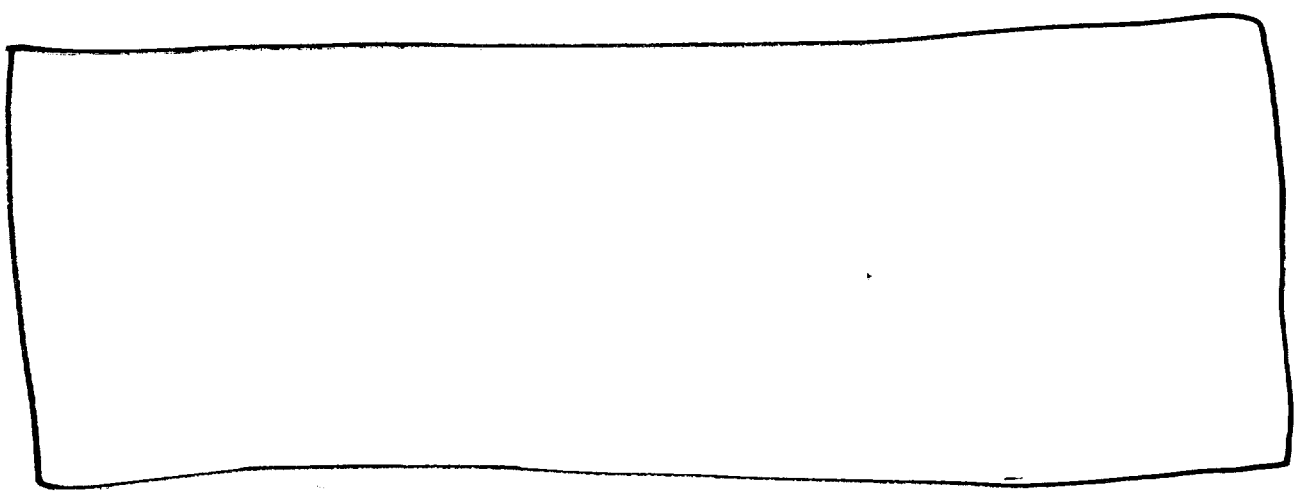
In an amendment, 021, received in two volumes by this reviewer on 10-3-00 and 10-17-00, related microbiological documents and data produced since the NDA filing were presented. Specifically mentioned were MRL reports that were used to support the information presented at ICAAC (September 17-20, 2000) and the Jones and Johnson papers that present additional information on List 2 organisms. The information from the Jones and Johnson papers were sent by TAP as an electronic submission on 20-November, 2000 in the form of 37 histograms as supplement No. 032. In these reports and histograms, sufficient numbers of organisms, conducted by NCCLS methods were presented to fulfill the requirements of the NDA Holder's letter and draft microbiological guidelines. These histograms will not be included in this report but will be referred to when discussing organisms for inclusion in list two.

Based on the requirement of an MIC 90 of ≤ 0.125 μ g/ml for sensitivity, the following organisms proposed by TAP will not be included in list two of the package insert-for which *invitro* data is available but the clinical significance is unknown: *S. epidermis, S. pneumoniae-penicillin intermediate, S. pneumoniae-penicillin resistance, S. viridans penicillin intermediate, E. coli, K. pneumoniae, P. vulgaris, Salmonella species,* and *Shigella species*.

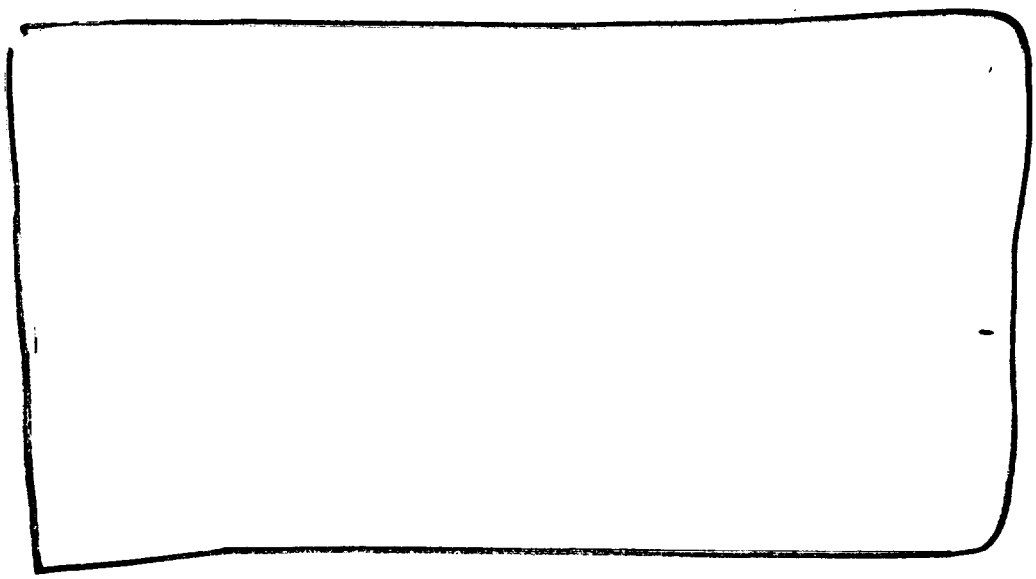
N. gonorrhoeae and N. meningitidis are not included in list two because they are not considered common pathogens in the indicated diseases sought by the applicant.

The organisms that met the requirement to be included in list two include: *S. viridans-penicillin sensitive, S. agalactae, Streptococcus groups C and G and P. mirabilis.*

Using the clinically and PK/PD based breakpoint for MIC of ≤ 0.125 μg/ml, a plot of zone size versus MIC result in large numbers of major errors and therefore, zone versus MIC correlates can not be determined.



1 page(s) of revised draft labeling has been redacted from this portion of the review.



Joel Unowsky
Microbiology Reviewer

CONCURRENCE ONLY

SMicro/ATSheldon
RD#1 Initialed 6/26/01, Final on
7/9/01 ATS

DepDir/LGavrilovich

Cc: Original NDA # 21,222
HFD-520
HFD-520/DepDir/LGavrilovich
HFD-520/Micro/JUnowsky
HFD-520/MO/JMulinde
HFD-520/Pharm/KSeethaler
HFD-520/Chem/B.V.Shetty
HFD-520/CSO/BDuvallmiller

10 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.