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TABLE 107 (continued)
Organisms with Gemifloxacin MICs or Zone Diameters that Indicate Resistance
Development during Treatment

Organism	Baseline MIC	Post-therapy MIC	Baseline Zone Diameter	Post-therapy Zone Diameter
CNS (n=29)	0.008 (0.008)	0.12 (0.12)	36 (36)	24 (25)
CNS	0.008	0.25	31	19
CNS	0.008	0.5	35	14
CNS	0.008	0.25	36	19
CNS	0.004	0.12	33	22
CNS	0.008	1	32	10
CNS	0.008	2	32	9
CNS	0.015	4	29	6
CNS	0.015	0.25	32	19
CNS	0.008	0.5	34	14
CNS	0.015	0.25	31	14
CNS	0.015	1	28	14
CNS	0.25	1	23	14
CNS	0.008	0.25	34	15
CNS	0.008	0.5	37	15
CNS	0.015	0.25	35	19
CNS	0.008	1	26	15
CNS	0.008	1	32	12
CNS	0.015	0.25		
CNS	0.015	0.5	29	15
CNS	0.015	2	29	13
CNS	0.008	0.5	36	13
CNS	0.008	0.5	29	18
CNS			40 (29)	32 (29)
CNS			43 (30)	35 (25)
CNS	0.03	2	38	21
CNS	0.004	0.5		
CNS	0.015	0.25		
<i>Staphylococcus aureus</i> (n=1)	0.008	0.5	31	15

CNS = coagulase-negative staphylococci

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EPIDEMIOLOGICAL STUDIES

Gemifloxacin mesylate tablets are not approved in any country. Worldwide marketing applications are currently being prepared for the use of gemifloxacin mesylate in the treatment of community-acquired pneumonia, acute exacerbation of chronic bronchitis,

There is, therefore, no epidemiological information to report.

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PRECLINICAL EFFICACY (IN VIVO)

PHARMACOKINETICS/BIOAVAILABILITY

A single dosage of 320 mg once daily, administered as a 320 mg tablet is proposed for marketing.

The information in this section is taken from the NDA studies submitted by the applicant and had not been reviewed by a Biopharmaceutical Reviewer at the time this review was written.

On average, the absolute bioavailability of the oral tablets is 71%. Absorption is rapid and maximum serum/plasma concentrations are seen between 0.5 and 2.0 hours. The terminal phase half-life is approximately 5 to 9 hours. A 320 mg single dose produced a mean C_{max} = 1.21 $\mu\text{g/mL}$ and an mean $AUC_{0-\infty}$ = 7.33 $\mu\text{g}\cdot\text{h/mL}$ based on the results from over 400 subjects.

Only weight and creatinine clearance affect gemifloxacin pharmacokinetics. Gemifloxacin is not extensively metabolized and is excreted predominantly unchanged following either oral or intravenous routes of administration. The metabolites are minor and include those arising from glucuronidation, N-acetylation and isomerization. The majority of the oral dose (61%) is excreted in the feces and urinary excretion accounts for 36% of the oral dose. The major route of elimination of the intravenous dose is urinary (59%). Urine concentrations were maintained above 20 $\mu\text{g/mL}$ for the 24 hours post-dose.

Following administration of 320 mg and 640 mg gemifloxacin after a high fat breakfast, C_{max} decreased by 12% and 14%, respectively, and T_{max} was prolonged by 0.75 and 0.21 hours, respectively. Involvement of CYP450 enzymes in the metabolism of gemifloxacin is negligible. Protein binding of gemifloxacin is approximately 70%.

Following repeat 320 mg gemifloxacin doses to patients, the maximal concentration (C_{max}) was 1.6 $\mu\text{g/mL}$. AUC was 8.4 $\mu\text{g}\cdot\text{h/mL}$ after repeat 320 mg dosing. After five daily doses of 320 mg concentration of gemifloxacin in bronchial mucosa was 7.21 times higher than plasma concentration. Concentration in alveolar macrophages exceeded those in plasma by 2.63 times.

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ANIMAL PROPHYLATIC AND THERAPEUTIC STUDIES

The *in vivo* efficacy of gemifloxacin has been evaluated in several models of experimental infection in animals.

The efficacy of gemifloxacin was also examined in experimental models of systemic and skin/skin structure infections. The effect obtained with gemifloxacin in these studies was usually compared with that of standard antibacterial agents and other fluoroquinolones.

MOUSE PROTECTION STUDIES

The protective effects of gemifloxacin against systemic infections were compared with those of ciprofloxacin and sparfloxacin (120). In this experiment mice were injected intraperitoneally with a bacterial suspension corresponding to 5 to 10 times the minimal lethal dose (MLD). Four dose levels were used for each drug. Mice were orally administered twice at one and four hours post-infection. Mortality was recorded for 7 days, and the median effective dose needed to protect 50% of mice (ED_{50}) was calculated. All untreated mice died 2 days after infection. The results of this experiment are presented in TABLE 108.

TABLE 108
Comparison of gemifloxacin and other quinolones
In Mouse Systemic Infection

Organism	ED_{50} (mg/kg)		
	Gemifloxacin	Ciprofloxacin	Sparfloxacin

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These data show that gemifloxacin exhibited the most potent protective effects against systemic infections caused by gram-positive bacteria. Ciprofloxacin showed the best activity against gram-negative pathogens. Gemifloxacin was usually the least active of the three drugs against the gram-negative bacteria.

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IN VIVO MODELS OF RESPIRATORY TRACT INFECTIONS

Experiments were performed investigating the efficacy of gemifloxacin in experimental respiratory tract infections in animals against strains of *Streptococcus pneumoniae* and *Haemophilus influenzae*.

Streptococcus pneumoniae

In preliminary studies, the protective effects of gemifloxacin against pneumonia caused by *S. pneumoniae* III were evaluated and compared with those of sparfloxacin and ciprofloxacin (121). In this experiment mice were inoculated intranasally with *S. pneumoniae* and drug was orally administered six hours after infection and then twice a day for 3 days. All animals in a control group developed subacute pneumonia and died within 5 days of infection. Results are summarized in TABLE 109.

TABLE 109
Survival rates (day 14) following administration of drug
To mice infected with *S. pneumoniae* III

Drug	Dose (mg/kg)					
	90	30	10	3.3	1.1	0
Gemifloxacin	100	100	100	33	20	0
Sparfloxacin	100	83	33	0	NT	0
Ciprofloxacin	17	0	0	0	NT	0

These data show that gemifloxacin was better than sparfloxacin against this model of pneumonia caused by *S. pneumoniae* III. Ciprofloxacin was not very effective. The ED₅₀ values of gemifloxacin, sparfloxacin, and ciprofloxacin were 3.1, 17.3, and >90 mg/kg of body weight, respectively. MIC values for gemifloxacin, sparfloxacin, and ciprofloxacin were 0.015, 0.13, and 0.5 µg/mL, respectively. It appears that the *in vivo* therapeutic effects correlated with *in vitro* potency. Although this study states that the ED₅₀ value for gemifloxacin is 3.1 mg/kg only 33% survived at a dose of 3.3 mg/kg. This indicates that the ED₅₀ value would have to be greater than 3.3 mg/kg and the value of 3.1 mg/kg seems to be in error.

To confirm the effect demonstrated in survival tests, efficacy studies that enumerated the bacterial numbers in lungs of mice were performed (122, 123). Respiratory infections were induced in mice by intranasal instillation of *S. pneumoniae* 1629 (Ciprofloxacin-susceptible MIC = 0.25 µg/mL; gemifloxacin MIC = ≤0.03 µg/mL) and *S. pneumoniae* 5303 (CipR: MIC > 32 µg/mL; gemifloxacin MIC = 0.13 µg/mL). Oral therapy was administered at doses of 20 and 50 mg/kg at 1, 5, and 24 hours post infection. TABLE 110 shows the results of this experiment.

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TABLE 110
Bacterial Counts in Lungs of Mice after Treatment in Experimental
S. pneumoniae Respiratory Tract Infection

Organism	Dosage	Log ₁₀ CFU/lungs						
		Control	Gemifloxacin		Ciprofloxacin		Amoxicillin	
			50	20	50	20	50	20
<i>S. pneumoniae</i> 1629 (CipS)		6.8 ± 1.28	≤ 1.7	2.3 ± 0.4	4.8 ± 0.8	5.2 ± 0.5	≤ 1.7	≤ 1.7
<i>S. pneumoniae</i> 5303 (CipR)		4.0 ± 2.02	2.56 ± 1.03	4.5 ± 1.6	4.5 ± 2.2	4.3 ± 1.8	≤ 1.7	≤ 1.7

The lower limit of detection was ≤ 1.7 log₁₀ cfu/lungs. Amoxicillin was effective against both strains. Gemifloxacin was as effective as amoxicillin at the higher dose against the ciprofloxacin susceptible strain. At the lower dose gemifloxacin was not as effective as at a dose of 50 mg/kg but was still more effective than ciprofloxacin, which was not very effective against either strain. Against the ciprofloxacin-resistant strain, as expected, ciprofloxacin was not effective. Gemifloxacin was somewhat effective but only at the higher dose.

Another experiment studied the efficacies of gemifloxacin and comparators against experimental respiratory tract infections in rats caused by *S. pneumoniae* strains with gemifloxacin MICs of 0.125 µg/mL or greater (124). In this study animals were infected intrabronchially with *S. pneumoniae*. Therapy commenced at one hour post infection and continued either once or twice daily for a further 3 days. Gemifloxacin was given at a dose of 150 mg/kg b.i.d.. The other once a day quinolones were given either at the normal o.d. dosing as indicated (TABLE 114) or at half doses b.i.d. The oral doses administered were chosen to approximate in the rat, the serum or tissue concentrations measured in man following therapeutic dosing (see TABLE 114). At approximately 17 hours after cessation of therapy the lungs were excised for the enumeration of viable bacterial counts. TABLE 111 shows the strains used in this experiment and their susceptibilities to the agents tested. The results of this experiment are summarized in TABLE 112.

TABLE 111
In vitro Susceptibilities (MIC-µg/mL) of *S. pneumoniae* used in *in vivo* testing (study 124)

Strain	GEMI	AMX/CA	CIP	GRP	LEVO	TRV	AZI	CXM	TOS
305313	0.125	0.06	32.0	0.5	1.0	4.0	≤ 0.03	0.25	0.5
622286	0.125	≤ 0.06	16.0	4.0	4.0	2.0	≥ 64	≤ 0.06	2.0
PT 9424123	0.25	≤ 0.06	64.0	8.0	16.0	8.0	≥ 64	≤ 0.06	16.0
402123	0.25	NT	32.0	4.0	8.0	8.0	NT	NT	NT
509063	0.25	NT	32.0	NT	NT	8.0	NT	NT	NT
214152	0.5	NT	64.0	NT	NT	8.0	NT	NT	NT

GEMI = gemifloxacin; AMX/CA = amoxicillin/clavulanate; CIP = ciprofloxacin;
GRP = grepafloxacin; LEVO = levofloxacin; TRV = trovafloxacin; AZI = azithromycin;
CXM = cefuroxime; TOS = tosufloxacin

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TABLE 112
Efficacy of gemifloxacin and Comparators Against *S. pneumoniae* Respiratory Tract Infections in Rats (study 124)
Log₁₀ CFU/lungs

Strain	CONTROL	GEMI	AMX/CA	CIP	GRP	LEVO	TRV	AZI	CXM	TOS
305313 MIC 0.125	7.9 ± 0.4	3.3 ± 1.3	NT	NT	6.9 ± 0.5	5.7 ± 1.3	5.3 ± 1.2	NT	NT	NT
622286 MIC 0.125	6.4 ± 1.3	2.5 ± 0.9	≤1.7	5.0 ± 1.2	5.5 ± 1.3	6.4 ± 2.0	5.6 ± 0.7	6.4 ± 2.0	≤1.7	4.0 ± 2.0
PT 9424123 MIC 0.25	8.1 ± 0.8	4.42 ± 0.7	≤1.7	6.3 ± 2.3	6.3 ± 0.6	6.8 ± 0.6	5.5 ± 1.5	2.3 ± 0.6	≤1.7	5.4 ± 1.1
402123 MIC 0.25	8.3 ± 0.8	5.7 ± 0.9	NT	NT	8.4 ± 1.2	7.3 ± 1.2	8.8 ± 0.6	NT	NT	NT
509063 MIC 0.25	6.2 ± 1.6	3.5 ± 1.1	NT	NT	6.5 ± 0.8	6.2 ± 0.7	6.6 ± 0.9	NT	NT	NT
214152 MIC 0.5	6.6 ± 1.6	3.8 ± 1.4	NT	NT	6.6 ± 0.9	5.0 ± 1.4	5.9 ± 1.3	NT	NT	NT

GEMI = gemifloxacin; AMX/CA = amoxicillin/clavulanate; CIP = ciprofloxacin; GRP = grepafloxacin; LEVO = levofloxacin; TRV = trovafloxacin;
AZI = azithromycin; CXM = cefuroxime; TOS = tosufloxacin

These data show that gemifloxacin has some activity against infections caused by ciprofloxacin-resistant *S. pneumoniae* with gemifloxacin MICs of 0.125 µg/mL to 0.5 µg/mL. In this experiment, however, the dose had to be divided in half and given twice a day instead of once a day. Dosing also had to begin one hour post infection. The other quinolones tested were ineffective or had poor activity and in the majority of cases were not as effective as gemifloxacin. As gemifloxacin's MIC value increase the amount of reduction in cell count goes from 4-4.5 logs against 0.125 µg/mL strains to about 3 logs against a 0.5 µg/mL strain. In experiments using the normal once a day dosing commencing 24 hours post infection, gemifloxacin was ineffective against strains with gemifloxacin MICs ≥ 0.125 µg/mL. As will be seen in TABLE 114 gemifloxacin was effective against strains with gemifloxacin MICs of ≤ 0.06 µg/mL.

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The efficacy of gemifloxacin mesylate was further evaluated in models of respiratory tract infections caused by penicillin-susceptible and -resistant, macrolide resistant, and ciprofloxacin-resistant strains of *S. pneumoniae*. TABLE 113 gives the MICs of each of these strains. In these studies gemifloxacin was tested in comparison with amoxicillin/clavulanate, cefuroxime, azithromycin, ciprofloxacin, grepafloxacin, levofloxacin, and trovafloxacin. Animals were infected with one of the nine indicated strains of *S. pneumoniae*. Therapy commenced 24 hours post infection and the oral doses administered were chosen to approximate in the rat, the serum and tissue concentrations measured in man following the normal human dose (TABLE 114). Against ciprofloxacin-resistant strains quinolone antibiotics were administered at half the dose twice daily. Treatment continued for 3 days and 17 hours after therapy the lungs were excised for enumeration of viable bacterial numbers.

TABLE 113
In Vitro Susceptibilities (MIC- μ g/mL) of *S. pneumoniae* used in *in vivo* testing

Strain	GEMI	AMX/CA	CIP	GRP	LEVO	TRV	AZI	CXM	TOS
1629 pen ^S	≤ 0.03	≤ 0.03	0.25	≤ 0.03	0.25	≤ 0.03	0.25	≤ 0.03	NT
10127 pen ^S	≤ 0.03	≤ 0.03	1.0	0.5	1.0	0.125	0.25	≤ 0.03	NT
L11259 pen ^S	≤ 0.03	≤ 0.03	1.0	0.5	1.0	0.25	0.25	≤ 0.03	NT
N1387 mac ^R	≤ 0.03	1.0	0.25	0.125	0.5	0.125	>32	2.0	NT
406081 mac ^R	≤ 0.03	2.0	1.0	0.125	0.5	0.125	>32	8.0	NT
205118 pen ^R	≤ 0.03	2.0	8.0	0.5	NT	1.0	≤ 0.06	≥ 64	NT
404053 pen ^R	≤ 0.03	8.0	0.25	0.06	0.5	0.06	≥ 64	16.0	NT
305313 cip ^R	0.125	≤ 0.06	16.0	0.5	1.0	2.0	≤ 0.06	0.25	0.5
622286 cip ^R	0.125	0.125	32.0	4.0	4.0	4.0	≥ 64.0	≤ 0.06	2.0

GEMI = gemifloxacin; AMX/CA = amoxicillin/clavulanate; CIP = ciprofloxacin;
GRP = grepafloxacin; LEVO = levofloxacin; TRV = trovafloxacin; AZI = azithromycin;
CXM = cefuroxime; TOS = tosufloxacin

TABLE 114
Dosing Regimen of Gemifloxacin and Comparators in Rats

Compound	Man	Rat
Gemifloxacin	400 mg o.d.	300 mg/kg o.d.
Amoxicillin/clavulanate	875/125 mg b.i.d.	350/50 mg/kg b.i.d.
Ciprofloxacin	750 mg b.i.d.	200 mg/kg b.i.d.
Cefuroxime	250 mg b.i.d.	70 mg/kg b.i.d.
Azithromycin	1 g day 1 followed by 500 mg o.d.	40 and 20 mg/kg o.d.
Trovafloxacin	200 mg o.d.	40 mg/kg o.d.
Grepafloxacin	600 mg o.d.	200 mg/kg o.d.
Levofloxacin	500 mg o.d.	125 mg/kg o.d.
Tosufloxacin	600 mg b.i.d.	25 mg/kg b.i.d.

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TABLE 105
Number of patient isolates meeting each criteria

Patient Categories	No. of Patients Identified	No. of Patients Remaining
Total number of patients with isolates with a Change in MIC or disk diameter	219	219
1. Isolates with changes only in comparator	55	164
2. Isolates or complete retest data not available	74	90
3. Isolates with no screening and end of therapy or post-therapy change	63	27
4. Isolates with a disk diameter <6 mm after retest	10	17
5. Isolates with a disk zone ≥6 mm but an initial MIC < 4-fold	1	16
6. Isolates with a retest MIC < 4-fold	9	7
7. Isolates not identical to identification with Vitek	1	6
8. Isolates not identical to identification by PFGE	5	1

TABLE 106 summarizes the Vitek and PFGE Identification results.

TABLE 106
Summary of Vitek and PFGE Identification

Study	Patient	Lab ID	Visit	Vitek	PFGE

^a CNS = coagulase negative *Staphylococcus*

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The efficacy of gemifloxacin was determined against three penicillin susceptible strains of *S. pneumoniae* (125,126). Following infection with *S. pneumoniae* 1629 (penicillin-susceptible) gemifloxacin was very effective compared to untreated controls (NTC) and reduced bacterial numbers in lungs to below the level of detection ($\leq 1.7 \log_{10}$ cfu/lungs). The response obtained was similar to that seen with amoxicillin/clavulanate, cefuroxime, and azithromycin. Ciprofloxacin, grepafloxacin, levofloxacin, and trovafloxacin were inferior to gemifloxacin (see TABLE 115).

In a similar study (127) the efficacy of gemifloxacin and comparators was examined against two macrolide-resistant strains of *S. pneumoniae*. Against strain 406081, gemifloxacin was comparable to amoxicillin/clavulanate. Cefuroxime, azithromycin, ciprofloxacin, grepafloxacin, levofloxacin and trovafloxacin were not very effective against this strain. Against strain N1387, gemifloxacin produced a good response. Gemifloxacin was superior to trovafloxacin and gave results similar to those for the other comparators (TABLE 115).

Another similar study (128) examined gemifloxacin and comparators against two penicillin-resistant strains of *S. pneumoniae*. Gemifloxacin had a good response against *S. pneumoniae* 404053 and reduced counts to near the level of detection ($\leq 1.7 \log_{10}$ cfu/lungs) in all animals. The effect obtained with gemifloxacin was superior to that seen with all comparators. Against strain 205118, gemifloxacin produced a good response. Amoxicillin/clavulanate, azithromycin, and cefuroxime showed a similar response to gemifloxacin. Ciprofloxacin, grepafloxacin, levofloxacin, and trovafloxacin produced poor responses (see TABLE 115).

Evaluation against infection caused by two ciprofloxacin-resistant strains of *S. pneumoniae* was also determined (129). Owing to the short-half life of gemifloxacin in rodents compared to man, it was necessary to extend the period of exposure while maintaining the same AUC. For these studies gemifloxacin and selected agents were administered twice daily at half the dose. Therapy commenced one hour post infection and treatment with gemifloxacin continued b.i.d. for a further 3 days. Gemifloxacin exhibited a good response against *S. pneumoniae* 305313. Amoxicillin/clavulanate, cefuroxime, azithromycin reduced the bacterial count in lungs to the detection limit. Grepafloxacin gave a result similar to gemifloxacin. Ciprofloxacin, tosufloxacin, levofloxacin, and trovafloxacin were significantly less effective. Against *S. pneumoniae* 622286, gemifloxacin produced a good response and was superior to azithromycin, ciprofloxacin, trovafloxacin, grepafloxacin, and levofloxacin (TABLE 115).

In all previous studies of pneumonia in rats (except study 124) the gemifloxacin *Streptococcus pneumoniae* was $\leq 0.06 \mu\text{g/mL}$. In the previous studies therapy (300 mg/kg o.d.) commenced at 24 hours post infection and continued for 3 days. When this regime was used against strains with gemifloxacin MICs $\geq 0.125 \mu\text{g/mL}$ efficacy was not shown. Prolonging the therapy to 4 and 7 days and decreasing the time to onset of therapy (8 hour, 3 hours, and 1 hour post infection) did not increase efficacy. Only the dosing (150 mg/kg b.i.d.) used above worked. Treatment also had to be started within one hour of infection. Normally treatment would not start this soon after infection in humans. Although using this alternate dosing regime showed that gemifloxacin was better than ciprofloxacin, trovafloxacin, or levofloxacin against ciprofloxacin-resistant

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strains, the use of gemifloxacin in humans against ciprofloxacin-resistant strains (gemifloxacin MICs ≥ 0.125 $\mu\text{g/mL}$) may not be as successful as treatment of strains with gemifloxacin MICs ≤ 0.06 $\mu\text{g/mL}$. This may mean that an appropriate breakpoint for *S. pneumoniae* should be set at 0.125 $\mu\text{g/mL}$.

In summary, gemifloxacin had a good effect against all strains of *S. pneumoniae* with gemifloxacin MICs ≤ 0.06 . Against penicillin-susceptible strains, gemifloxacin exhibited activity equivalent to amoxicillin/clavulanate and cefuroxime. Gemifloxacin was the most effective quinolone tested. Against penicillin-resistant strains, gemifloxacin was the most effective agent tested. Gemifloxacin has good activity against the macrolide-resistant strains of *Streptococcus pneumoniae*.

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TABLE 115
Efficacy of gemifloxacin and Comparators Against *S. pneumoniae* Respiratory Tract Infections in Rats
Log₁₀ CFU/lungs

Strain	CONTROL	GEMI	AMX/CA	CIP	GRP	LEVO	TRV	AZI	CXM	TOS
1629 pen-S	6.8 ± 1.2	≤1.7	≤1.7	4.1 ± 0.9	3.8 ± 1.7	4.3 ± 1.6	3.6 ± 1.9	2.8 ± 2.6	≤1.7	NT
10127 pen-S	6.4 ± 1.9	1.9 ± 0.5	≤1.7	5.6 ± 1.0	4.1 ± 1.1	4.1 ± 1.3	5.3 ± 1.4	2.5 ± 1.9	≤1.7	NT
L11259 pen-S	6.4 ± 1.9	≤1.7	≤1.7	6.0 ± 1.3	4.8 ± 1.6	5.7 ± 1.1	5.7 ± 1.7	1.9 ± 0.4	1.73 ± 0.1	NT
406081 mac-R	5.0 ± 0.9	2.2 ± 0.6	2.4 ± 1.0	4.1 ± 1.0	4.8 ± 1.3	4.5 ± 1.8	5.1 ± 1.0	5.1 ± 0.7	4.7 ± 1.3	NT
N1387 mac-R	5.1 ± 0.9	2.5 ± 1.1	2.3 ± 0.7	3.5 ± 1.3	3.6 ± 1.4	3.5 ± 0.8	4.4 ± 0.7	3.6 ± 1.1	3.3 ± 1.5	NT
404053 pen-R	5.9 ± 2.9	1.8 ± 0.2	4.2 ± 2.5	5.3 ± 0.8	3.4 ± 1.6	4.0 ± 1.4	4.3 ± 1.6	5.5 ± 1.2	6.1 ± 1.1	NT
205118 pen-R	6.3 ± 0.6	3.6 ± 1.9	3.2 ± 1.0	6.5 ± 0.7	5.6 ± 1.4	6.3 ± 0.7	5.5 ± 0.7	2.6 ± 1.5	4.9 ± 2.6	NT
305313 cip-R	7.1 ± 1.4	2.1 ± 1.4	≤1.7	6.7 ± 1.0	2.6 ± 1.0	6.7 ± 0.2	4.3 ± 1.0	≤1.7	≤1.7	6.1 ± 0.7
622286 cip-R	6.4 ± 1.3	2.4 ± 1.1	≤1.7	5.0 ± 1.2	5.5 ± 1.3	5.1 ± 1.3	3.9 ± 2.3	6.4 ± 2.0	≤1.7	3.9 ± 2.3

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Haemophilus influenzae

The efficacy of gemifloxacin mesylate against an experimental respiratory tract infection in rats caused by β -lactamase positive (BLA+) and β -lactamase negative, ampicillin resistant (BLNAR) strains of *Haemophilus influenzae* was examined in comparison with amoxicillin/clavulanate, cefuroxime, azithromycin, ciprofloxacin, grepafloxacin, levofloxacin, trovafloxacin, and tosufloxacin. Animals were infected intrabronchially with ciprofloxacin-susceptible and -resistant strains of *H. influenzae*. TABLE 116 summarizes the strains used in this study and the MICs for the various agents used. Therapy commenced 24 hours post infection and the oral doses administered were chosen to approximate in the rat, the serum and tissue concentration measured in man following therapeutic dosing. Dosing is the same as that used in most of the *S. pneumoniae* experiments (see TABLE 114). Treatment continued for three days and 17 hours after cessation of therapy the lungs were excised for the enumeration of viable bacterial numbers.

TABLE 116
In Vitro Susceptibilities (MIC- μ g/mL) of *H. influenzae* used in *in vivo* testing

Strain	GEMI	AMX/CA	CIP	GRP	LEVO	TRV	AZI	CXM	TOS
H 128 BLA+	≤ 0.008	1.0	0.016	≤ 0.008	NT	≤ 0.008	0.5	NT	NT
Chesterfield BLNAR	≤ 0.008	4.0	0.13	0.016	0.25	0.03	4.0	16.0	≤ 0.008
LA 85021 BLA+	≤ 0.008	4.0	0.016	≤ 0.008	0.5	≤ 0.008	1.0	4.0	≤ 0.016
HI43 Cip MIC =1	≤ 0.125	2.0	1.0	1.0	0.5	4.0	0.125	4.0	4.0

GEMI = gemifloxacin; AMX/CA = amoxicillin/clavulanate; CIP = ciprofloxacin;
GRP = grepafloxacin; LEVO = levofloxacin; TRV = trovafloxacin; AZI = azithromycin;
CXM = cefuroxime; TOS = tosufloxacin

Following infection with *H. influenzae* H128 (BLA+) gemifloxacin had a good effect and reduced bacterial counts in lungs to below the level of detection (130). The efficacy seen with gemifloxacin was similar to that seen with the other tested quinolones, but was significantly better than that seen with ciprofloxacin. Amoxicillin/clavulanate, cefuroxime, and azithromycin were not effective (see TABLE 117).

Gemifloxacin produced a marked response compared with untreated animals against infection caused by *H. influenzae* Chesterfield (BLNAR). Ciprofloxacin, grepafloxacin, and levofloxacin produced a similar effect to gemifloxacin. Trovafloxacin was slightly less effective. Amoxicillin/clavulanate, cefuroxime, and azithromycin were ineffective (TABLE 117).

Gemifloxacin was highly effective against *H. influenzae* LA8502 (BLA+) reducing bacterial numbers to below the detection level. The other quinolones gave similar results. The other comparators were ineffective (TABLE 117)

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The efficacy of gemifloxacin was examined against a strain of *H. influenzae* with a ciprofloxacin MIC of 1.0 µg/mL (131). In this study both immunocompetent and immunocompromised (neutropenia induced by cyclophosphamide) animals were used in order to enhance the infection with this strain (HI43), which is poorly virulent. Once again the normal once daily dose was divided into two doses and given b.i.d. Therapy commenced either 1 hour or 24 hours post infection. Treatment continued for 3-4 days.

Following infection with *H. influenzae* HI43 to immunocompetent animals, gemifloxacin produced a good response when given at 300 mg/kg o.d. starting 24 hours post infection. The effect obtained with gemifloxacin compared favorably with that of cefuroxime and levofloxacin. Amoxicillin/clavulanate reduced bacterial counts to the level of detection. Azithromycin was slightly better than gemifloxacin. The other tested quinolones produced outcomes only slightly better than control (see TABLE 117)

The effect of extending the period of exposure while maintaining the same AUC was also studied. For this study gemifloxacin (150 mg/kg), azithromycin (20 mg/kg day 1 followed by 10 mg/kg thereafter), trovafloxacin (20 mg/kg), grepafloxacin (100 mg/kg) and levofloxacin (62.5 mg/kg) were administered to neutropenic animals commencing 1-hour post infection and continued twice a day. The doses for the other comparators were not altered. In this experiment gemifloxacin reduced bacterial numbers to the level of detection. This effect was similar to that obtained with amoxicillin/clavulanate, grepafloxacin, and levofloxacin. Ciprofloxacin and cefuroxime had a slight effect. Azithromycin, trovafloxacin, and tosufloxacin were not effective (see TABLE 117)

In summary, gemifloxacin produced a good response against respiratory tract infections caused by *Haemophilus influenzae*. In general against ciprofloxacin-susceptible strains, the efficacy seen with gemifloxacin was better than that seen with amoxicillin/clavulanate, cefuroxime, and azithromycin and was similar to that seen with the comparator quinolones. Against a ciprofloxacin resistant strain of *Haemophilus influenzae*, none of the fluoroquinolones tested was as effective as against the susceptible strains. When the dosing was changed to twice a day and drug was started one hour post infection then gemifloxacin had much better activity.

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TABLE 117
Efficacy of gemifloxacin and Comparators Against *H. influenzae* Respiratory Tract Infections in Rats
Log₁₀ CFU/lungs

Strain	CONTROL	GEMI	AMX/CA	CIP	GRP	LEVO	TRV	AZI	CXM	TOS
H128 (BLA+)	4.3 ± 1.2	≤1.7	3.04 ± 1.61	2.5 ± 0.6	2.0 ± 0.48	1.8 ± 0.2	≤1.7	2.83 ± 1.7	4.2 ± 2.33	1.9 ± 0.5
Chesterfield	4.94 ± 1.06	≤1.7	4.5 ± 1.5	≤1.7	1.8 ± 0.2	≤1.7	2.5 ± 0.65	4.5 ± 0.6	4.0 ± 1.4	NT
LA8502 (BLA +)	6.9 ± 0.9	≤1.7	5.8 ± 1.1	1.76 ± 0.2	≤1.7	≤1.7	≤1.7	5.3 ± 1.2	5.9 ± 1.1	2.06 ± 0.9
HI43 (IM+) o.d. dosing Cip = 1 µg/mL	5.1 ± 1.2	2.5 ± 1.5	1.8 ± 0.3	4.3 ± 1.2	3.7 ± 1.4	3.1 ± 1.4	3.9 ± 1.8	≤1.7	2.8 ± 1.3	3.8 ± 1.4
HI43 (IM-) b.i.d. dosing	6.0 ± 1.2	≤1.7	≤1.7	4.0 ± 2.8	2.2 ± 1.1	2.3 ± 1.5	5.2 ± 2.2	5.2 ± 1.9	3.6 ± 1.9	6.0 ± 2.3

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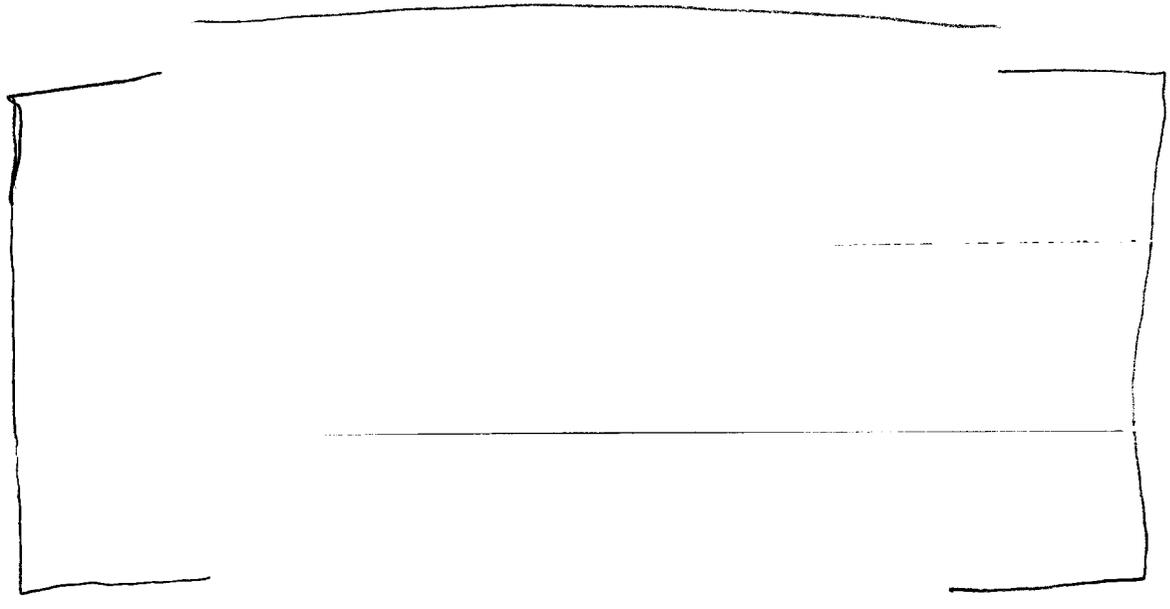
Klebsiella pneumoniae

The therapeutic efficacy of gemifloxacin was compared to ciprofloxacin and sparfloxacin in a mouse respiratory tract infection model caused by *Klebsiella pneumoniae* DT-S (132). The infection was introduced to the mice by aerosol inhalation. Drugs were dosed at 1.2 mg/mouse and given 18 hours post infection. Mice were killed at 4, 7, and 24 hours after drug administration and viable counts were performed on lung tissue. The results of this experiment are given in TABLE 118.

TABLE 118
In vivo Activity of Gemifloxacin against Respiratory Tract Infection
In Mice caused by *K. pneumoniae* DT-S

Drug	MIC ($\mu\text{g/mL}$)	Viable cells in lungs (\log_{10} CFU/lung)			
		0 hr	4 hr	7 hr	24 hr
Control	---	6.8 ± 0.3	7.5 ± 0.2	7.6 ± 0.2	8.6 ± 0.1
Gemifloxacin	0.13	6.8 ± 0.3	4.9 ± 0.1	4.2 ± 0.4	3.3 ± 0.3
Ciprofloxacin	0.031	6.8 ± 0.3	4.8 ± 0.4	4.4 ± 0.3	3.4 ± 0.3
Sparfloxacin	0.13	6.8 ± 0.3	4.9 ± 0.3	4.5 ± 0.2	3.6 ± 0.5

These data show that gemifloxacin was equivalent to ciprofloxacin and sparfloxacin in this infection model.



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SUMMARY OF EFFICACY IN ANIMAL MODELS OF INFECTION

Gemifloxacin appears to be effective in animal models of respiratory tract infections caused by *S. pneumoniae*, *H. influenzae*, and *K. pneumoniae*. It also appears to be effective in models of _____ In almost all cases it was equivalent or more active than other tested quinolones. Activity is reduced against ciprofloxacin-resistant strains and in the respiratory tract models dosing had to be altered and given shortly after infection in order for any of the quinolones to be effective. Whether gemifloxacin has sufficient efficacy against ciprofloxacin-resistant strains to be effective clinically is not known.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

ISOLATES/RELEVANCE TO APPROVED INDICATIONS

The clinical program to evaluate the efficacy of gemifloxacin in the treatment of community acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), _____

_____ consists of 11 randomized, double-blind, controlled pivotal studies. Five supportive studies were also conducted as well as a Phase II _____ This latter study was terminated early as the sponsor made the decision not to pursue the indication.

Two thousand eight hundred forty-four patients were randomized to receive gemifloxacin in the respiratory tract infections. Another 572 patients were randomized to receive gemifloxacin in the _____ Patients from Phase II AECB Study 001 were not included in the above tabulation as the duration of study medication was 10 days. Patients from _____ Study 010 are not included in the above tabulation as



TABLE 126 summarizes the clinical trials.

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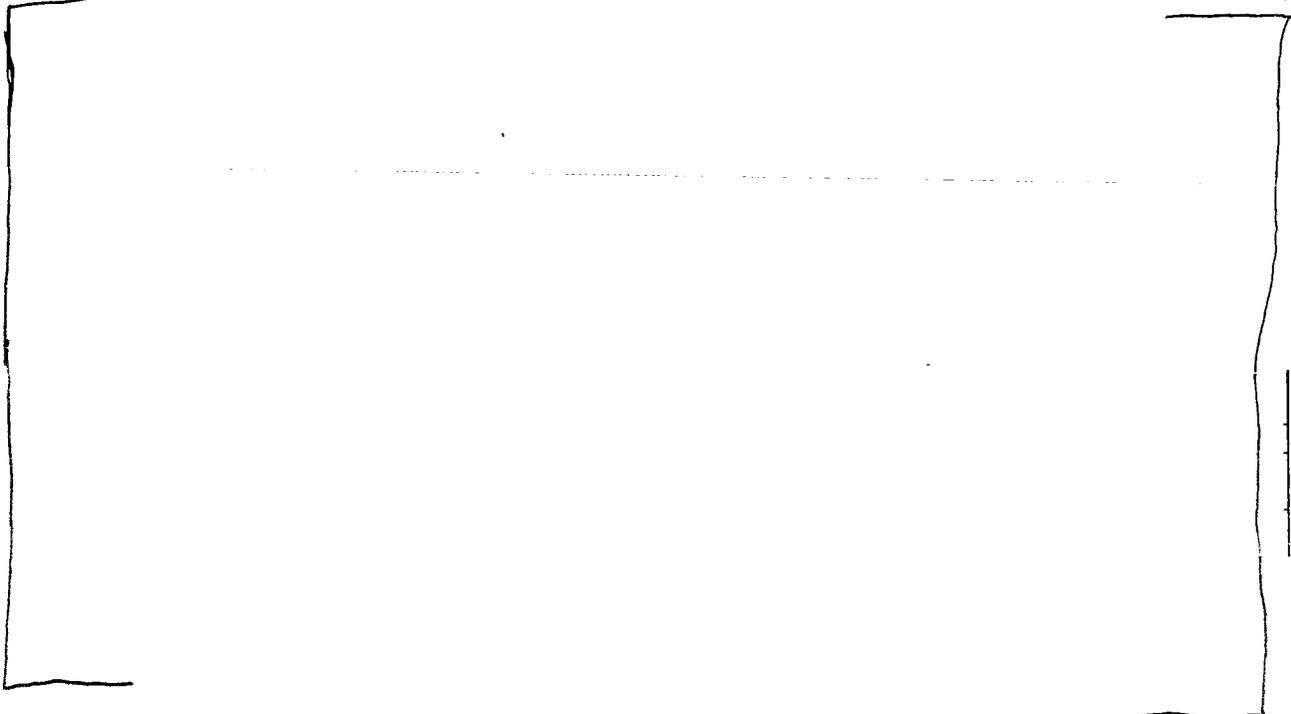
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**TABLE 126
Summary of Gemifloxacin Clinical Studies**

Indication Study No.	Total No. of Patients		Gemifloxacin Duration*	Comparator Drug	Primary Endpoint
	G	C			
CAP					
011	320		7 days	Amoxicillin/clavulanate 1g/125 mg tid 10 days	Clinical response at Follow-up
	167	153			
012	640		7 or 14 days	Clarithromycin and Cefuroxime 500 mg for 7 or 14 days	Clinical response at Follow-up
	319	321			
049	571		7 or 14 days	Trovafloracin 200 mg od 7 or 14 days	Clinical response at Follow-up
	290	281			
061	216 (CAP)		7 days	None	Clinical response at Follow-up
AECB					
008	586		7 days	Levofloxacin 500 mg od 7 days	Clinical response at Follow-up
	293	293			
068	709		5 days	Clarithromycin 500 mg bid 7 days	Clinical response at Follow-up
	351	358			
069	616		5 days	Trovafloracin 200 mg od 5 days	Clinical response at Follow-up
	302	314			
070	600		5 days	Amoxicillin/clavulanate 500/125 mg tid 7 days	Clinical response at Follow-up
	304	296			
001	267		For 10 days 80 mg, 160 mg, or 320 mg od	Ofloxacin 400 mg bid 10 days	Clinical response at Follow-up
	67	69			
	67				
	64				
061	261 (AECB)		7 days	None	Clinical response at Follow-up

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Respiratory Tract Infections

Acute Exacerbation of Chronic Bronchitis

The applicant is requesting an indication of acute bacterial exacerbations of chronic bronchitis caused by *Streptococcus pneumoniae*, including penicillin and macrolide-resistant strains; *Haemophilus influenzae* including β -lactamase-producing strains; *Haemophilus parainfluenzae*; *Moraxella catarrhalis*; and *Staphylococcus aureus*. The requested treatment is 320 mg once daily for 5 days..

Gemifloxacin was evaluated in acute exacerbation of chronic bronchitis in two controlled clinical studies (Studies 068 and 070) for five days of treatment. In Study 068 clarithromycin 500 mg twice daily was compared to 320 mg of gemifloxacin once daily. In Study 070 amoxicillin/clavulanate 500 mg/125 mg three times a day was compared to 320 mg of gemifloxacin once daily. In a supportive study (Study 069) gemifloxacin at 320 mg for 5 days was compared to trovafloxacin 200 mg once a day for 5 days.

Two other studies studied gemifloxacin 320 mg once daily for 7 days. Study 008 compared gemifloxacin to levofloxacin 500 mg once daily for 7 days. Study 061 was an open-label study of gemifloxacin at 320 mg once daily for 7 days.

Community Acquired Pneumonia

The applicant is requesting an indication of community acquired pneumonia caused by *Streptococcus pneumoniae*, including penicillin and macrolide-resistant strains; *Haemophilus influenzae*, including β -lactamase-producing strains; *Moraxella catarrhalis*; *Mycoplasma pneumoniae*; *Chlamydia pneumoniae*; _____

_____The requested treatment is 320 mg once daily for 7 to _____

Gemifloxacin was evaluated in community-acquired pneumonia in three controlled clinical studies (049, 011, and 012). In Study 049 gemifloxacin 320 mg once daily for 7 to 14 days was compared to trovafloxacin 200 mg once daily for 7 or 14 days. In Study 011 gemifloxacin at 320 mg once daily for 7 days was compared to amoxicillin/clavulanate 1 gram/125 mg given three times a day for 10 days. In Study 012 gemifloxacin 320 mg once daily for 7 or 14 days was compared to clarithromycin and cefuroxime 500 mg given three times a day for 7 to 14 days.

An open label study (Study 061) evaluated gemifloxacin 320 mg once daily for 7 days.

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BACTERIOLOGICAL OUTCOMES

Bacteriological response was based on clinical response of patients to study medication in trials examining respiratory infections. If patients demonstrated resolved or improved signs and symptoms of the disease under study at the end of therapy they did not undergo additional bacteriological assessments. An outcome of "presumed eradication" was used.

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TABLE 127
Bacteriological Eradication Rates by Pathogen at Test-of-Cure Visit
(Bacteriological Per Protocol Patients)

Indication—Pathogen	Gemifloxacin		Comparator Drug	
	n/N**	(%)	n/N**	(%)
CAP^a				
<i>M. pneumoniae</i>	84/97	(86.6)	80/93	(86.0)
<i>S. pneumoniae</i>	58/62	(93.5)	48/51	(94.1)
<i>C. pneumoniae</i>	39/41	(95.1)	27/30	(90.0)
<i>H. influenzae</i>	33/38	(86.8)	15/16	(93.8)
AECB^b				
<i>M. catarrhalis</i>	9/9	(100.0)	1/1	(100.0)
<i>M. catarrhalis</i>	29/30	(96.7)	25/28	(82.1)
<i>H. influenzae</i>	45/49	(91.8)	36/42	(85.7)
<i>S. pneumoniae</i>	15/20	(75.0)	21/25	(84.0)
<i>H. parainfluenzae</i>	16/18	(88.9)	16/18	(88.9)

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** n/N = number of pathogens eradicated or presumed eradicated /number of pathogens

^a Patients from Studies 011, 012, 049, and 061;

^b Patients from Studies 068, 069, and 070

The data in the above table indicate that the eradication rate for gemifloxacin is at least equivalent to that of the comparator drugs in each of the proposed indications.

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DISK CONTENT STUDIES

The disk potency of other quinolones is either 5 or 10- μ g depending on the diffusion characteristics of the drug. Both a 5- μ g and 10- μ g disk were evaluated in preliminary tests. Jones (137) showed that the zone diameter produced by a doubling of the disk drug content was approximately one millimeter and the frequency of zone diameters in the ranges of zones near the proposed breakpoints (15-20 mm) was relatively uncommon, 38 or nearly 1,000 tests. These results indicate a low likelihood of interpretive errors and a minimal need for a 10- μ g disk.

NCCLS document M-23 states that "The ideal disk is one that provides zone diameters greater than 15 mm and less than 45 mm for most susceptible strains but only small zone diameters of inhibition with resistant strains. However, susceptible breakpoints should, ideally, be between 15 and 24 mm". The 5- μ g disk appears to produce zone diameters close to this ideal.

MIC BROTH/AGAR DILUTION COMPARISONS

Appelbaum (138) used agar dilution, microdilution, E-test, and disk diffusion methodology to test the activity of gemifloxacin against 200 pneumococci. With agar dilution as the reference method, 187/200 strains (93.5%) gave essential agreement ($\pm 1 \log_2$ dilution) with microdilution, and 98.0% agreement with the E-test.

In another study (82) gemifloxacin macrotube dilution and agar dilution results were compared to microbroth dilution results against a panel of 100 clinical isolates. Ninety-five (95%) of the macrotube dilution MICs and 87% of the agar dilution MICs were within ± 1 dilution of the microbroth results.

It appears that agar dilution and broth dilution results are basically equivalent.

FREEZE DRIED PANELS/FROZEN REFERENCE PANELS COMPARISONS

The use of commercially-produced dried panels for microbroth dilution testing is becoming common practice in both clinical microbiology laboratories and in investigational surveillance studies. Dried panels were used in many of the studies presented in the NDA, including the Alexander Project and the Global Gemifloxacin Surveillance Study. They were also used by the central laboratories for testing the Phase III clinical isolates. Two studies were conducted to compare the MICs obtained using dried panels with MICs obtained using standard NCCLS recommended broth microdilution methods.

A study was performed to prove the equivalence of Dade MicroScan Inc. dried overnight antimicrobial susceptibility testing panels to frozen reference method panels when testing gemifloxacin (139). Trovafloxacin and ciprofloxacin were used as comparators. Two hundred stock cultures (including 97 challenge CDC strains) were

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tested on both MicroScan dried and reference method frozen panels. Total agreement (± 1 dilution) pre- and post-repeat testing was 97.0/99.0, 94.0/99.0, and 94.5/99.0 for gemifloxacin, trovafloxacin, and ciprofloxacin, respectively. There were more +1 well than -1 well discrepancies for gemifloxacin and ciprofloxacin, but the reverse was true for trovafloxacin. These data indicate that MicroScan dried panels give essentially equivalent MIC results as the reference microdilution method.

A similar study was conducted to establish the equivalency of Sensititre dried panels and frozen panels (140). Trovafloxacin and ciprofloxacin were included as comparators. Two hundred isolates consisting of CDC challenge strains and clinical isolates were tested by both methods. The ± 1 well agreement on initial and repeat testing was 98.0/100.0, 99.0/100.0, and 98.0/99.0 for gemifloxacin, ciprofloxacin, and trovafloxacin, respectively. On initial testing of gemifloxacin clinical isolates, 4 isolates yielded discrepancies of >1 dilution. Upon repeat testing, all 4 isolates were within ± 1 dilution. Seventy-four percent (74%) of results matched exactly between the dried and frozen panels and 98% were within ± 1 well dilution. Once again it appears that Sensititre dried panels and frozen panels give essentially equivalent results.

QUALITY CONTROL STUDIES (MIC AND DISK DIFFUSION)

Collaborative studies were performed in order to establish the quality control limits for standard susceptibility test assay strains of *Escherichia coli* ATCC 25922,

Haemophilus influenzae ATCC 49247, *Streptococcus pneumoniae* ATCC 49619, and *Enterococcus faecalis* ATCC 29212 (broth only). Nine laboratories participated under the direction of Ronald N. Jones, M.D., Department of Pathology, Medical Microbiology Division, Iowa City, Iowa. All laboratories performed susceptibility test by microdilution or disk diffusion according to NCCLS guidance.

5- μ g GEMIFLOXACIN DISK QUALITY CONTROL STUDIES

Jones (141) oversaw a collaborative study in July, 1998. Each of nine laboratories performed susceptibility tests on ten separate days using two different lots of 5- μ g gemifloxacin disks, one made by BBL and one by Oxoid. Three different lots of agar were used in order to determine the effects of medium on zone diameters. There were 60 replicates/site (2 lots of disks x 3 media lots x 10 days). Ciprofloxacin and ofloxacin disks were used as controls for all organisms. Most ciprofloxacin and ofloxacin results were within current NCCLS QC ranges. The results of this study are presented in TABLE 128.

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TABLE 128
Gemifloxacin Disk Quality Control Data
Zone diameter in mm, surrounding 5- μ g Gemifloxacin Disk

Organism	Median	Range	$\frac{1}{2}$ MR ^a
<i>E. coli</i> ATCC 25922	33	27-38	3
<i>H. influenzae</i> ATCC 49247	34	28-40	3
<i>S. pneumoniae</i> ATCC 49619	31	27-36	3

^a $\frac{1}{2}$ MR = $\frac{1}{2}$ the median of the ranges

For *E. coli* ATCC 25922, the median \pm $\frac{1}{2}$ MR is 30-36 mm. This includes 96.5% of the data. NCCLS approved a range of 29-36 mm in January, 1999. This approved range included 98.0% of the data.

For *H. influenzae* ATCC 49247, the data from one laboratory were significantly discordant from the other eight sites and the data were deleted from analysis. Using the other eight sites the median \pm $\frac{1}{2}$ MR is 31-37 mm. This range includes 95.4% of the data. NCCLS approved a range of 30-37 mm. This new range includes 98.3% of the data.

For *S. pneumoniae* ATCC 49619, the data from one laboratory were significantly discordant from the other eight sites and the data were deleted from analysis. Using the other eight sites the median \pm $\frac{1}{2}$ MR is 28-34 mm. This includes 97.3% of the data. This range was approved by NCCLS in January, 1999.

TABLE 129 gives a summary of the data for each organism.

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TABLE 129
 Summary of gemifloxacin zone diameter results for QC strains

Zone diameter (mm)	<i>E. coli</i>	<i>H. influenzae</i>	<i>S. pneumoniae</i>
19			
20			
21			
22			
23			
24			
25			
26			
27	1		4
28	6	1	19*
29	8*	3	53*
30	45*	14*	106*
31	72*	26*	99*
32	131*	79*	102*
33	138*	84*	72*
34	85*	112*	15*
35	39*	80*	2
36	8	52*	1
37	3	21*	473
38	1	1	
39	537	1	
40		2	
41		476	

* Indicates within approved NCCLS range

The following disk diffusion quality control limits were approved by NCCLS for the 5-µg gemifloxacin disk.

ORGANISM	GEMIFLOXACIN ZONE DIAMETER (mm)
<i>Escherichia coli</i> ATCC 25922	29-36
<i>Haemophilus influenzae</i> ATCC 49247	30-37
<i>Streptococcus pneumoniae</i> ATCC 49619	28-34

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MIC QUALITY CONTROL STUDIES

To determine the range of MICs that should be expected for susceptibility test of the ATCC quality control strains, microbroth dilution MIC studies were conducted (142). A total of nine laboratories participated in the study. Each of the nine laboratories tested three lots of Mueller-Hinton broth on each QC strain (five lots were tested for *H. influenzae* ATCC 49247) for ten days. Levofloxacin and trovafloxacin were used as control drugs. Most levofloxacin and trovafloxacin results were within current NCCLS QC ranges.

A total of 270 data points were generated for gemifloxacin for each QC strain (10 days x 3 lots x 9 laboratories). There were 450 data points for *H. influenzae* (10 days x 5 lots x 9 laboratories). The results of this study are presented in TABLE 130.

TABLE 130
Quality Control Data, Gemifloxacin MICs

Control Strain	MIC Values and No. Times Each Reported				
<i>E. coli</i> ATCC 25922	0.004 [58	0.008 188	0.016 23]	0.03 1	
<i>E. faecalis</i> ATCC 29212	0.008 1	0.016 [4	0.03 141	0.06 124	0.125 0]
<i>S. aureus</i> ATCC 29213	0.008 [34	0.016 235	0.03 1]		
<i>H. influenzae</i> ATCC 49247	0.002 [125	0.004 311	0.008 14]		

Brackets enclose proposed ranges.

The authors proposed the limits indicated by brackets in TABLE 130. These limits include 99.6% of the data for *E. coli* ATCC 25922, 99.6% of the data for *E. faecalis* ATCC 29212, and 100% of the data for the other QC organisms.

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These ranges were approved by NCCLS in January, 1999.

ORGANISM	GEMIFLOXACIN MIC ($\mu\text{g/mL}$)
<i>Escherichia coli</i> ATCC 25922	0.004-0.016
<i>Enterococcus faecalis</i> ATCC 29212	0.016-0.12
<i>Haemophilus influenzae</i> ATCC 49247	0.002-0.008
<i>Streptococcus pneumoniae</i> ATCC 49619	0.008-0.03

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E. coli ATCC 25922 and _____ will be included in the label and thus the required two strains for nonfastidious organisms will be in the label. *Enterococcus faecalis* will also be included although not in the indications for gemifloxacin since some laboratories may want to use it as a control instead of *E. coli* or _____ and it appears to be susceptible. The NCCLS QC limits are acceptable and will be placed in the label except for _____

MIC/DISK DIFFUSION CORRELATION STUDIES

Studies were performed to determine interpretive criteria for gemifloxacin. Breakpoints have been proposed for nonfastidious bacteria, streptococci including *Streptococcus pneumoniae*, and *Haemophilus* species. Gemifloxacin 5- μg disks were used for susceptibility testing. All testing was performed according to NCCLS guidelines.

NONFASTIDIOUS ORGANISMS

The indications under consideration at the present time do not include treatment of enterococci, _____, or other non-enterobacteriaceae with gemifloxacin, therefore, no breakpoints will be determined for these groups of organisms. Only staphylococci and enterobacteriaceae will be discussed in this section.

In an early study (February 1999) Fuchs et al. at the Clinical Microbiology Institute (CMI) tested 648 strains from their stock collection of recent clinical isolates to determine tentative disk breakpoints (35). The disk diffusion test was performed in parallel with the broth microdilution test with 439 nonfastidious organisms. Both 5- μg and 10- μg disk were used. They proposed the same disk breakpoints for both disk masses. In their first report they assumed that the susceptible MIC breakpoint for gemifloxacin would be similar to that of other fluoroquinolones (i.e. either $\leq 1.0 \mu\text{g/mL}$ or $\leq 2.0 \mu\text{g/mL}$). They used the error rate bounded method and proposed the following disk breakpoints:

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MIC Breakpoint	Disk Breakpoint	Interpretation
≤ 1.0 µg/mL	≥ 15 mm	(S) Susceptible
2.0 µg/mL	12-14 mm	(I) Intermediate
≥ 4.0 µg/mL	≤ 11 mm	(R) Resistant
≤ 2.0 µg/mL	≥ 12 mm	(S) Susceptible
4.0 µg/mL	9-11 mm	(I) Intermediate
≥ 8.0 µg/mL	≤ 8 mm	(R) Resistant

The scattergram for staphylococci showed a bimodal population. The more resistant cluster contained the ciprofloxacin-resistant strains. Most of these strains are also methicillin-resistant. The authors suggested gemifloxacin breakpoints of ≤ 0.12 µg/mL and ≥ 0.5 µg/mL to separate the two populations.

In an addendum (March 1999) the authors reevaluated the data using a susceptible breakpoint of ≤ 0.5 µg/mL for gemifloxacin. Figure 27 is a scattergram of gemifloxacin MICs and the 5-µg disk diffusion zone diameters for 440 nonfastidious organisms tested. The authors proposed the following breakpoints:

MIC Breakpoint	Disk Breakpoint	Interpretation
≤ 0.5 µg/mL	≥ 18 mm	(S) Susceptible
1.0 µg/mL	15-17 mm	(I) Intermediate
≥ 2.0 µg/mL	≤ 14 mm	(R) Resistant

Using these criteria there were 5 (1.1%) very major errors (all Gram-negative bacilli), 2 (0.5%) major errors and 29 (6.6%) minor errors.

The authors did not propose any disk breakpoints for a susceptible breakpoint of ≤ 0.25 µg/mL, but from the scattergram it appears that the following breakpoints might be appropriate:

MIC Breakpoint	Disk Breakpoint	Interpretation
≤ 0.25 µg/mL	≥ 22 mm	(S) Susceptible
0.5 µg/mL	19-21 mm	(I) Intermediate
≥ 1.0 µg/mL	≤ 18 mm	(R) Resistant

Error rates for these breakpoints are 7 (1.6%) very major, 7 (1.5%) major, and 40 (9.1%) minor. The very major error rate is greater than the 1.5% set by NCCLS. Raising the susceptible breakpoint to 23 mm will not help. Going to a susceptible breakpoint of ≥ 24 mm would lower the very major error rate but the minor error rate would be much greater.

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Figure 28 shows the scattergram for staphylococci. The authors have proposed a susceptible breakpoint of $\leq 0.5 \mu\text{g/mL}$. It appears that the following breakpoints for staphylococci might be appropriate if a susceptible breakpoint of $\leq 0.12 \mu\text{g/mL}$ is chosen:

MIC Breakpoint	Disk Breakpoint	Interpretation
$\leq 0.12 \mu\text{g/mL}$	$\geq 24 \text{ mm}$	(S) Susceptible
$0.25 \mu\text{g/mL}$	21-23 mm	(I) Intermediate
$\geq 0.5 \mu\text{g/mL}$	$\leq 20 \text{ mm}$	(R) Resistant

With these criteria there are no very major or major errors and only 2 (2.5%) minor errors. These breakpoints separate the two distinct populations very nicely.

Figure 29 shows the scattergram for Enterobacteriaceae. The authors have proposed breakpoints determined for a susceptible MIC breakpoint of $\leq 0.5 \mu\text{g/mL}$. It appears that the following breakpoints for Enterobacteriaceae might be appropriate if a susceptible breakpoint of $\leq 0.25 \mu\text{g/mL}$ is chosen:

MIC Breakpoint	Disk Breakpoint	Interpretation
$\leq 0.25 \mu\text{g/mL}$	$\geq 20 \text{ mm}$	(S) Susceptible
$0.5 \mu\text{g/mL}$	16-19 mm	(I) Intermediate
$\geq 1.0 \mu\text{g/mL}$	$\leq 15 \text{ mm}$	(R) Resistant

Using these criteria there is 1 (0.5%) very major, no major errors and only 7 (3.5%) minor errors.

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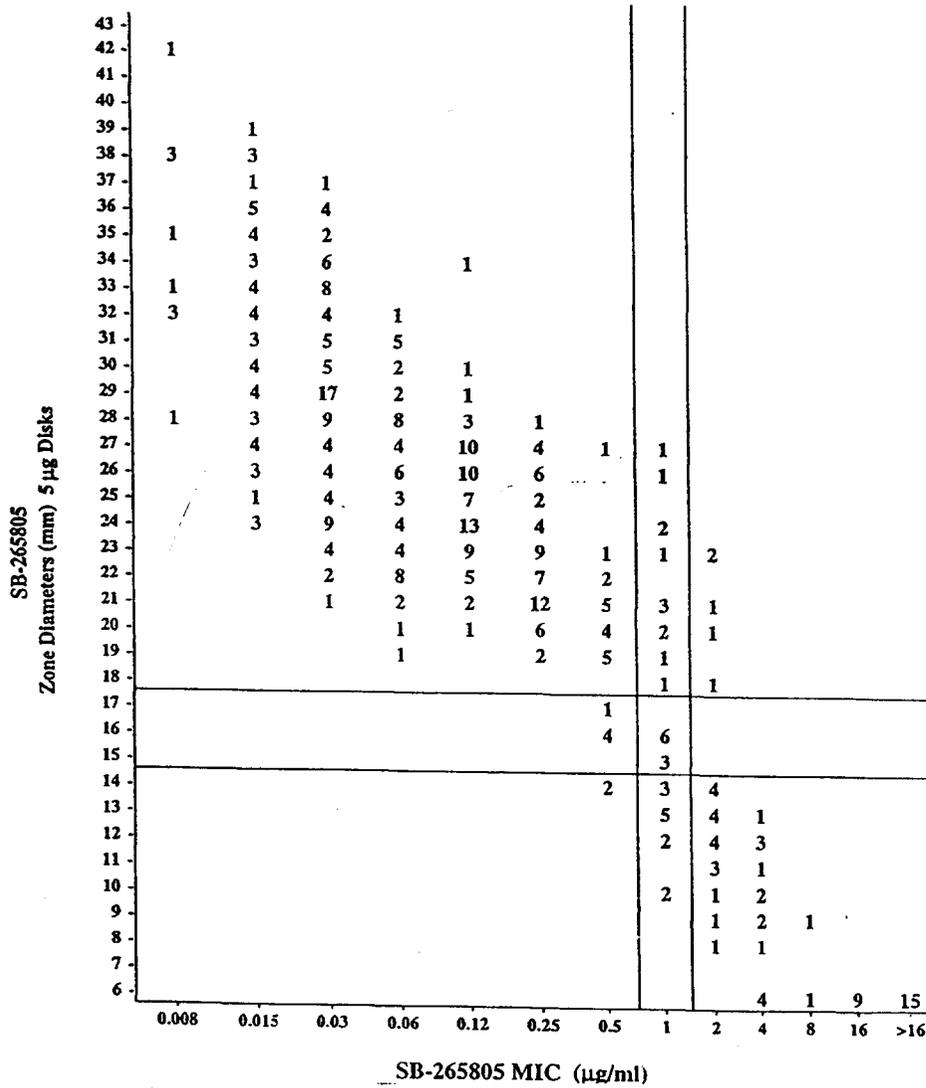
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Figure 27—Gemifloxacin 5-µg/mL Disk Zone Diameters vs MICs (N=440)

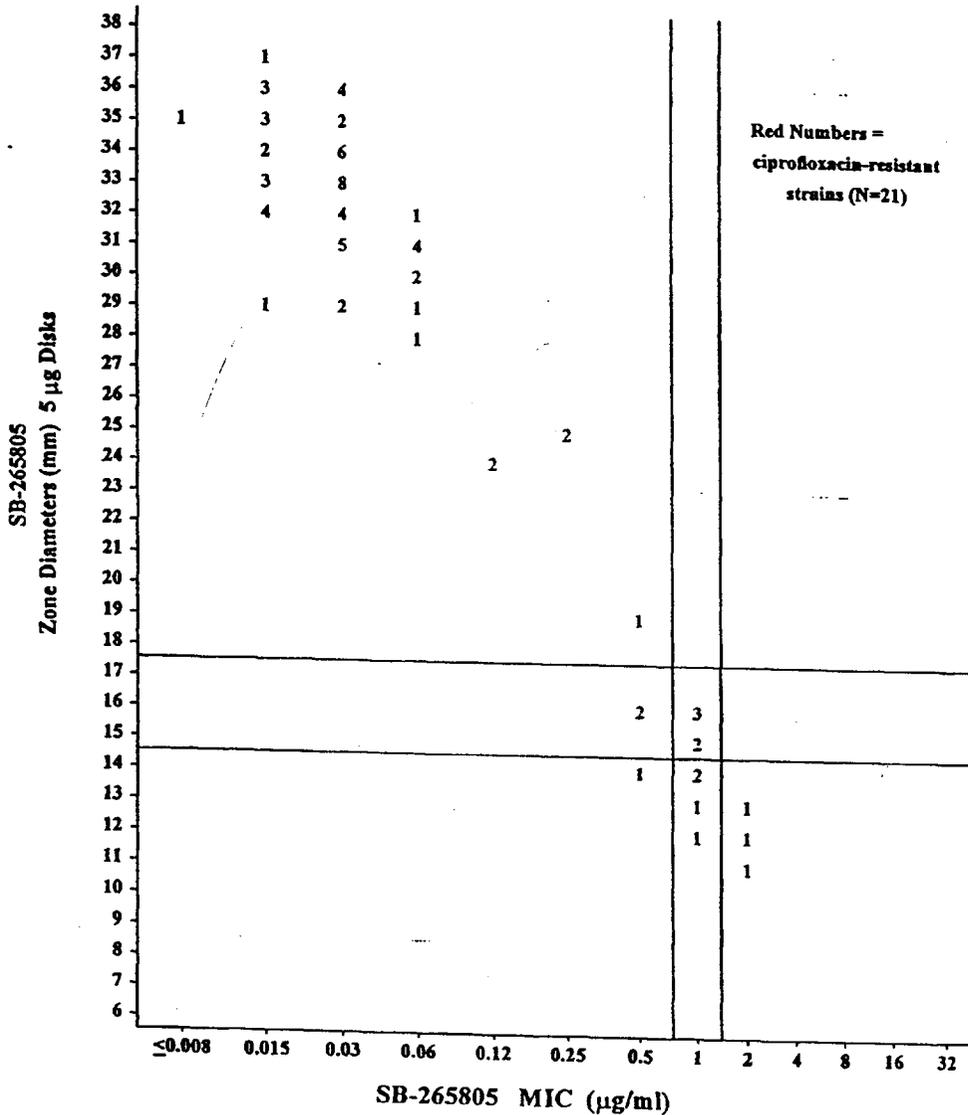
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Figure 28—Gemifloxacin MICs vs Zone Diameter for Staphylococci (N = 80)

Red Numbers could not be shown on graph—all ciprofloxacin resistant strains had gemifloxacin MICs ≥ 0.12 µg/mL and all ciprofloxacin susceptible strains had gemifloxacin MICs ≤ 0.06 µg/mL.

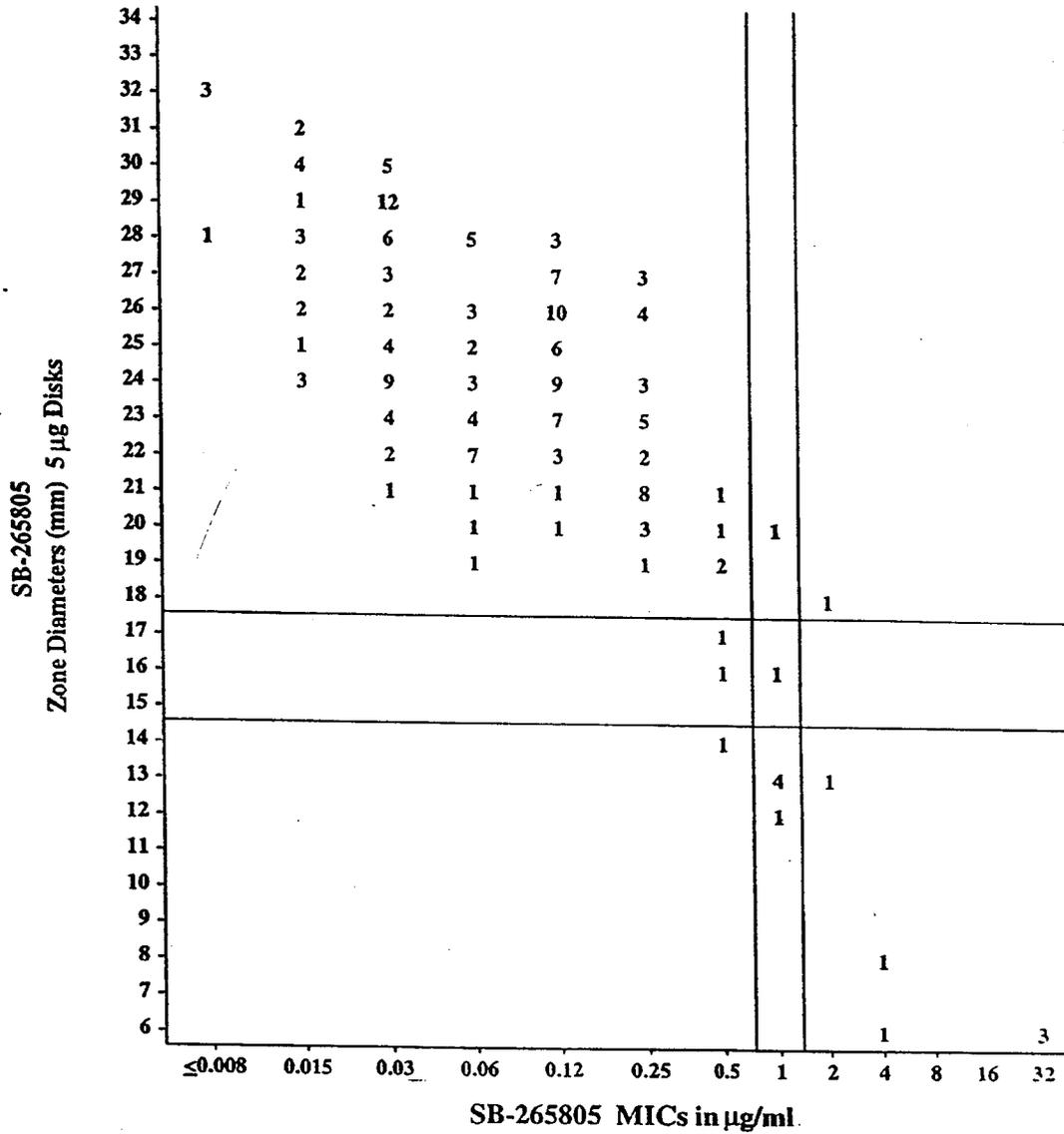
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Figure 29—Gemifloxacin MICs vs Zone Diameter for Enterobacteriaceae (N = 195)

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In an initial study to define tentative disk susceptibility breakpoints, Dr. R. Jones used 986 rapidly growing pathogens to investigate the correlation between MIC and disk zone diameters (137). These organisms included 480 strains of *Enterobacteriaceae*, 125 strains of non-fermentative Gram-negative bacilli, 290 strains of staphylococci, and 91 strains of enterococci. Representative susceptible and resistant strains of each species were tested when possible. Quality control strains were also tested. Levofloxacin and/or ofloxacin MIC and disk diffusion tests were used as a concurrent control. The error rate bounding method was applied to select the zone diameter interpretive criteria for gemifloxacin using a breakpoint concentration (usually $\leq 0.5 \mu\text{g/mL}$) based on pharmacokinetic results. Figure 32 shows the scattergram comparing gemifloxacin MICs and the zone diameters for 5- μg disks. The regression equation was $y = 14.8 - 0.41x$. The author proposed the following criteria:

MIC Breakpoint	Disk Breakpoint	Interpretation
$\leq 0.5 \mu\text{g/mL}$	$\geq 17 \text{ mm}$	(S) Susceptible
$1.0 \mu\text{g/mL}$	14-16 mm	(I) Intermediate
$\geq 2.0 \mu\text{g/mL}$	$\leq 13 \text{ mm}$	(R) Resistant

There was one very major error (0.1%) and no major errors. There were 3.2% minor errors. Using a breakpoint of $\leq 0.25 \mu\text{g/mL}$ for susceptible the following criteria seem appropriate.

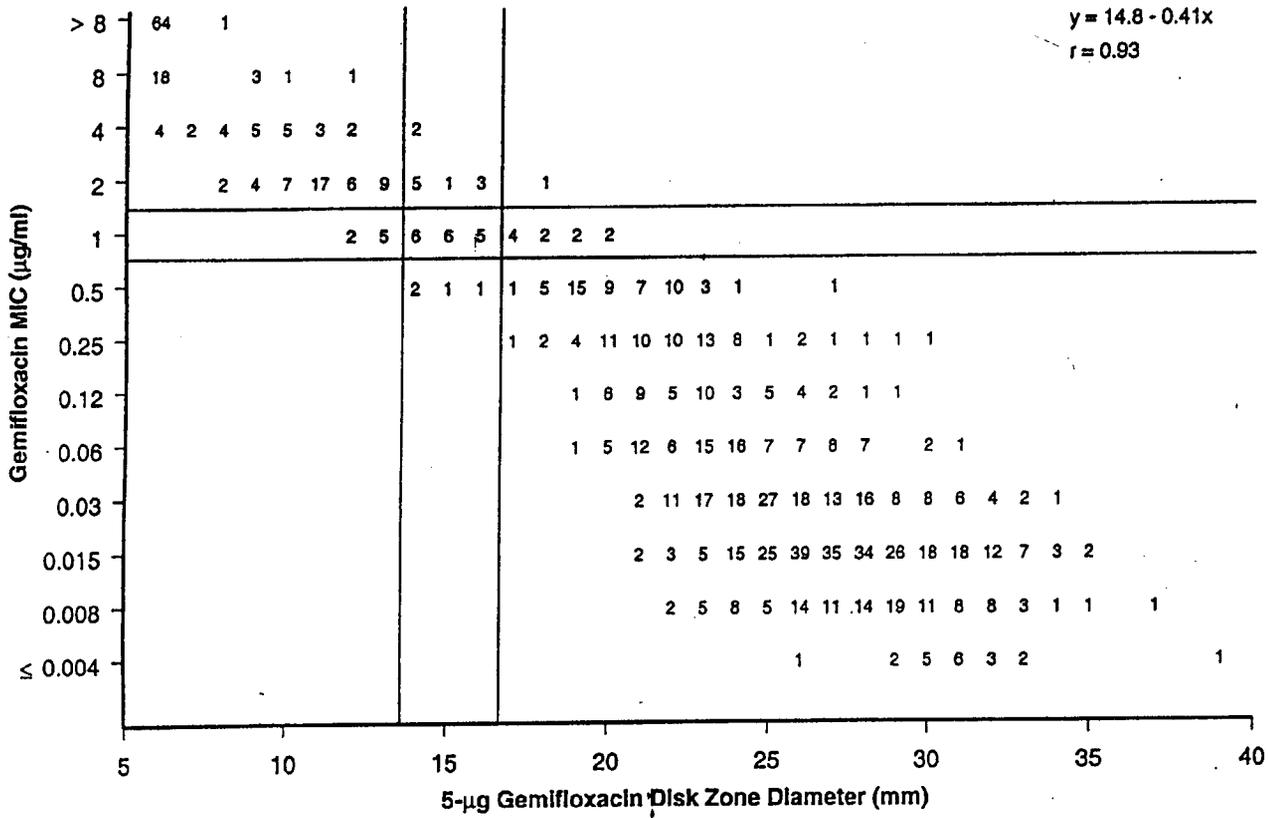
MIC Breakpoint	Disk Breakpoint	Interpretation
$\leq 0.25 \mu\text{g/mL}$	$\geq 20 \text{ mm}$	(S) Susceptible
$0.5 \mu\text{g/mL}$	17-19 mm	(I) Intermediate
$\geq 1.0 \mu\text{g/mL}$	$\leq 16 \text{ mm}$	(R) Resistant

Error rates for these criteria are 0.2% very major, 0% major, and 5.4% minor. This study did not separate out the different groups of nonfastidious organisms (i.e. staphylococci, _____ and enterobacteriaceae). Various groups of streptococci and *Haemophilus influenzae* were separated out and will be discussed in the appropriate study section.

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Figure 32—Scattergram of gemifloxacin MICs vs Zone Diameters

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TABLE 131 gives a summary of the above zone diameter criteria studies. It appears from pharmacokinetic studies that the proposed dose will provide an AUC of 8.36 $\mu\text{g}\cdot\text{h}/\text{mL}$. To obtain the usual 20-30 AUC/breakpoint ratio would require a susceptible breakpoint of 0.25 $\mu\text{g}/\text{mL}$. In order to separate the methicillin-resistant strains of staphylococci from the -susceptible strains a susceptible breakpoint of 0.12 $\mu\text{g}/\text{mL}$ seems appropriate. Many methicillin-resistant strains have MICs of 0.5 $\mu\text{g}/\text{mL}$.

TABLE 131
Susceptibility Criteria Proposed from Pre-Clinical Studies

Reference	Proposed by Authors	Proposed from Scattergram	Staphylococci	Enterobacteriaceae
35—CMI	$\leq 0.5 = \geq 18$ mm 1.0 = 15-17 mm $\geq 2.0 = \leq 14$ mm	For Nonfastidious $\leq 0.25 = \geq 22$ mm 0.5 = 19-21 $\geq 1.0 = \leq 18$ mm	Proposed From Scattergram $\leq 0.12 = \geq 24$ mm 0.25 = 21-23 mm $\geq 0.5 = \leq 20$ mm	Proposed From Scattergram $\leq 0.25 = \geq 20$ mm 0.5 = 16-19 mm $\geq 1.0 = \leq 15$ mm
31—CMI	$\leq 0.5 = \geq 20$ mm 1.0 = 17-19 mm $\geq 2.0 = \leq 16$ mm			
57				$\leq 0.25 = \geq 20$ mm 0.5 = 16-19 mm $\geq 1.0 = \leq 15$ mm
143		For staphylococci $\leq 0.12 = \geq 25$ mm 0.25 = 22-24 mm $\geq 0.5 = \leq 21$ mm	$\leq 0.25 = \geq 23$ mm 0.5 = 20-22 mm $\geq 1.0 = \leq 19$ mm	
137	$\leq 0.5 = \geq 17$ mm 1.0 = 14-16 mm $\geq 1.0 = \leq 13$ mm	For Nonfastidious $\leq 0.25 = \geq 20$ mm 0.5 = 17-19 mm $\geq 1.0 = \leq 16$ mm		

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Most of these studies proposed a susceptible breakpoint of $\leq 0.5 \mu\text{g/mL}$ and thus the proposed disk diffusion breakpoints are not those that would be used for the now proposed $\leq 0.25 \mu\text{g/mL}$ breakpoint. The scattergrams, however, can be used to determine what disk diffusion breakpoints are appropriate for this new proposed susceptible breakpoint. It appears that the following are the most appropriate breakpoints for Enterobacteriaceae and staphylococci:

For testing Enterobacteriaceae:

	<u>MIC ($\mu\text{g/mL}$)</u>	<u>Zone Diameter (mm)</u>
Susceptible	≤ 0.25	≥ 20
Intermediate	0.5	16-19
Resistant	≥ 1.0	≤ 15

For testing Staphylococci:

	<u>MIC ($\mu\text{g/mL}$)</u>	<u>Zone Diameter (mm)</u>
Susceptible	≤ 0.25	≥ 23
Intermediate	0.5	20-22
Resistant	≥ 1.0	≤ 19

Or

	<u>MIC ($\mu\text{g/mL}$)</u>	<u>Zone Diameter (mm)</u>
Susceptible	≤ 0.12	≥ 25
Intermediate	0.25	22-24
Resistant	≥ 0.5	≤ 21

The final breakpoints will be decided when zone diameters in the clinical trials are compared to bacteriological and clinical outcomes and discussed in this review under the section titled "Correlation of Test Results with Outcome Statistics".

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STREPTOCOCCUS SPECIES INCLUDING *STREPTOCOCCUS PNEUMONIAE*

Since the only streptococci species that gemifloxacin is proposed for is *Streptococcus pneumoniae* this is the only species that breakpoint criteria will be determined for.

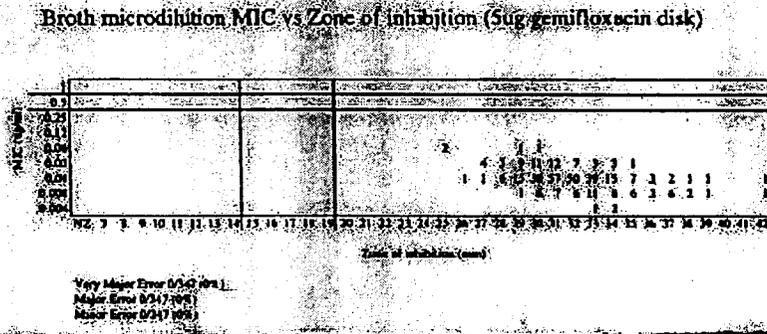
Gemifloxacin broth microdilution and disk diffusion susceptibility testing was conducted in parallel for 347 clinical isolates of *Streptococcus pneumoniae* (41). The methods were correlated using scattergram analysis. Figure 33 shows the scattergram for this study. The authors proposed the following criteria:

MIC Breakpoint	Disk Breakpoint	Interpretation
≤ 0.25 µg/mL	≥ 20 mm	(S) Susceptible
0.5 µg/mL	15-19 mm	(I) Intermediate
≥ 1.0 µg/mL	≤ 14 mm	(R) Resistant

Using these criteria there were no very major, major, or minor errors.

All the isolates in this study had MIC ≤ 0.06 µg/mL and zone diameters ≥ 25 mm. Using the rule of setting breakpoints one dilution higher than the highest MIC value for 99% of the population would give a susceptible MIC value of ≤ 0.12 µg/mL. A zone diameter breakpoint set 3 mm smaller than the smallest zone diameter for 99% of the population gives a susceptible zone diameter breakpoint of ≥ 23 mm. Since there are no resistant isolates in this study only a susceptible breakpoint should be used.

Figure 33—Scattergram analysis of gemifloxacin against 347 recent clinical *Streptococcus pneumoniae* isolates



In another study (138) Appelbaum compared the MICs and zone diameters for gemifloxacin against 200 strains of *Streptococcus pneumoniae* including 39 ciprofloxacin-resistant strains. The following breakpoints were proposed:

MIC Breakpoint	Disk Breakpoint	Interpretation
≤ 0.25 µg/mL	≥ 23 mm	(S) Susceptible
0.5 µg/mL	21-22 mm	(I) Intermediate
≥ 1.0 µg/mL	≤ 20 mm	(R) Resistant

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In this study quinolone-susceptible strains had MICs ≤ 0.06 $\mu\text{g/mL}$ and zone diameters ≥ 26 mm. The quinolone-resistant strains had MICs between 0.03 $\mu\text{g/mL}$ and 1.0 $\mu\text{g/mL}$ and zone diameters between 18 and 31, but were mostly 21-26 mm. This indicates that a zone diameter of 26 mm appears to separate the resistant strains from the susceptible strains and that a MIC of ≤ 0.12 $\mu\text{g/mL}$ may be appropriate.

In a study by Jones, 304 strains of *Streptococcus pneumoniae* were used to define tentative disk susceptibility breakpoints (137). Eleven of these strains were levofloxacin-resistant (MIC ≥ 32 $\mu\text{g/mL}$). In addition 142 strains of β -haemolytic streptococci, and 163 stains of viridans group streptococci (4 resistant to levofloxacin), along with quality control strains were also tested. Levofloxacin and/or ofloxacin MIC and disk diffusion tests were used as concurrent controls. The error rate bounding method was applied to select the zone diameter interpretive criteria for gemifloxacin using a breakpoint concentration (usually ≤ 0.5 $\mu\text{g/mL}$) based on pharmacokinetic results. Figure 35 shows the scattergram for *Streptococcus pneumoniae*. The levofloxacin-resistant strains are circled. These strains had elevated gemifloxacin MICs (0.12 to 0.5 $\mu\text{g/mL}$) compared to MICs of ≤ 0.008 to 0.12 $\mu\text{g/mL}$ for the other strains.

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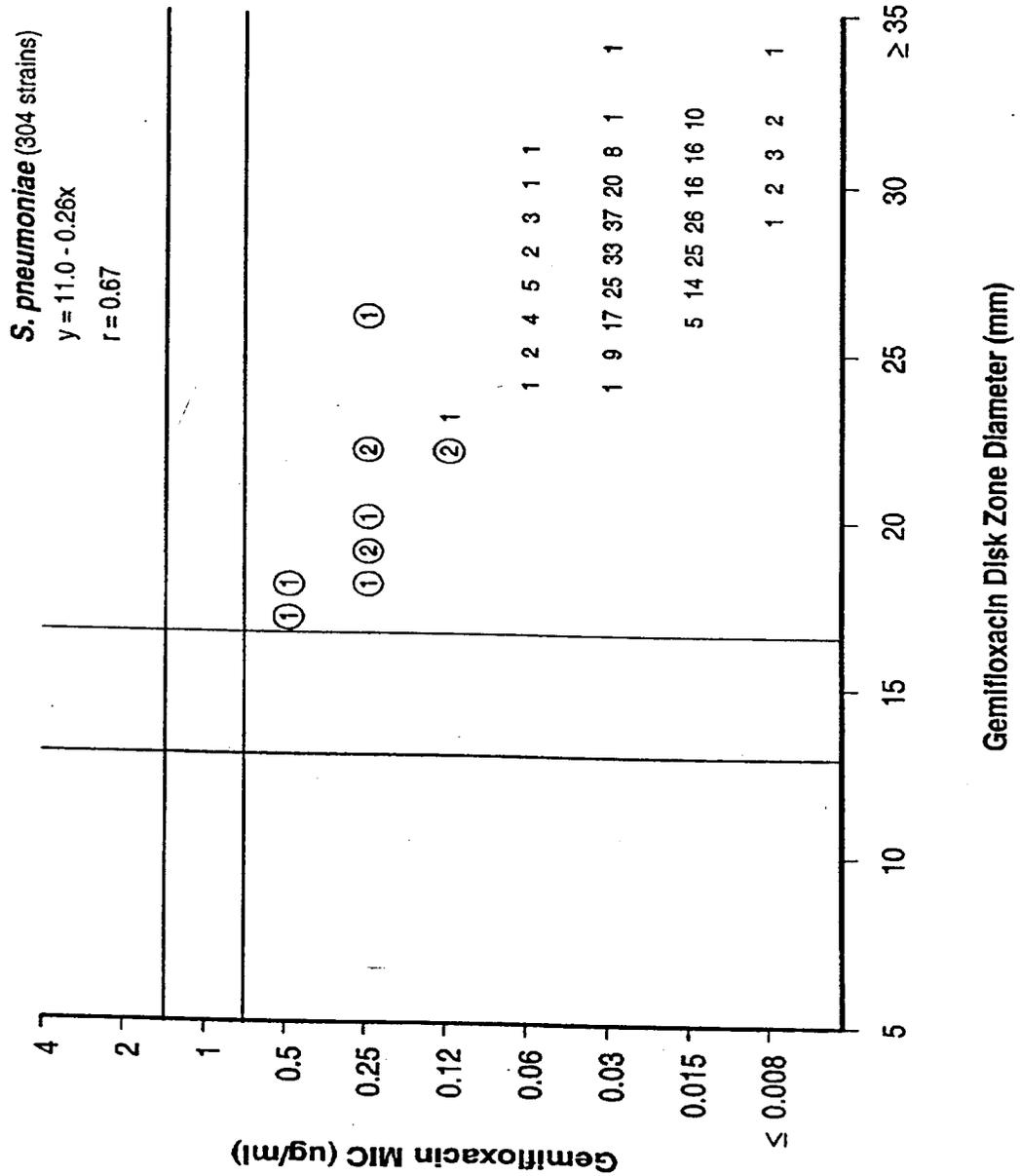


Figure 35—Scattergram of *S. pneumoniae* (n=304)

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The author proposed using the following susceptibility criteria:

MIC Breakpoint	Disk Breakpoint	Interpretation
≤ 0.5 µg/mL	≥ 17 mm	(S) Susceptible
1.0 µg/mL	14-16 mm	(I) Intermediate
≥ 2.0 µg/mL	≤ 13 mm	(R) Resistant

Using these criteria the correlation between methods was only $r = 0.67$ and the regression line equation was $y = 11.0 - 0.26x$. No interpretive errors were noted.

From this scattergram it appears that a susceptible breakpoint of ≤ 0.12 µg/mL would separate most of the levofloxacin-susceptible and -resistant strains. A susceptible breakpoint of ≥ 23 also seems appropriate. The following criteria appear to be appropriate for testing *S. pneumoniae*:

MIC Breakpoint	Disk Breakpoint	Interpretation
≤ 0.12 µg/mL	≥ 23 mm	(S) Susceptible
0.25 µg/mL	20-22 mm	(I) Intermediate
≥ 0.5 µg/mL	≤ 19 mm	(R) Resistant

Using these criteria error rates would be 0% very major, 0% major, and 2.0% minor.

TABLE 132 gives a summary of the above zone diameter criteria studies. It appears that a MIC breakpoint of ≤ 0.12 µg/mL separates the quinolone-susceptible from the quinolone-resistant strains. A review of the clinical trials is needed to see if the quinolone-resistant isolates are eradicated. At the present time it seems that this separation into two different populations may be appropriate.

TABLE 132
Susceptibility Criteria Proposed from Pre-Clinical Studies (*S. pneumoniae*)

Reference	Proposed by Authors	Proposed from Scattergram
41	≤ 0.25 = ≥ 20 mm 0.5 = 15-19 mm ≥ 1.0 = ≤ 14 mm	≤ 0.12 = ≥ 23 mm
138	≤ 0.25 = ≥ 23 mm 0.5 = 21-22 mm ≥ 1.0 = ≤ 20 mm	≤ 0.12 = ≥ 26 mm 0.25 = 23-25 mm ≥ 0.5 = ≤ 22 mm
137	≤ 0.5 = ≥ 17 mm 1.0 = 14-16 mm ≥ 2.0 = ≤ 13 mm	≤ 0.12 = ≥ 23 mm 0.25 = 20-22 mm ≥ 0.5 = ≤ 19 mm

Most of these studies proposed a susceptible breakpoint of ≤ 0.25 µg/mL and thus the proposed disk diffusion breakpoints are not those that would be used for the proposed ≤ 0.12 µg/mL breakpoint. The scattergrams, however, can be used to determine what disk diffusion breakpoints are appropriate for this new proposed susceptible breakpoint. It appears that the following are the most appropriate breakpoints for *Streptococcus pneumoniae*:

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For testing *Streptococcus pneumoniae*:

	MIC ($\mu\text{g/mL}$)	Zone Diameter (mm)
Susceptible	≤ 0.12	≥ 23
Intermediate	0.25	20-22
Resistant	≥ 0.5	≤ 19

The final breakpoints will be decided when zone diameters in the clinical trials are compared to bacteriological and clinical outcomes and discussed in this review under the section titled "Correlation of Test Results with Outcome Statistics".

HAEMOPHILUS SPECIES STUDIES

In a study conducted by the sponsor (47) broth microdilution and disk diffusion susceptibility testing was performed against 198 strains of *Haemophilus influenzae* and 26 strains of *H. parainfluenzae*. The MICs for *H. influenzae* were between ≤ 0.008 and $0.06 \mu\text{g/mL}$ ($\text{MIC}_{90} = \leq 0.008 \mu\text{g/mL}$). The MICs for *H. parainfluenzae* were between ≤ 0.008 and $0.06 \mu\text{g/mL}$. The zone diameters for *H. influenzae* were between 25 mm and 45 mm and for *H. parainfluenzae* were between 24 mm and 38 mm. This indicates that breakpoints of $\leq 0.12 \mu\text{g/mL}$ and ≥ 21 mm may be appropriate (one dilution higher than the highest MIC for 99% of the population and zone diameter 3 mm less than the smallest zone diameter for 99% of the population—from *H. parainfluenzae* population).

In the CMI study (31) gemifloxacin MIC and zone diameters were compared for 403 strains of *Haemophilus* species. The authors proposed breakpoints of $\leq 0.5 \mu\text{g/mL}$ and ≥ 20 mm for susceptible and $\geq 2 \mu\text{g/mL}$ and ≤ 16 mm for resistant, but said they should be considered highly tentative. Figure 36 shows the scattergram for these data. Only 3 strains had MICs $> 0.12 \mu\text{g/mL}$ and zone diameters > 19 mm. Using the 99% rule this would indicate that a susceptible breakpoint of $\leq 0.25 \mu\text{g/mL}$ and ≥ 16 mm should be chosen.

In a study by Jones (137) susceptibility testing by broth microdilution and disk diffusion was performed against 300 *Haemophilus influenzae* isolates. Gemifloxacin had a MIC_{90} value of $0.008 \mu\text{g/mL}$ and most strains had MICs $\leq 0.004 \mu\text{g/mL}$. Only one isolate had a MIC value greater than $0.03 \mu\text{g/mL}$. Most zone diameters were ≥ 27 mm. Only two isolates had zone diameters greater than 24 mm. A single strain resistant to fluoroquinolones (ciprofloxacin) had an elevated gemifloxacin MIC of $0.25 \mu\text{g/mL}$ and zone diameter of 18 mm. Only susceptible breakpoints were proposed by the author. These were $\leq 0.5 \mu\text{g/mL}$ for dilution testing and ≥ 17 mm for diffusion testing. Figure 37 shows the scattergram for this study. Using the 99% rule would indicate that only a susceptible breakpoint is needed and the criteria should be as follow:

	MIC ($\mu\text{g/mL}$)	Zone Diameter (mm)
Susceptible	≤ 0.06	≥ 21

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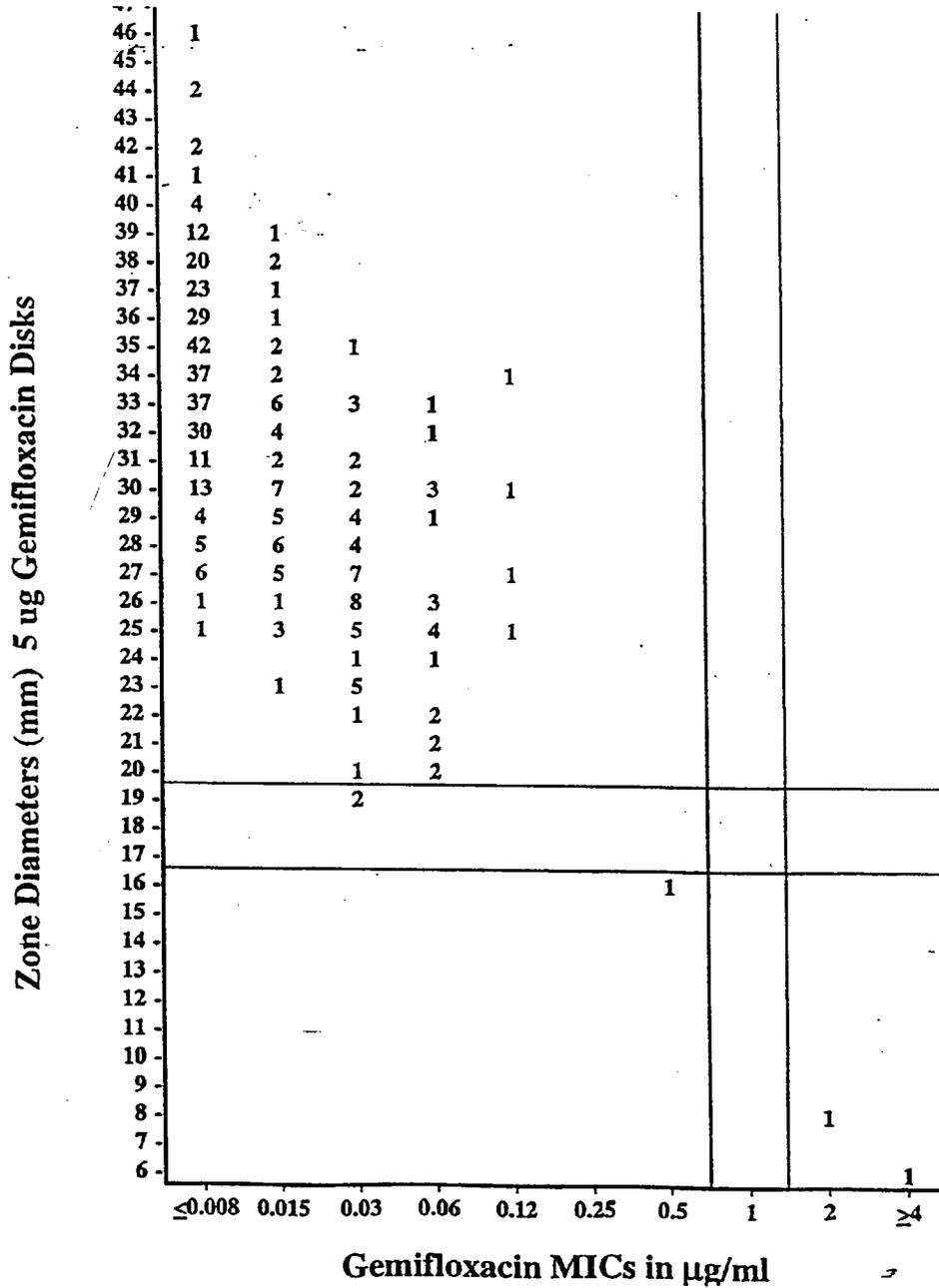


Figure 36—Gemifloxacin scattergram for *Haemophilus* species (n= 403)

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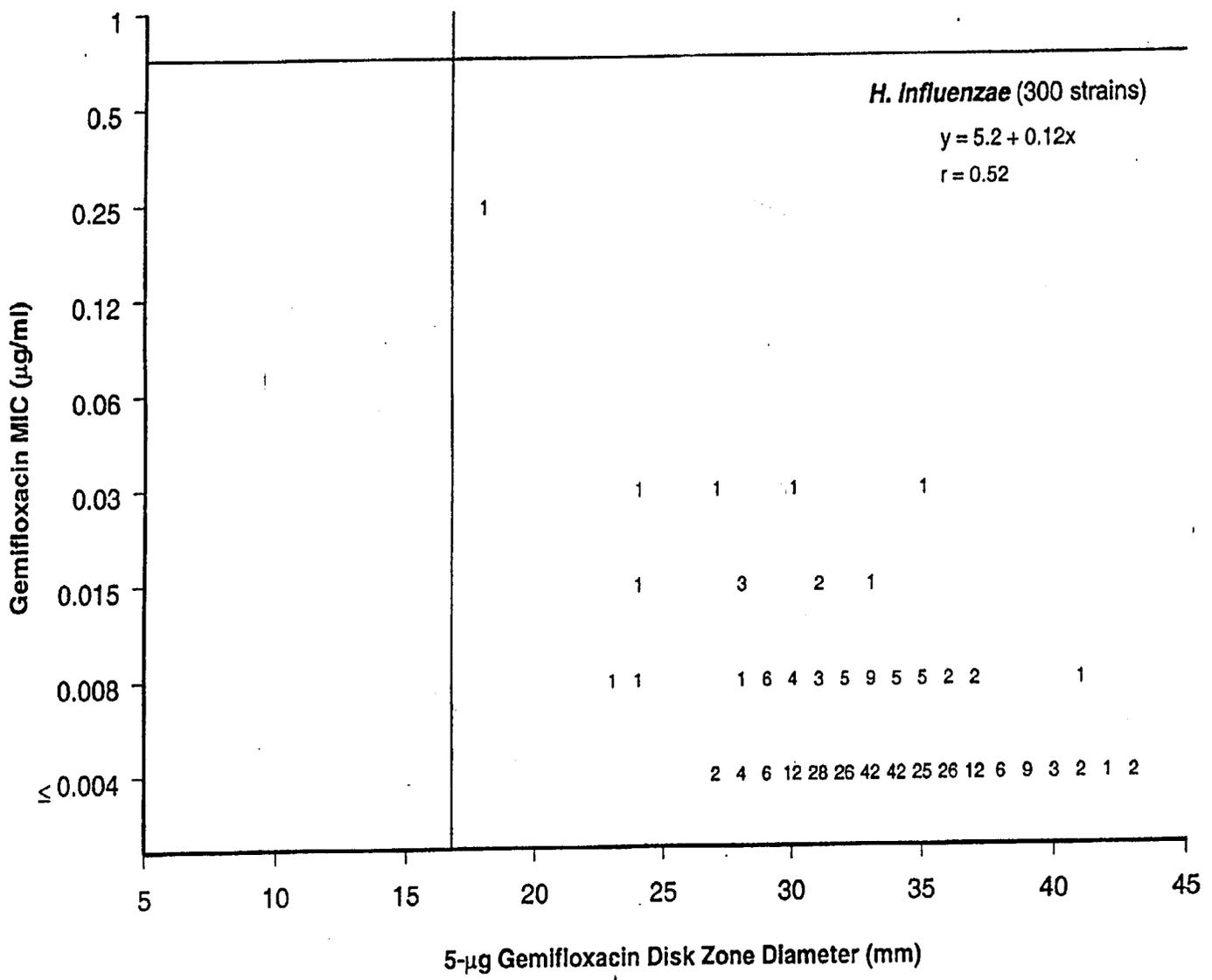


Figure 37—Scattergram for *Haemophilus influenzae* (n=300)

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TABLE 133 gives a summary of the above zone diameter criteria studies.

TABLE 133
Susceptibility Criteria Proposed from Pre-Clinical Studies (*Haemophilus* sp.)

Reference	Proposed by Authors	Proposed from Scattergram
47	None Proposed	$\leq 0.12 = \geq 21$ mm
31-CMI	$\leq 0.5 = \geq 20$ mm 1.0 = 17-19 mm $\geq 2.0 = \leq 16$ mm	$\leq 0.25 = \geq 16$ mm
137	$\leq 0.5 = \geq 17$ mm	$\leq 0.06 = \geq 21$ mm

Since only three studies were performed and each suggest different breakpoint criteria no criteria will be suggested until after the clinical trial data have been reviewed and the MICs and zone diameters for *Haemophilus* species have been correlated with bacteriological outcomes.

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BACTERIOLOGICAL EFFICACY

CORRELATION OF TEST RESULTS WITH OUTCOME STATISTICS

Fourteen Phase IIIA clinical studies were conducted to assess the efficacy of oral gemifloxacin. Four studies were conducted in acute exacerbation of chronic bronchitis (AECB), three in community-acquired pneumonia (CAP), one study in lower respiratory tract infections (AECB and CAP patients).

Based on colonial morphology and Gram stains routine microbiology laboratory procedures were used to isolate and identify all organisms that were present. MICs were determined by microbroth dilution using dried microtiter plates. Disk diffusion susceptibility testing was performed for gemifloxacin and the comparator drug for each study. For *Staphylococcus aureus* an oxacillin disk was tested to determine methicillin resistance.

Blood cultures were performed in the complicated UTI studies on patients with pyelonephritis. Blood cultures were also performed on patients in the CAP studies. Blood cultures were performed on screening and also on-therapy when the screening cultures was positive or if clinically indicated.

Quantitative cultures were performed using 1 μ l and 10 μ l sterile loops on all UTI cultures. Identification and susceptibility testing was performed on isolates with a colony count of $\geq 10^3$ CFU/mL. Only identification was performed on isolates with a colony count $< 10^3$ CFU/mL. Quantitative culture and identification was performed on sinus

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aspirate in the acute bacterial sinusitis studies. Cultures and Gram stains were performed on lower respiratory tract samples.

A patient was considered to have pneumonia due to *Legionella pneumophila* if the patient was culture positive, and/or had a positive urine antigen, and/or had a four-fold rise in antibody titer between acute and convalescent sera. A patient was considered to have pneumonia due to *Chlamydia pneumoniae* if the patient was culture positive, and/or had a four-fold rise in IgM or IgG titers between acute and convalescent sera. A patient was considered to have pneumonia due to *Mycoplasma pneumoniae* if the patient was culture positive, and/or had a $\geq 46\%$ rise in Single Immune Status Ratio (ISR) for IgG between acute and convalescent sera, and/or was positive for IgM (ISR $\geq 1:10$) at either visit.

Data for the most common pathogens isolated during the clinical trials are summarized in TABLE 134.

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TABLE 134
Baseline Pathogens Susceptibility to Gemifloxacin
All geographic Regions—Bacteriologically Intent-to-Treat Population

Pathogen	No. Times Isolated	% Susceptible (MIC \leq 0.25 μ g/mL)	MIC ₅₀ (μ g/mL)	MIC ₉₀ (μ g/mL)	MIC Range (μ g/mL)
<i>E. coli</i>	1170	96.2	0.008	0.015	\leq 0.001-256
<i>K. pneumoniae</i>	171	97.1	0.015	0.06	0.004-32
<i>Pseudomonas</i> sp	105	72.4	0.12	16	0.008-256
<i>S. aureus</i>	150	92.0	0.008	0.12	0.004-256
<i>S. pneumoniae</i>	372	90.7 (\leq 0.12) 100 99.7 (\leq 0.12) 99.2 (\leq 0.06)	0.015	0.03	\leq 0.001-0.25
<i>Haemophilus</i> sp	372	99.5 99.5 (\leq 0.12) 99.2 (\leq 0.06)	0.002	0.015	\leq 0.001-256
<i>H. influenzae</i>	287	99.3 99.3 (\leq 0.12) 99.0 (\leq 0.06)	0.002	0.008	\leq 0.001-256

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