Therefore, it is the view of this reviewer that the breakpoints shown in Table 20. be used as a starting point for interpretation of clinical isolates.

Table 20. Tentative Breakpoints and Interpretive Criteria for Trovafloxacin (10 μg disk)

	Zone size (mm) (10 μg disk)			MIC (μg/mL)		
Organism	**S**	**I**	**R**	**S**	**I**	**R**
N. gonorrhoeae	--	--	--	≤ 0.25	--	--
All Other Aerobes	≥ 16	13-15	≤ 12	≤ 1.0	2.0	≥ 4.0
All Anaerobes	--	--	--	≤ 2.0	4.0	≥ 8.0

B. Bacteriological Efficacy

1. Activity of Trovafloxacin Against Bacteria Resistant to Non-Quinolone Antibacterial Agents

The following discussion will highlight the activity of trovafloxacin against organisms that are resistant to other classes of antimicrobials than fluoroquinolones. Some of these bacteria have been discussed in previous sections of this document and will not be covered extensively here. The major groups of pathogens to be discussed include: 1) penicillin/macrolide-resistant *S. pneumoniae*, 2) ampicillin-resistant *H. influenzae*, 3) MRSA, 4) gentamicin-resistant *E. faecalis*, 5) erythromycin-resistant *Mycoplasma* spp., 6) ceftazidime-resistant Gram-negative bacilli, and 7) *Mycobacterium tuberculosis.*

Trovafloxacin is active against isolates of pneumococci regardless of their susceptibility status to penicillin (Table 1). Trovafloxacin was active against 145 penicillin-resistant pneumococci tested in three *in vitro* studies (Table 21). The MIC_{90} range for trovafloxacin was _ compared with for penicillin G, for ceftriaxone, and >16 μg/mL for erythromycin and azithromycin

The activity of trovafloxacin against isolates of MRSA has been reviewed in Table 1. The MIC_{90} range of trovafloxacin against 487 MRSA (that also demonstrated high-level resistance to ciprofloxacin) was with a median MIC_{90} of 2.0 μg/mL. Thus trovafloxacin can be expected to show inhibitory activity against only a few MRSA. In one study (98) the activity of trovafloxacin was compared with those of several new antimicrobials selected for their activity against MRSA. In this study, trovafloxacin was similar in potency to two new oxazolidinones (U 100592 and U 100766), and vancomycin. Rifampin was more potent than any of the other agents tested (Table 21).

The activity of trovafloxacin against clinical isolates of enterococci is variable. Against 574 isolates of vancomycin susceptible *E. faecalis* the MIC_{90} range for trovafloxacin was 0.25-8.0 μg/mL with a median MIC_{90} of 2.0 μg/mL (Table 2). In one study (52) trovafloxacin had an MIC_{90} of 8 μg/mL against 17 isolates of *E. faecalis* demonstrating high-level resistance to gentamicin. In a study by Freeman *et al.* (97) MIC_{90}s for trovafloxacin were out of the clinically useful range for vancomycin-resistant enterococci containing either *vanA* or *vanB* (Table 21). Only ramoplanin had potent activity against this group of isolates. Collectively, the available data suggest that while trovafloxacin is active against a very few isolates of multi-drug resistant enterococci, achievable blood levels in man will not be above the MIC for many isolates rendering the drug useless in treating infections due to Enterococci.

Table 21. Activity of Trovafloxacin Against Bacteria Resistant to Non-Quinolone Antibacterials

Organism	No. Strains	Compound	MIC_{90} Range (μg/mL)	Reference
S. pneumoniae Pen-R	(145)[a]	Trovafloxacin		
		Ciprofloxacin		48
		Penicillin G		48
		Ceftriaxone		
		Erythromycin	>16	
		Azithromycin	>16	
S. aureus MRSA	(118)	Trovafloxacin	1.0	98
		Ciprofloxacin	16.0	
		U 100592	1.0	
		U 100766	1.0	
		Synercid	0.5	
		Rifampin	0.006	
		Vancomycin	1.0	
Enterococci *vanA*	(27)	Trovafloxacin	32	97
		Vancomycin	1024	
		Teicoplanin	>64	
		Ciprofloxacin	>64	
		Ramoplanin	2.0	
		Fusidic acid	4.0	
		Minocycline	8.0	
		Synercid	0.5	
Enterococci *vanB*	(17)	Trovafloxacin	8.0	97
		Ciprofloxacin	32	
		Vancomycin	512	
		Teicoplanin	0.5	
		Ramoplanin	2.0	
		Fusidic acid	8.0	
		Minocycline	16.0	
		Synercid	8.0	

Organism	No. Strains	Compound	MIC_{90} Range (µg/mL)	Reference
H. influenzae **(Amp-R) Beta-lactamase positive**	(50)	Trovafloxacin	0.03	40
		Ciprofloxacin	0.03	
		Amoxicillin	>16	
		Amoxicillin/ clavulanate	2.0	
		Ceftriaxone	0.03	
		Trimethoprim/ sulphamethoxazole	32	
		Erythromycin	4.0	
E. cloacae	(47)	Trovafloxacin	0.5	41
		Ciprofloxacin	0.5	
		Ceftazidime	128	
		Augmentin	128	
		Amikacin	2.0	
		Gentamicin	16.0	
K. pneumoniae	(124)	Trovafloxacin	0.5	41
		Ciprofloxacin	4.0	
		Ceftazidime	128	
		Augmentin	64	
		Amikacin	64	
		Gentamicin	64	
M. morganii	(45)	Trovafloxacin	2.0	41
		Ciprofloxacin	0.125	
		Ceftazidime	16	
		Augmentin	>128	
		Amikacin	4.0	
		Gentamicin	8.0	
P. mirabilis	(57)	Trovafloxacin	4.0	41
		Ciprofloxacin	1.0	
		Ceftazidime	4.0	
		Augmentin	4.0	
		Amikacin	8.0	
		Gentamicin	8.0	
S. marcescens	(28)	Trovafloxacin	1.0	41
		Ciprofloxacin	1.0	
		Ceftazidime	16	
		Augmentin	>128	
		Amikacin	>128	
		Gentamicin	128	
P. aeruginosa	(92)	Trovafloxacin	2.0	41
		Ciprofloxacin	2.0	
		Ceftazidime	32	
		Amikacin	16	
		Gentamicin	128	

Organism	No. Strains	Compound	MIC_{90} Range (μg/mL)	Reference
Mycobacterium tuberculosis	(33)	Trovafloxacin	32	37,38
		Ciprofloxacin	0.5	
		Ofloxacin	1.0	
M. avium intracellulare	(22)	Trovafloxacin	64	37,38
		Ciprofloxacin	32	
		Ofloxacin	32	

a. The number of isolates in parenthesis were already presented in Table 1, page 10 of this review.

The *in vitro* activity of trovafloxacin against ampicillin-resistant beta-lactamase-positive *H. influenzae* was investigated by Sefton *et al.* (40). Trovafloxacin was equivalent in potency to ciprofloxacin, with an MIC_{90} of 0.03 μg/mL (Table 21). Ceftriaxone had an identical MIC_{90}. Trovafloxacin was at least 500-fold more active than amoxicillin and 67-fold more active than amoxicillin/clavulanate against these strains. This collection of fifty isolates was multi-resistant, as MIC_{90}s to trimethoprim/sulphamethoxazole and erythromycin were 32 and 4.0 μg/mL, respectively. Comparable results were obtained in another report (41) involving 28 isolates of *H. influenzae* demonstrating MIC_{90}s to ampicillin and cefuroxime of 16 μg/mL. The MIC_{90}s for trovafloxacin and ciprofloxacin were $\leq$0.03 and 0.06 μg/mL, respectively.

Trovafloxacin is active against multi-resistant isolates of *Enterobacteriaceae* that are susceptible to ciprofloxacin. One report (41) evaluated the activity of trovafloxacin against Gram-negative bacilli that were resistant to ceftazidime and gentamicin. MIC_{90}s for trovafloxacin ranged between 0.5 and 4.0 μg/mL for species including *E. cloacae*, *K. pneumoniae*, *M. morganii*, *P. mirabilis*, *S. marcescens*, and *P. aeruginosa* (Table 21). MIC_{90}s to ceftazidime and gentamicin ranged from 4.0 to 128 μg/mL and 8.0 to 128 μg/mL, respectively. Such high-level aminoglycoside resistant strains often contain multiple drug modifying determinants including enzymes for acetylating, adenylating, and phosphorylating aminoglycosides. In this regard, the isolates *K. pneumoniae*, *S. marcescens*, and *P. aeruginosa* had MIC_{90}s to amikacin of 16.0 to >128 μg/mL. The MIC_{90}s for trovafloxacin against these three species ranged from 0.5 to 2.0 μg/mL. The data suggest that trovafloxacin could be active against Gram-negative bacilli that are resistant to beta-lactams and aminoglycosides. Clearly, the potency of trovafloxacin against such isolates is dependent upon them being generally susceptible to the newer fluoroquinolones.

Multi-resistant isolates of *Mycobacterium tuberculosis* and *M. avium*-intracellulare are being isolated from a broad range of clinical settings. Preliminary results indicate that trovafloxacin does not possess good activity against these mycobacteria. The data in Table 21 indicate that the MIC_{90}s of trovafloxacin for these two species are 32 and 64 μg/mL, respectively (37,38). Against *M. tuberculosis*, trovafloxacin appears to be significantly less active than ciprofloxacin or ofloxacin.

2. Summary of Clinical Trials

Thirty three clinical studies were conducted in order to determine the safety and efficacy of trovafloxacin in treating the following infections:

- Community Acquired Pneumonia
- Nosocomial Pneumonia
- Acute Bacterial Exacerbation of Chronic Bronchitis
- Sinusitis
- Intra-Abdominal Infections
- Gynecologic and Pelvic Infections
- Pelvic Inflammatory Disease
- Skin and Skin Structure Infections
- Uncomplicated Urinary Tract Infections
-
- Prostatitis
- Sexually Transmitted Disease (Gonorrhea and Chlamydia)
- Surgical Prophylaxis

(b)(4) [redacted]

Tablet and I.V. formulations were studied. In most protocols, dosages included 300 or 200 mg I.V. followed by 200 mg oral QD. Some of the protocols had a dosage of 100 mg QD. Different protocols studied different dosing protocols any where from a single dose for treatment of gonorrhea to 28 days for treatment of prostatitis. A summary of all pivotal and supporting clinical studies are shown in Table 22. A total of 6,205 patients were randomized in these studies.

Table 22. Summary of Clinical Trials Which Evaluated the Effectiveness of Trovafloxacin

Protocol	Dose	No.	Type of Study
Community Acquired Pneumonia (Oral Regimen)			
154-102	200 mg QD (10 days) 300 mg QD (10 days)	50	Phase II Double-Blind
154-112	200 mg QD (7 or 10 days)	150	Phase III Double-Blind
154-134	200 mg QD (7 or 10 days)	179	Phase III Double-Blind
Community Acquired Pneumonia (IV/PO Regimen)			
154-110	Alatrofloxacin 200 mgQD IV → trovafloxacin 200 mg QD PO (7 to 10 days total)	198	Phase III Double-Blind
145-111	Alatrofloxacin 200 mgQD IV → trovafloxacin 200 mg QD PO (7 to 10 days total)	218	Phase III Double-Blind
Nosocomial pneumonia			
154-113	Alatrofloxacin 300 mgQD IV → trovafloxacin 200 mg QD PO (7 to 14 days total)	129	Phase III Double-Blind
154-137	Alatrofloxacin 300 mgQD IV → trovafloxacin	135	Phase III Open Randomized

	200 mg QD PO (7 to 10 days total)		
Acute Bacterial Exacerbation of Chronic Bronchitis			
154-101	100 mg QD (10 days) 300 mg QD (10 days)	74 76	Phase II Double-Blind
154-109	100 mg QD (7 days)	210	Phase III Double-Blind
154-141	100 mg QD (7 days)	131	Phase III Double-Blind
Sinusitis			
154-114	200 mg QD (10 days)	255	Phase III Open Non-randomized
154-115	200 mg QD (10 days)	206	Phase III Double-Blind
154-138	200 mg QD (10 days)	207	Phase III Open Randomized
Intra-Abdominal Infections			
154-124	Alatrofloxacin 300 mgQD IV → trovafloxacin 200 mg QD PO (max 14 days total)	204	Phase III Double-Blind
Gynecologic and Pelvic Infections			
154-144	Alatrofloxacin 300 mgQD IV → trovafloxacin 200 mg QD PO (14 days total)	161	Phase III Double-Blind
Pelvic Inflammatory Disease			
154-122	Alatrofloxacin 200 mgQD IV → trovafloxacin 200 mg QD PO (max 14 days total)	79	Phase III Investigator-Blind
154-125	200 mg QD PO (14 days)	155	Phase III Double-Blind
Uncomplicated Skin and Skin Structure Infections			
154-129	100 mg QD (7 days)	141	Phase III Double-Blind
154-130	100 mg QD (7 to 10 days)	221	Phase III Double-Blind
Complicated Skin and Skin Structure Infections			
154-131	Alatrofloxacin 200 mgQD IV → trovafloxacin 200 mg QD PO (10 or 14 days total)	145	Phase III Double-Blind
154-132	200 mg QD PO (10 or 14 days)	255	Phase III Open
154-139	200 mg QD PO (10 or 14 days)	166	Phase III Open Randomized
Uncomplicated Urinary Tract Infection			
154-103	100 mg QD (7 days) 300 mg BID (7 days)	72 74	Phase II Double-Blind
154-116	100 mg BID (7 days)	182 182	Phase II Double-Blind

Prostatitis			
154-119	200 mg QD (28 days)	142	Phase III Double-Blind
Gonorrhea			
154-120	100 mg single dose	311	Phase III Double-Blind
Chlamydia			
154-105	200 mg QD (7 days) 200 mg QD (5 days) 100 mg QD (7 days) 50 mg QD (7 days)	31 34 28 37	Phase II Open Randomized
154-123	200 mg QD (5 days)	495	Phase III Double-Blind
Elective Colo-Rectal Surgery Prophylaxis			
154-128	Alatrofloxacin 200 mg single dose IV	269	Phase III Double-Blind
Elective Hysterectomy Prophylaxis			
154-146	200 mg single dose PO	196	Phase III Double-Blind

(b)(4) [redacted]

3. Correlation of MIC Interpretive criteria with Therapeutic Outcome

If interpretive breakpoints are accurate, susceptibility test results should predict the therapeutic efficacy of an antibiotic. To validate proposed trovafloxacin interpretive breakpoints, bacteriologic eradication and clinical cure rates obtained during clinical studies were examined for correlation with MIC and disk diffusion results.

For analyses in this section, the sponsor has included all clinically and microbiologically evaluable trovafloxacin-treated patients that had a baseline isolate with both MIC and zone size values. Data are presented in Tables G. 33.1a. to G. 45.1b. in Appendix A. Using the MIC breakpoint of $\leq$ 1.0, 2.0, and $\geq$4 µg/mL for susceptible, intermediate and resistant respectively, 1,954 isolates from clinical trials were tested, 55 (2.8%) were resistant, 28 (1.4%) were intermediate and 1871 (95.8%) were susceptible to trovafloxacin. As might be predicted, resistance was observed most frequently in isolates of enterococci, *P. aeruginosa*, and members of the *Enterobacteriaceae*. Few resistant isolates of *S. aureus*, *S. epidermidis*, and *S. haemolyticus*, Streptococci, and *Corynebacterium*, were also encountered.

Tables 23 and 24 show overall trends in the data demonstrating that the proposed MIC interpretive breakpoints serve as good predictors of therapeutic outcome for all target species. There is a direct correlation between a susceptible MIC result and both bacterial eradication and

clinical cure rates. As seen in Table 23, when all organisms are considered, susceptible MIC results correspond with 87% bacterial eradication rate and 89% clinical cure rate.

The correlation between susceptible results and positive therapeutic outcome was generally uniform among bacterial species (Tables 24). Two exceptions are the lower eradication and clinical cure rates seen for gram-negative nonfermenters (including *Acinetobacter* spp., *Pseudomonas* spp. and *S. maltophilia*) and *Enterococcus* spp.

As seen in Table 23, there is an overall trend for lower eradication and cure rates with intermediate and resistant isolates. Specifically there were 83/1954 (4.3%) isolates that had resistant or intermediately resistant MICs to trovafloxacin. Among these isolates 57/83 (69%) were eradicated as compared to an eradication rate of 87% for the isolates with susceptible MICs. The cure rates were also lower for isolates with intermediate and resistant MICs (72/83, 87%) as compared to isolates with susceptible MICs with cure rates of 89%.

The clinical efficacy and pathogen eradication data obtained supports the use of a ≤1 μg/mL susceptibility breakpoint for trovafloxacin

TABLE 23. Overall Summary of Results Relationship Between Susceptibility to Trovafloxacin and Pathogen Eradication and Clinical Cure Rates

		Pathogen Eradication Rate			Clinical Cure Rate		
Methodology	**Susceptibility**	**No. of Pathogens**	**No. of Pathogens Eradicated[a]**	**% Eradicated[a]**	**No. of Patients**	**No. of Patients Cured[b]**	**% Cured[b]**
MIC	R (≥ 4.0 μg/mL)	55	42	76	55	49	89
	I (2.0 μg/mL)	28	15	54	28	23	82
	S (≤ 1.0 μg/mL)	1854	1613	87	1854	1659	89

[a] Including eradicated and presumed eradicated pathogens
[b] Including cured and improved patients

TABLE 24. Relationship Between MIC and Pathogen Eradication and Clinical Cure Rates in patients treated with Trovafloxacin I.V. and Tablets

		Pathogen Eradication Rate			Clinical Cure Rate		
Organism Group	**Susceptibility**	**No. of Pathogens**	**No. of Pathogens Eradicated[a]**	**% Eradicated[a]**	**No. of Patients**	**No. of Patients Cured[b]**	**% Cured[b]**
***Haemophilus* spp.**	R (≥ 4.0 μg/mL)	0	--	--	0	--	--
	I (2.0 μg/mL)	0	--	--	0	--	--
	S (≤ 1.0 μg/mL)	165	158	96	165	151	92
S. pneumoniae	R (≥ 4.0 μg/mL)	0	--	--	0	--	--
	I (2.0 μg/mL)	0	--	--	0	--	--
	S (≤ 1.0 μg/mL)	100	91	91	100	91	91
***Streptococcus* spp**	R (≥ 4.0 μg/mL)	1	1	100	1	1	100

other than *S. pneumoniae*	I (2.0 µg/mL) S (≤ 1.0 µg/mL)	3 149	0 127	0 85	3 149	3 134	100 90
M. catarhalis	R (≥ 4.0 µg/mL) I (2.0 µg/mL) S (≤ 1.0 µg/mL)	0 0 58	-- -- 55	-- -- 95	0 0 58	-- -- 53	-- -- 91
N. gonorrhoeae	R (≥ 4.0 µg/mL) I (2.0 µg/mL) S (≤ 1.0 µg/mL)	0 0 25	-- -- 25	-- -- 100	0 0 25	-- -- 23	-- -- 92
S. aureus	R (≥ 4.0 µg/mL) I (2.0 µg/mL) S (≤ 1.0 µg/mL)	4 4 321	2 3 264	50 75 82	4 4 321	4 3 293	100 75 91
Staphylococcus* spp. other than *S. aureus	R (≥ 4.0 µg/mL) I (2.0 µg/mL) S (≤ 1.0 µg/mL)	12 9 202	10 6 182	83 67 90	12 9 202	12 7 185	100 78 92
***Enterococcus* spp.**	R (≥ 4.0 µg/mL) I (2.0 µg/mL) S (≤ 1.0 µg/mL)	9 1 116	6 1 92	67 100 79	9 1 116	7 1 100	78 100 86
***Enterobacteriaceae* spp.[c]**	R (≥ 4.0 µg/mL) I (2.0 µg/mL) S (≤ 1.0 µg/mL)	15 3 577	11 1 513	73 33 89	15 3 577	12 2 530	80 67 92
Gram-negative nonfermenters[d]	R (≥ 4.0 µg/mL) I (2.0 µg/mL) S (≤ 1.0 µg/mL)	8 7 110	7 3 75	88 43 68	8 7 110	8 6 92	100 86 84

[a] Including eradicated and presumed eradicated pathogens
[b] Including cured and improved patients
[c] Excluding all *Acinetobacter* spp., *Pseudomonas* spp., and *S. maltophilia*
[d] Includes all *Acinetobacter* spp., *Pseudomonas* spp. and *S. maltophilia*

Table 25 is an attempt to summarize all the data available for the anaerobic isolates recovered from patients treated with Trovafloxacin regardless of the clinical outcome. The data indicates that a susceptible MIC interpretation correlate with a 86% bacterial eradication rate. When compared with other anaerobic organisms, susceptible determination corresponded to lower eradication rate for *Bacteroides* spp. The data is very limited and one is not able to determine whether these bacterial eradication rates correlates with successful clinical outcome. If one was to set susceptibility breakpoints for anaerobes at this point, this reviewer would reside to the pharmacokinetic and population distribution data and would suggest ≤ 2.0, 4.0, and ≥ 8.0 µg/mL for susceptible, intermediate, and resistant, respectively.

Table 25. Relationship Between MIC and Anaerobic Pathogen Eradication Rates in patients treated with Trovafloxacin I.V. and Tablets

		Pathogen Eradication Rate		
Organism Group	**Susceptibility**	**No. of Pathogens**	**No. of Pathogens Eradicated[a]**	**% Eradicated[a]**
***Peptostreptococcus* spp.**	R (≥ 8.0 µg/mL) I (4.0 µg/mL) S (≤ 2.0 µg/mL)	0 0 9	-- -- 8	-- -- 98

	Missing	6	5	83
Peptostreptococcus magnus	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--
	S (≤ 2.0 µg/mL)	6	6	100
	Missing	3	2	67
Propionibacterium acnes	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--
	S (≤ 2.0 µg/mL)	1	1	100
	Missing	0	--	--
Anaerobic gram-positive cocci	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--
	S (≤ 2.0 µg/mL)	0	--	--
	Missing	2	2	100
Bacteroides distasonis	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--
	S (≤ 2.0 µg/mL)	0	--	--
	Missing	1	1	100
Bacteroides fragilis	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--
	S (≤ 2.0 µg/mL)	4	3	75
	Missing	3	3	100
***Bacteroides* spp.**	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--
	S (≤ 2.0 µg/mL)	4	2	50
	Missing	1	0	0
Peptostreptococcus prevotii	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--
	S (≤ 2.0 µg/mL)	1	1	100
	Missing	2	2	100
***Prevotella* spp.**	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--
	S (≤ 2.0 µg/mL)	3	3	100
	Missing	1	1	100
Actinomyces israelii	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--
	S (≤ 2.0 µg/mL)	0	--	--
	Missing	1	1	100
***Bifidobacterium* spp.**	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--
	S (≤ 2.0 µg/mL)	0	--	--
	Missing	1	1	100
Eubacterium limosum	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--
	S (≤ 2.0 µg/mL)	0	--	--
	Missing	1	1	100
Bacteroides thataiotaomicron	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--
	S (≤ 2.0 µg/mL)	0	--	--
	Missing	1	1	100
Total	R (≥ 8.0 µg/mL)	0	--	--
	I (4.0 µg/mL)	0	--	--

	S ($\leq$ 2.0 µg/mL) Missing	28 22	24 20	86 91

[a] Including eradicated and presumed eradicated pathogens

4. Discussion of Disk Diffusion Interpretive Breakpoints for *Haemophilus* spp.

Figures 9 to 11 are scattergrams for clinical isolates of *Haemophilus* spp. obtained during the clinical trials. In this section the sponsor has included all the isolates regard less of the clinical outcome. When one compares the U.S./Canada strains (Figure 10) with the non-U.S./Canada strains (Figure 11) it becomes evident that there is not much difference between the susceptibility patterns of the two groups. The only two resistant isolates came from non-U.S./Canada studies and are not sufficient to warrant selection of a resistant break point either for MIC or disk diffusion methods. One can combine the data from the U.S. and non-U.S. studies (Figure 9) and using the error rate-bound method determine the disk diffusion breakpoint based on MIC susceptible breakpoint of $\leq$ 1 µg/mL.

Using the error rate-bound method and the fact that the ideal (in the sense of reading accuracy) zone sizes should not be less than 15 mm, the disk diffusion susceptible breakpoint should be set at $\geq$ 22 mm. This would result in an acceptable very major and major error rates of 0.36% and 1.4% respectively (the acceptable limits for very major and major error rates are < 1.5% and < 3% respectively).

If one applies the error rate-bound method to the scattergram from U.S./Canada isolates (Figure 10), the $\geq$ 22 mm susceptible breakpoint would generate a 2.0% major error rate, which is within the acceptable limit. Similarly if one does the same thing with the scattergram from the non-U.S./Canada isolates (Figure 11), the very major error of 0.95% is within the acceptable limit.

Table 26 show overall trends in the data demonstrating that the above disk diffusion interpretive breakpoint serves as good predictors of therapeutic outcome for *Haemophilus* species. There is a direct correlation between a susceptible disk diffusion result and both bacterial eradication and clinical cure rates. As seen in Table 26, susceptible disk diffusion result correspond with 96% bacterial eradication and 92% clinical cure rates.

Figure 9. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm)

All Hemophilus spps (n=562)

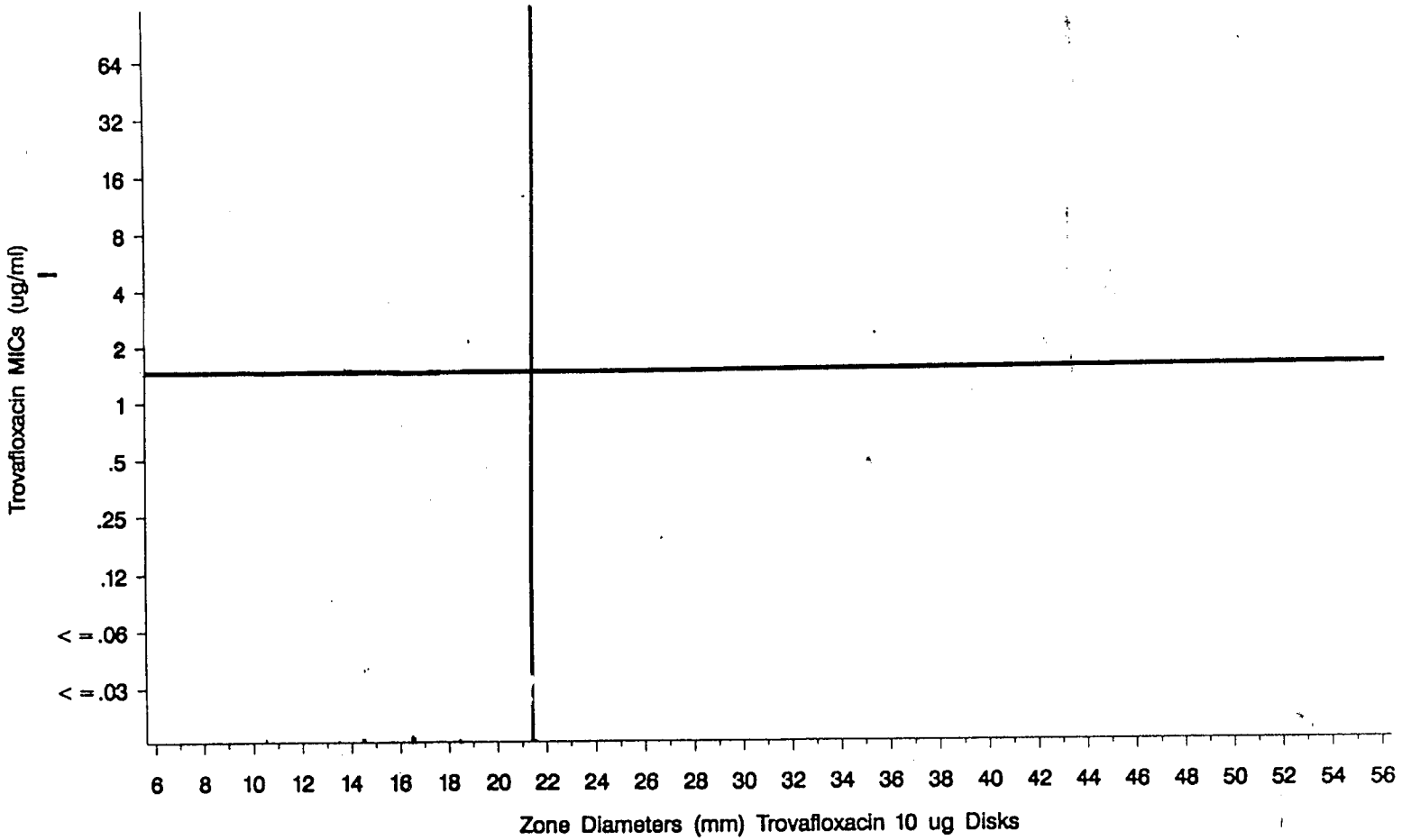


Figure 10. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) USA/Canada

All Hemophilus spps (n=245)

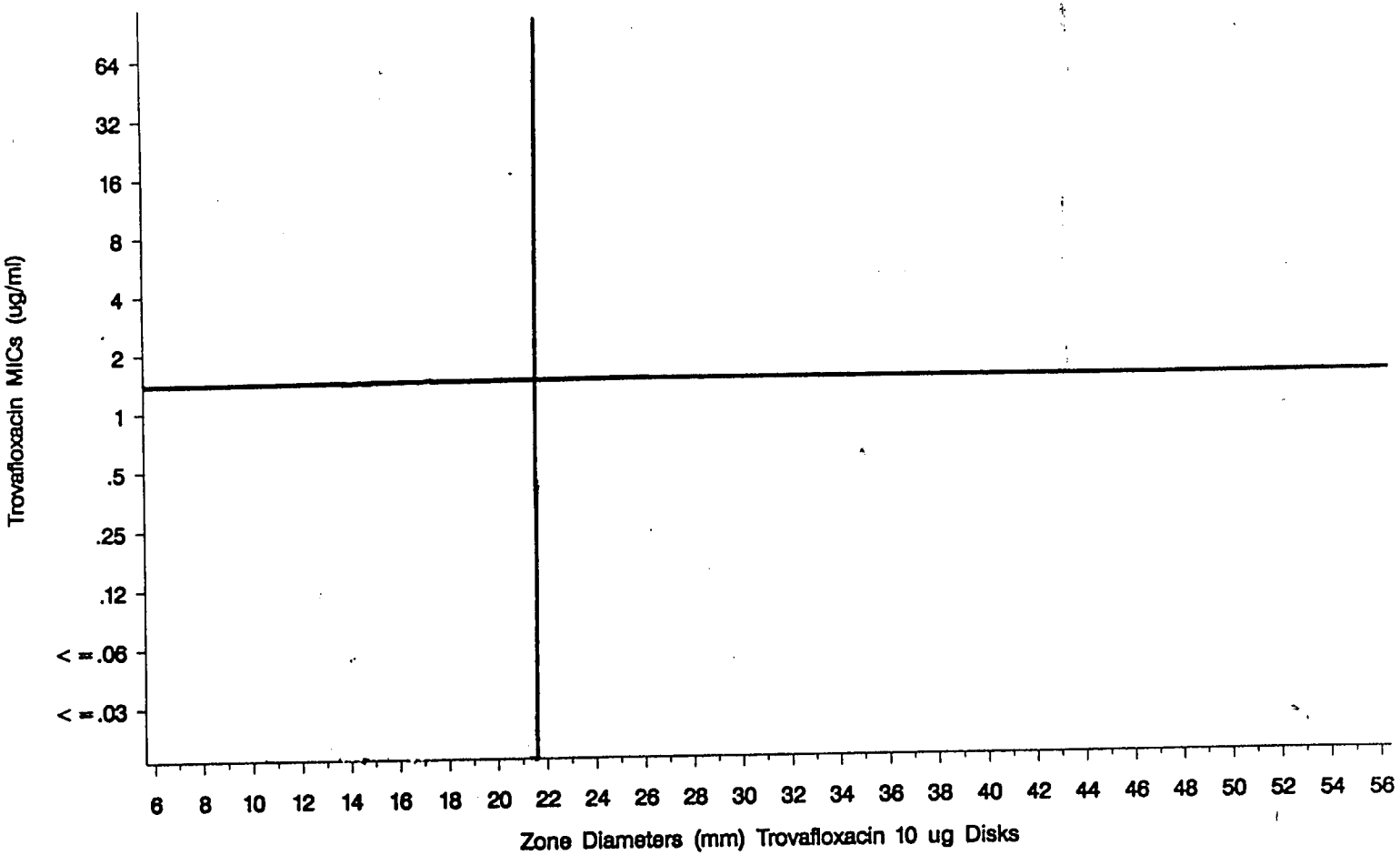
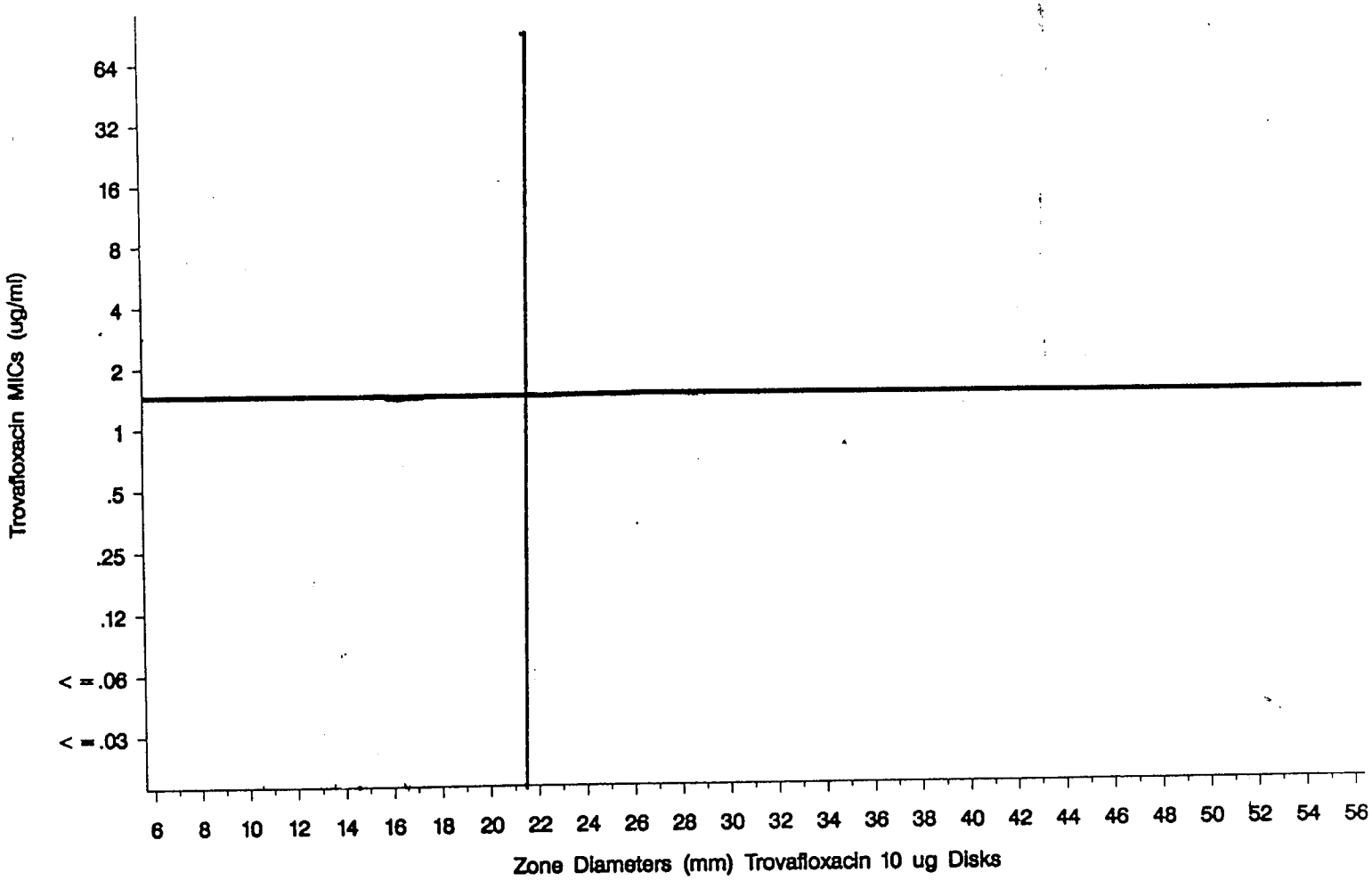


Figure 11. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) Non – USA/Canada

All Hemophilus spps (n = 317)



5. Discussion of Disk Diffusion Interpretive Breakpoints for *Streptococcus pneumoniae*

Figure 12 is the scattergram for clinical isolates of *Streptococcus pneumoniae* obtained during the clinical trials. In this scattergram the sponsor has included all the U.S. and non-U.S. isolates regard less of the clinical outcome. The isolates were not divided into U.S. and non-U.S. because there were no resistant isolates recovered from the clinical studies. According to these data the highest MIC was 0.5 μg/mL so the proposed (by this reviewer) susceptible MIC breakpoint of 1 μg/mL would seem appropriate. The smallest zone diameter obtained was 21 mm. Using the error rate-bound method or the rule of 3 mm smaller than the zone for 99.9 % of the isolates, the disk diffusion susceptible breakpoint based on MIC susceptible breakpoint of ≤ 1 μg/mL would be ≥ 18 mm. Since there were no resistant isolates recovered in the clinical trials this reviewer will refer to two studies performed by Arthur Barry et al. and James Jorgensen et al. that were presented in the NCCLS fastidious organism working group during the general meeting on June 1-3, 1997. Arthur Barry presented a scattergram on 80 *Streptococcus pneumoniae* isolates (Figure 13). The highest MIC and lowest zone diameter obtained from these isolates were 0.25 μg/mL and 24 mm, respectively. This study like the sponsor's clinical trials did not allow for setting any breakpoints other than susceptible for both MIC and disk diffusion methods. However this study reconfirmed that the susceptible MIC of ≤ 1 μg/mL and susceptible zone diameter of ≥ 18 mm were appropriate. James Jorgensen presented a scattergram on 161 *Streptococcus pneumoniae* isolates (Figure 14). These isolates included ofloxacin resistant isolates (marked by an * in the scattergram in Figure 14) with known single *parC* (ofloxacin MIC) and double *parC* and *gyrA* (ofloxacin MIC,) mutations that resulted in fluoroquinolone resistance. As it is shown in Figure 14 the MIC susceptible breakpoint of ≤ 1 μg/mL would separate all the double mutations and most of the single mutations from the non-mutated susceptible isolates. The intermediate MIC breakpoint of 2 μg/mL would allow for some of the organisms with single mutation to be categorized appropriately as such. Using the error rate-bound method the corresponding zone diameters would be ≥ 19 mm, , and ≤ 15 mm for susceptible, intermediate, and resistant, respectively. With these breakpoints there are no very major or major errors and only 5.6% minor errors. Of course based only on this scattergram one could set the disk diffusion breakpoints at ≥ 20 mm and ≤ 16 for susceptible , intermediate, and resistant respectively. With these breakpoints there are no very major or major errors and only 3.1% minor errors. And finally one could also choose ≥ 21 mm and ≤ 17 for Susceptible , intermediate, and resistant respectively. With these breakpoints there are no very major or major errors and only 1.9% minor errors. However for the sake of consistency with the clinical isolates this reviewer prefers the breakpoints of ≥ 19 mm and ≤ 15 mm for susceptible, intermediate, and resistant, respectively.

Table 26 shows overall trends in the data demonstrating that the above disk diffusion interpretive breakpoints serve as good predictors of therapeutic outcome for *Streptococcus pneumoniae*. There is a direct correlation between a susceptible disk diffusion result and both bacterial eradication and clinical cure rates. As seen in Table 26, susceptible disk diffusion result correspond with 91% bacterial eradication and 91% clinical cure rates.

Figure 12. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm)

Strep. Pneumoniae (n=336)

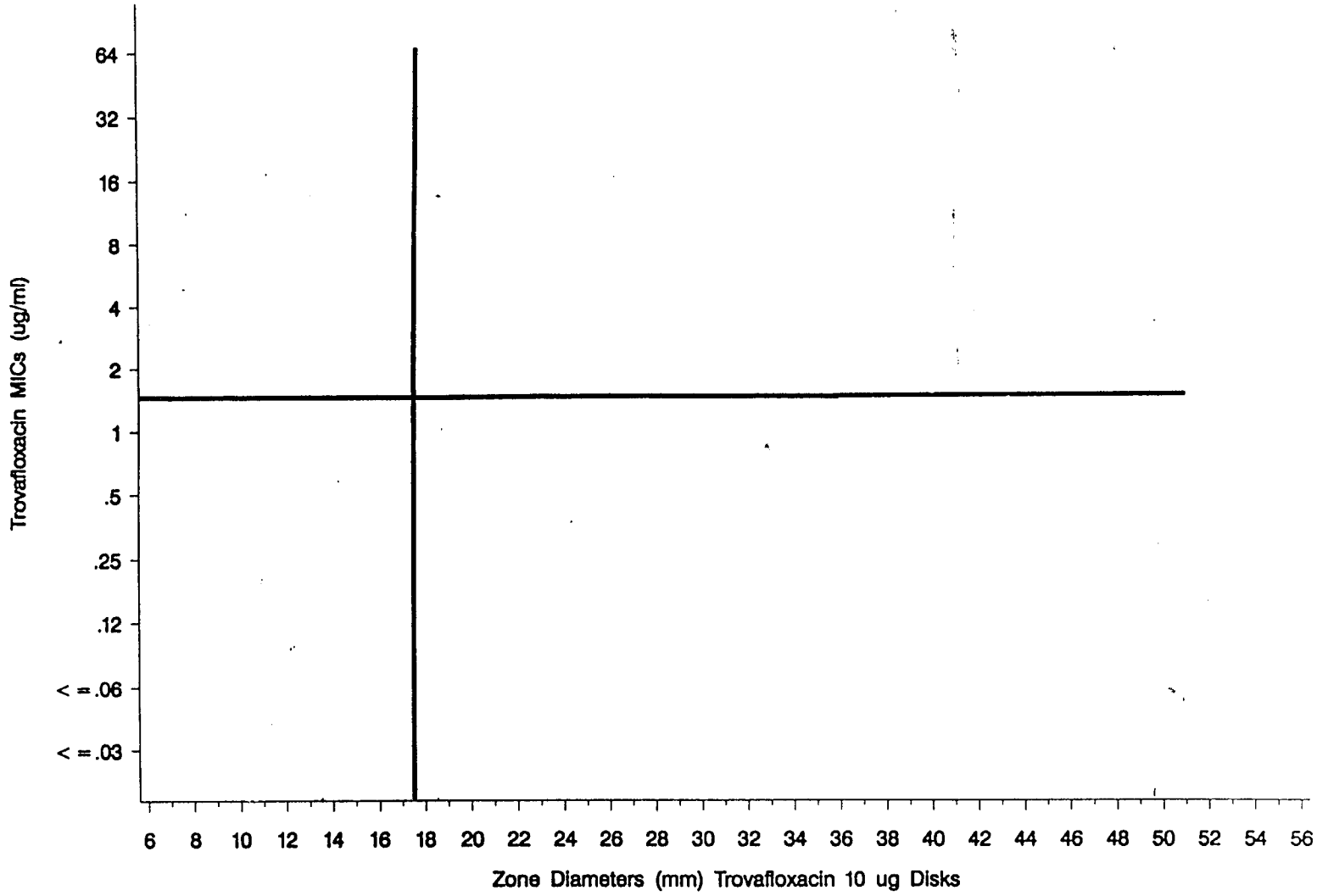


Figure 13. Scattergram generated from 80 selected pneumococcal culture collection against trovafloxacin.

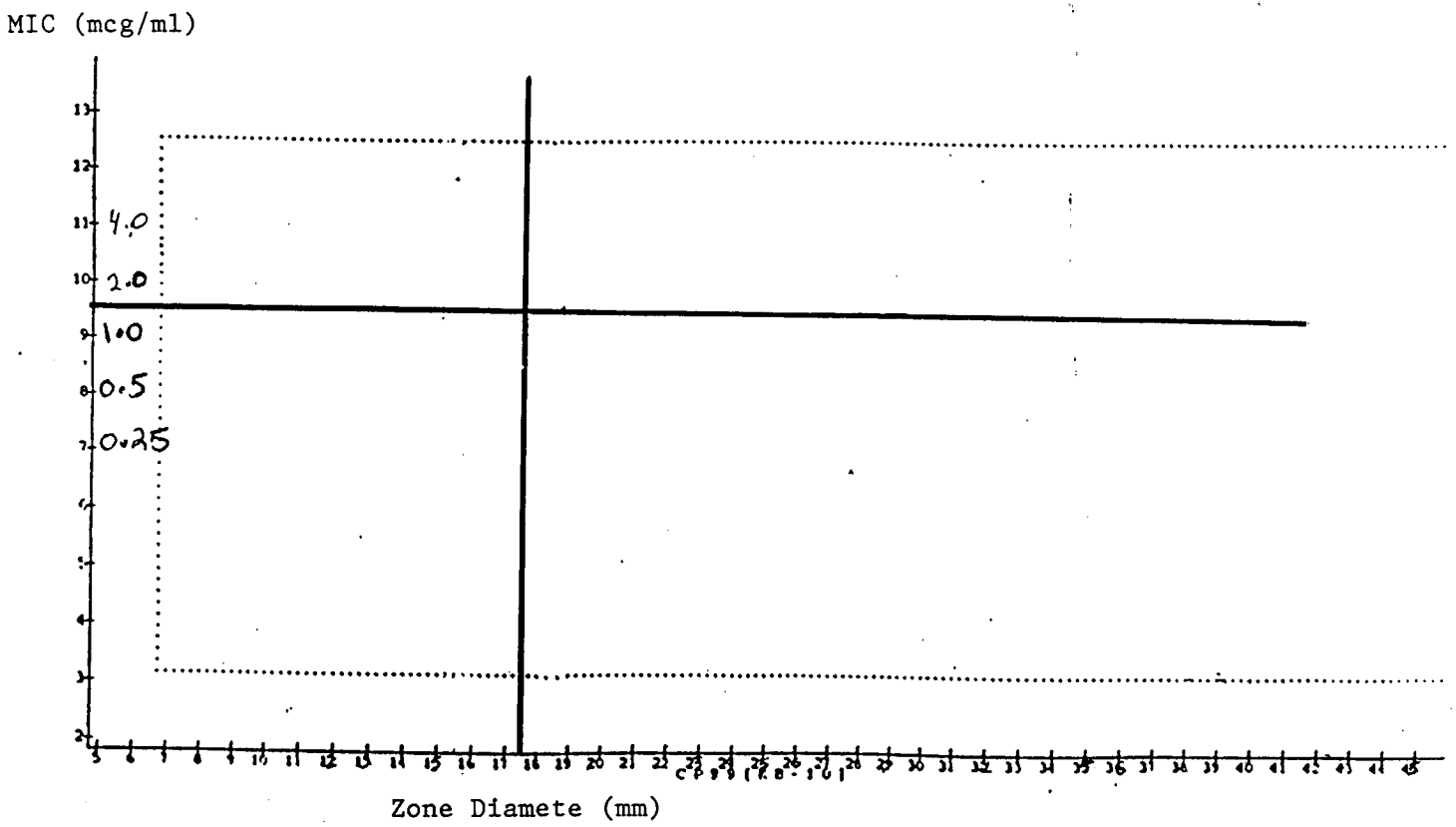
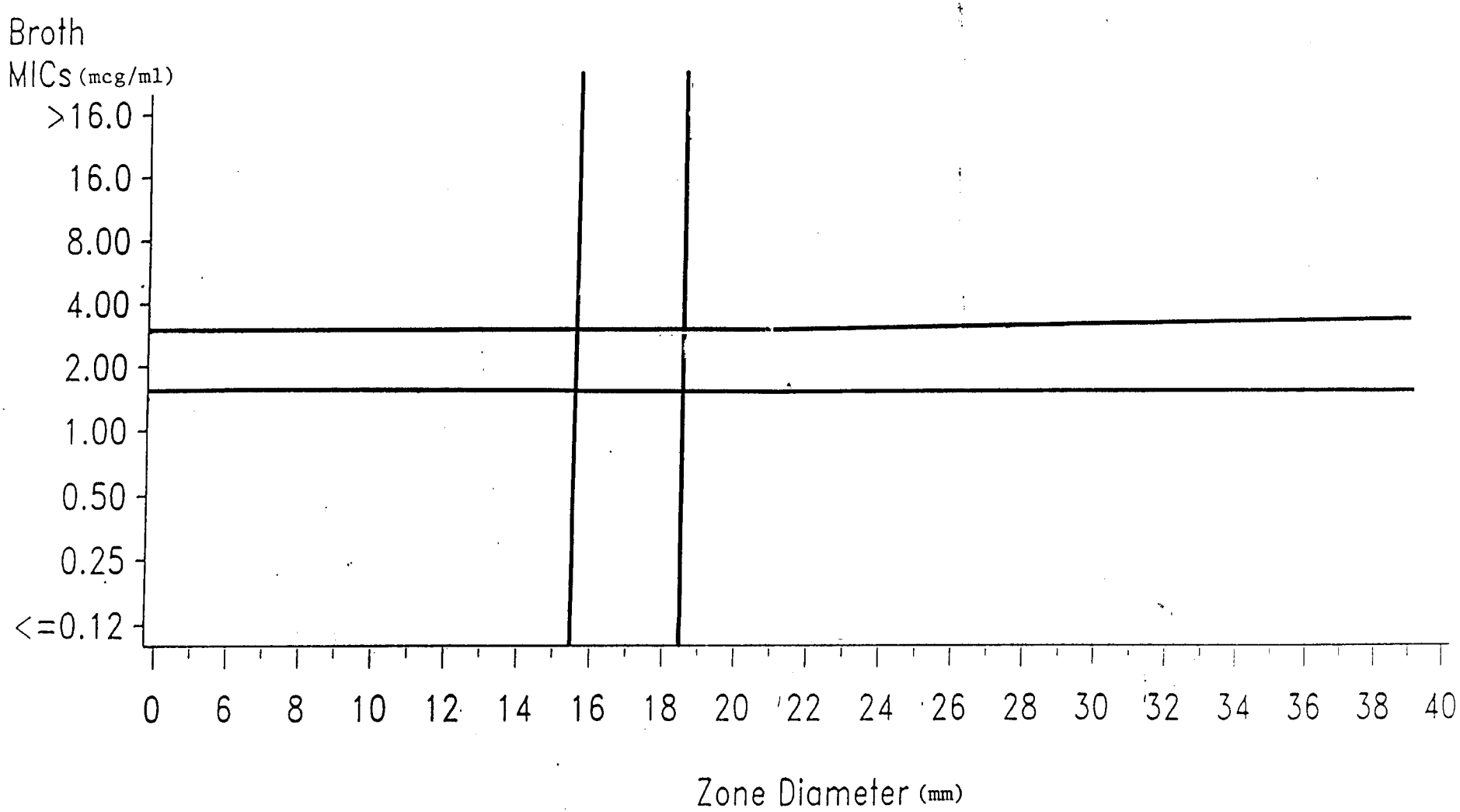


Figure 14. Scattergram generated from testing of 161 selected pneumococcal culture collection agsinst trovafloxacin. The isolates marked with an * are resistant to ofloxacin and containe either single parC (MIC = 4-8 mcg/ml)or double parC & gyrA (MIC = 16-128 mcg/ml) mutations.



6. Discussion of Disk Diffusion Interpretive Breakpoints for *Streptococcus* spp. other than *Streptococcus pneumoniae*

Figures 15 to 17 are scattergrams for clinical isolates of *Streptococcus* spp. other than *S. pneumoniae* obtained during the clinical trials. In this section the sponsor has included all the isolates regardless of the clinical outcome. When one compares the U.S./Canada strains (Figure 15) with the non-U.S./Canada strains (Figure 16) it becomes evident that there is a tendency for the U.S./Canada isolates to have slightly higher MICs than the non-U.S./Canada strains. So it is the opinion of this reviewer that combining the data would strengthen the data. Figure 17 is the scattergram resulting from the combined data. There were only five resistant isolates, two from U.S./Canada and 3 from one-U.S./Canada. These five isolates are not sufficient to warrant selection of a resistant break point either for MIC or disk diffusion methods. However, it is apparent that the susceptible MIC breakpoint of 1 μg/mL nicely separates the susceptible from non-susceptible isolates. If one would want to set a resistant breakpoint despite the limited data for the resistant isolates, 4 μg/mL would seem appropriate leaving 2 μg/mL as intermediate.

Using the error rate-bound method and the fact that the ideal (in the sense of reading accuracy) zone sizes should not be less than 15 mm, the disk diffusion susceptible breakpoint should be set at $\geq$ 18 mm. This would result in an acceptable very major and major error rates of 0.27% and 0.53% respectively.

In a study by Arthur Barry et al. that was presented in the NCCLS fastidious organism working group during the general meeting on June 1-3, 1997 a scattergram was presented on 405 *Streptococcus* spp. other than *S. pneumoniae* isolates (Figure 18). The highest MIC and zone diameter obtained from these isolates were 2.0 μg/mL and 18 mm, respectively. This study like the sponsor's clinical trials did not allow for setting any breakpoints other than susceptible for both MIC and disk diffusion methods. However this study reconfirmed that the susceptible MIC of $\leq$ 1 μg/mL and susceptible zone diameter of $\geq$ 18 mm were appropriate.

For the sake of simplicity and consistency, despite the limited data for resistant Streptococcal isolates other than *S. pneumoniae,* this reviewer would like to also set intermediate and resistant breakpoints for both MIC and disk diffusion methods. If one chooses MICs of 1.0, 2.0, and 4.0 μg/mL for susceptible, intermediate, and resistant breakpoints respectively, then using the error rate-bound method, the corresponding zone sizes from the clinical data would be $\geq$ 19 and $\leq$ 15 for susceptible, intermediate, and resistant, respectively. These breakpoints would result in no very major error rate, 0.53% major error rate, and 0.8% minor error rate. The corresponding zone sizes from Arthur Barry's data would be the same with no very major or major error rates and only 0.25% minor error rate.

Table 26 shows overall trends in the data demonstrating that the above disk diffusion interpretive breakpoints serve as good predictors of therapeutic outcome for Streptococcus spp. other than *S. pneumoniae*. There is a direct correlation between a susceptible disk diffusion result and both bacterial eradication and clinical cure rates. As seen in Table 26, susceptible disk diffusion result correspond with 85% bacterial eradication and 88% clinical cure rates

Figure 15 . Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) USA/Canada

All Strepococcus spps, except S. Pneumoniae (n=314)

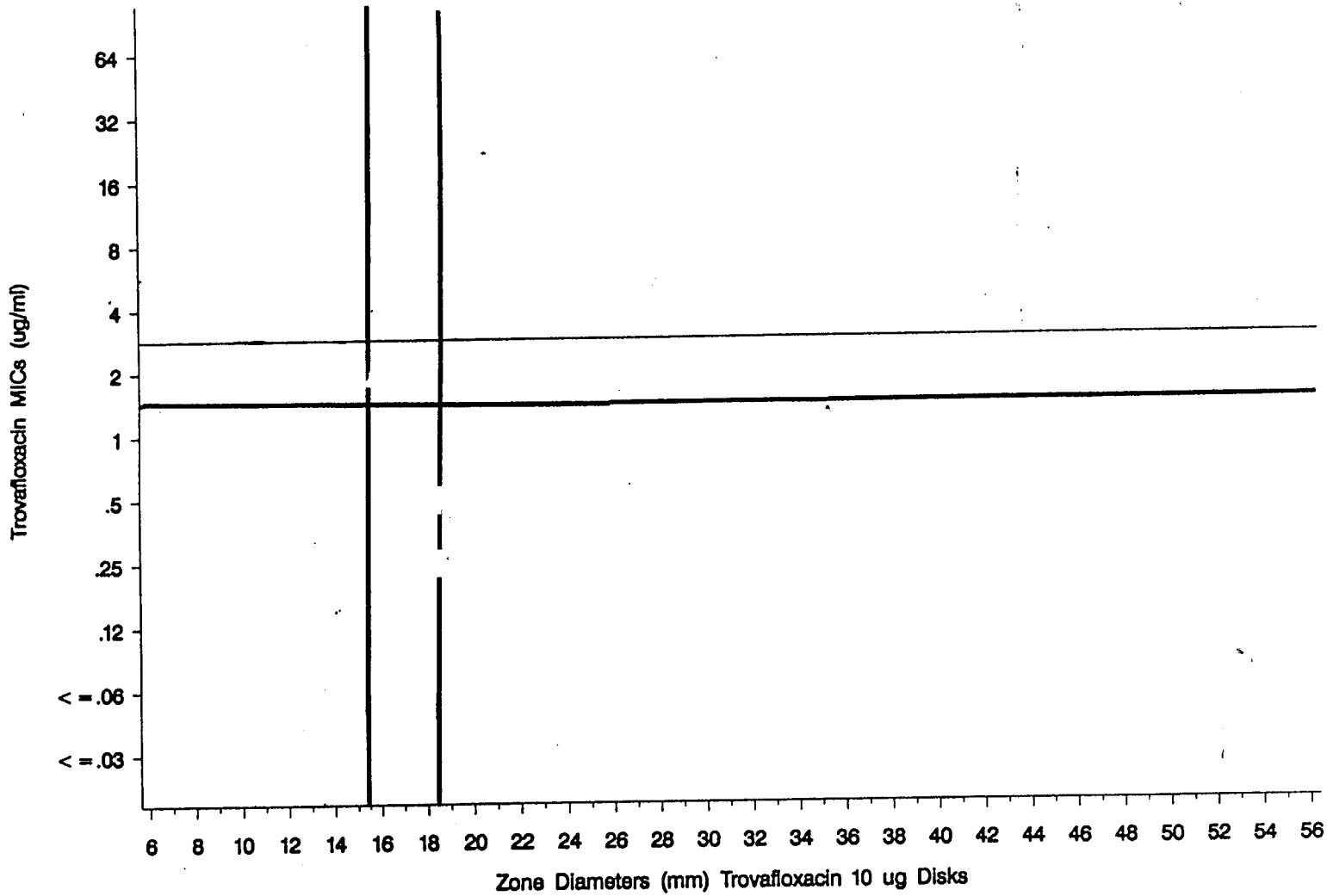


Figure **16.** Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) Non – USA/Canada

All Strepococcus spps, except S. Pneumoniae (n = 61)

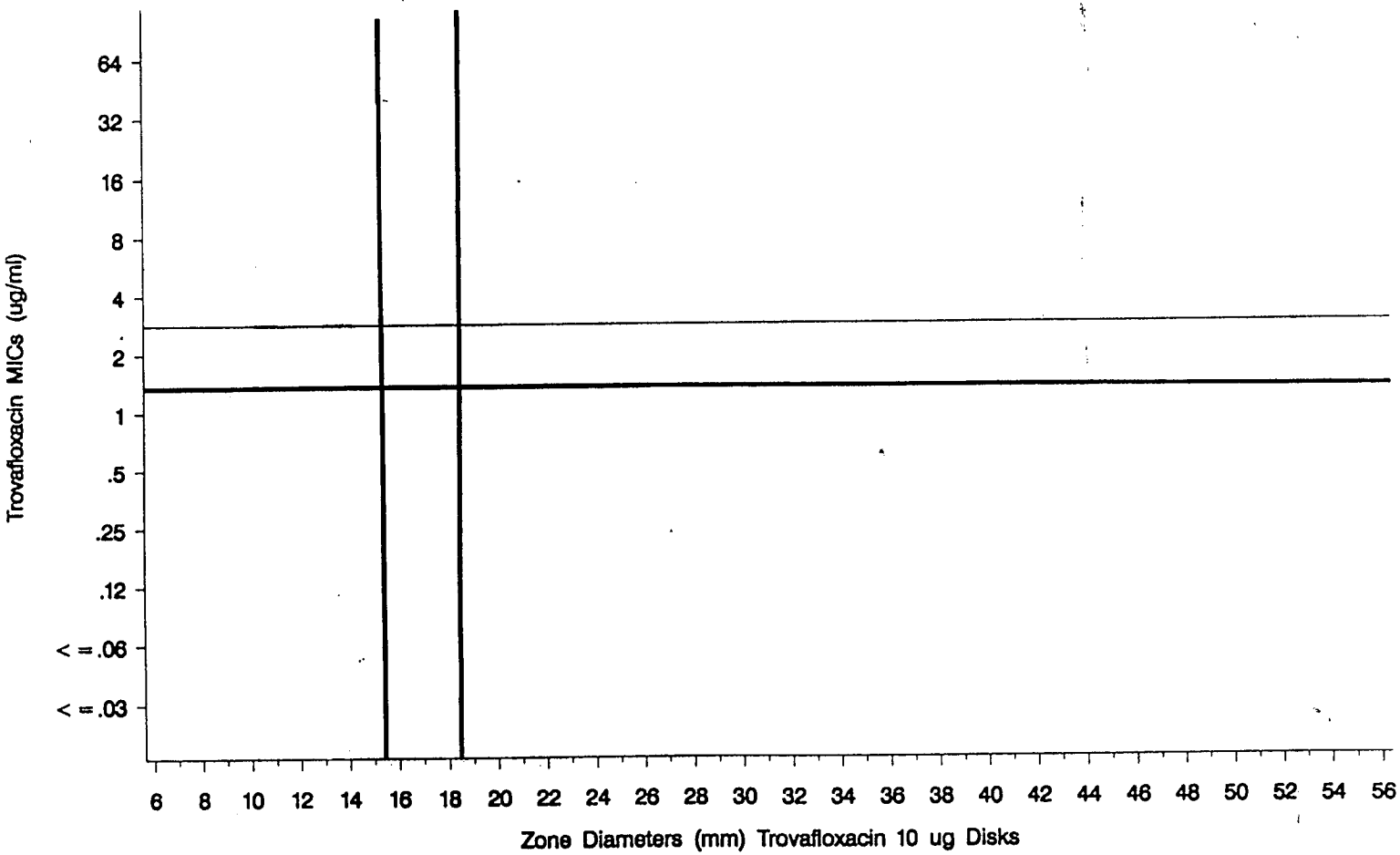


Figure 17. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm)

All Strepococcus spps, except S. Pneumoniae (n=375)

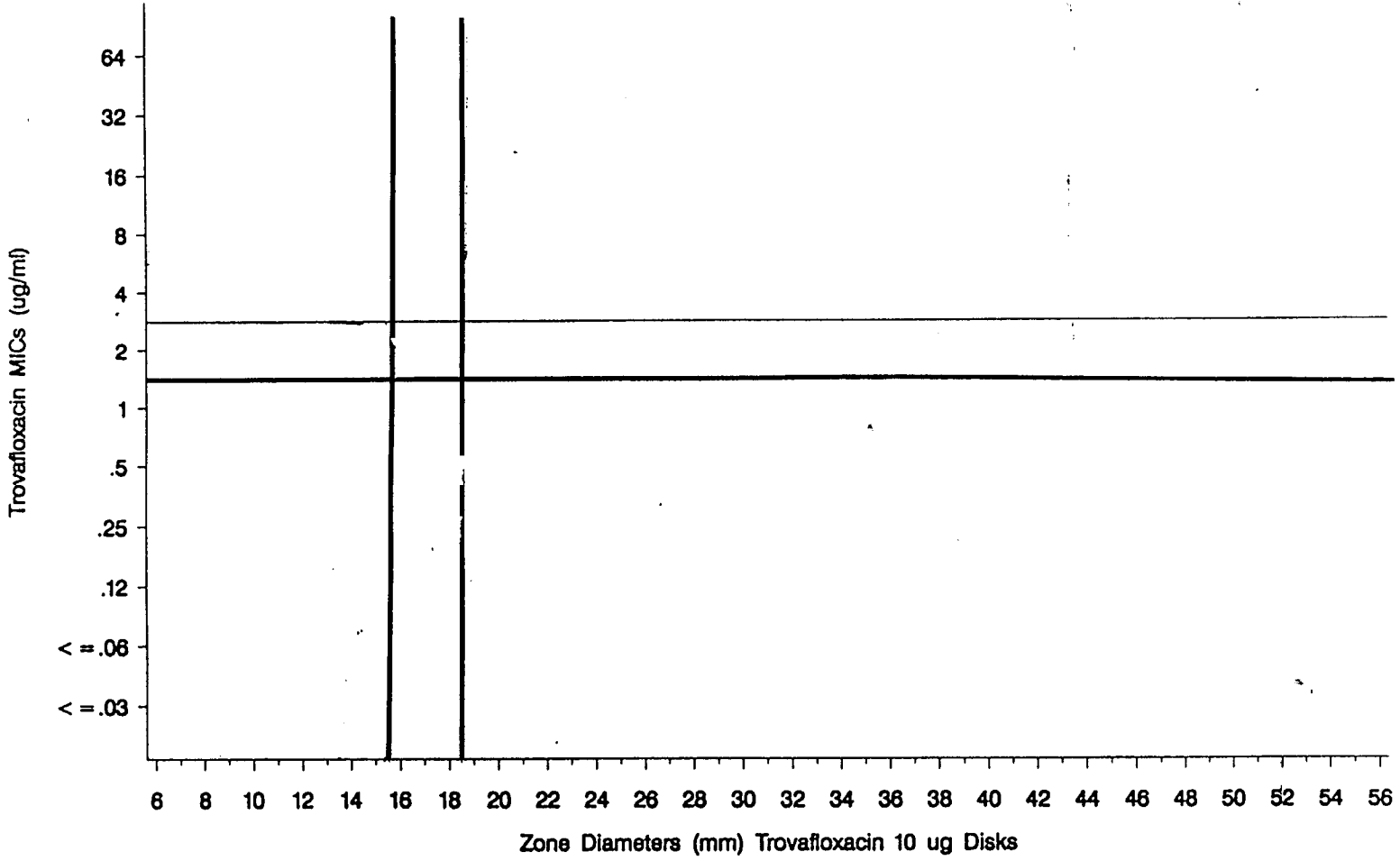
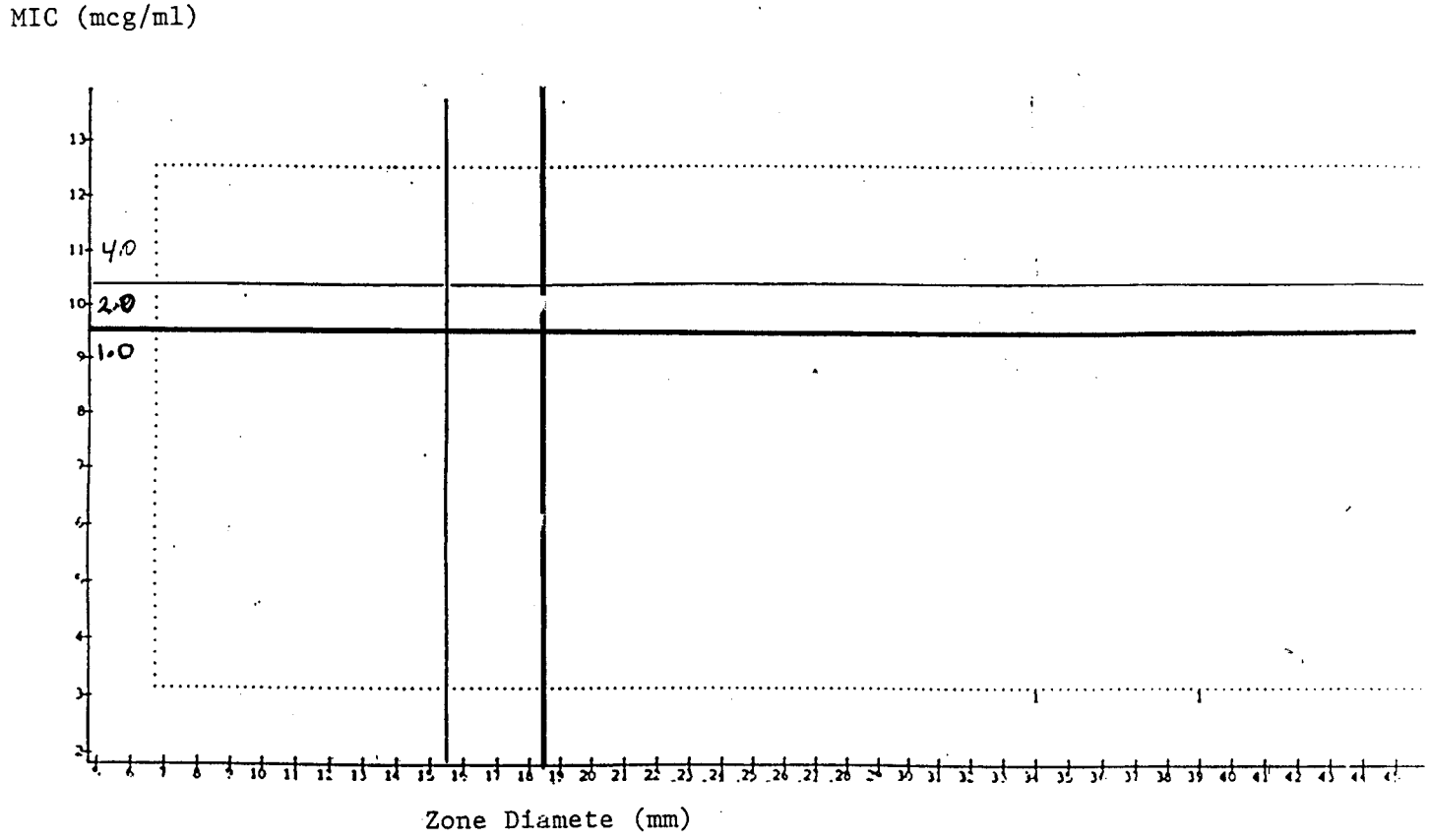


Figure 18. Scattergram generated from 405 selected Streptococcus spp. other than S. pneumoniae culture collection against Trovan



7. Discussion of Disk Diffusion Interpretive Breakpoints for *Neisseria gonorrhoeae*

Figure 19 is the scattergram for clinical isolates of *Neisseria gonorrhea* obtained during the clinical trials. In this scattergram the sponsor has included all the U.S. isolates regard less of the clinical outcome. The isolates were not divided into U.S. and non-U.S. because there were no non-U.S. isolates in these studies. According to these data the highest MIC obtained was 0.03 μg/mL. Considering that the $AUC_{0\text{-}24}$ for the proposed 100 mg single dose is 9.4 ± 1.5 μg .h/mL, the MIC susceptible breakpoint of 0.125 μg/mL would seem appropriate (AUC/MIC ratio would be 78). The smallest disk diffusion zone diameter obtained was 30 mm (excluding an out-lire at 6 mm). Using the error rate-bound method or the rule of 3 mm smaller than the zone for 99.9 % of the isolates, the disk diffusion susceptible breakpoint based on MIC susceptible breakpoint of ≤ 0.125 μg/mL would be ≥ 27 mm. Since there were no resistant isolates recovered in the clinical trials this reviewer will refer to a study performed by Ronald Jones et al. that was presented to the NCCLS fastidious organism working group during the general meeting on June 1-3, 1997. Ronald Jones presented a scattergram on 150 selected strains of *Neisseria gonorrhoeae* having defined mechanism of resistance (Figure 20). One hundred strains were classified as ciprofloxacin-susceptible. These ciprofloxacin-susceptible strains exhibited varied patterns of susceptibility to penicillin: seven strains susceptible, 54 strains intermediate, 24 strains resistant by means of beta-lactamase production, and 15 additional strains with chromosomally mediated resistance. Fifty strains demonstrated decreased susceptibility to ciprofloxacin: 44 strains were classified as having low-level resistance and six strains had high-level resistance The MIC_{50} and MIC_{90} of these 50 isolates against trovafloxacin were 0.06 and 0.25 μg/mL These strains were collected from diverse geographic locations with 27 strains coming from Japan, 17 strains from the U.S., and six strains from the Netherlands. The 27 strains from Japan included 16 strains with *gyrA*, and 11 strains with double gyrA and parC mutations. The highest MIC and lowest disk diffusion zone diameter obtained from these isolates were 0.5 μg/mL and 29 mm, respectively. As it is shown in Figure 20 the MIC susceptible breakpoint of ≤ 0.125 μg/mL would separate most of the double mutations from the single and non-mutated isolates. Using the error rate-bound method the corresponding zone diameters would be ≥ 37 mm. Choosing 0.25 and ≥ 0.5 μg/mL for intermediate and resistant categories, respectively the corresponding intermediate and resistant zone diameters would be and ≤ 33 respectively. With these breakpoints there are no very major or major errors and only 0.7% minor errors.

If these breakpoints are chosen, the error rate-bound examination of the scattergram from the clinical isolates (excluding an out-lire at 6 mm) would predict no very major or minor errors and 3.0% major errors. This major error rate, even thought on the high side, is acceptable. Therefore this reviewer would suggest the MIC and disk diffusion breakpoints of ≤ 0.125, 0.25, ≥ 0.5 μg/mL and ≥ 37 ≤ 33 mm for susceptible, intermediate, and resistant respectively.

Table 26 shows overall trends in the data demonstrating that the above disk diffusion interpretive breakpoints serve as good predictors of therapeutic outcome for *Neisseria gonorrhea.* There is a direct correlation between a susceptible disk diffusion result and both bacterial eradication and

clinical cure rates. As seen in Table 26, susceptible disk diffusion result correspond with 100% bacterial eradication and 91% clinical cure rates.

TABLE 26. Relationship Between Zone Diameter and Pathogen Eradication and Clinical Cure Rates in patients treated with Trovafloxacin I.V. and Tablets

		Pathogen Eradication Rate			Clinical Cure Rate		
Organism Group	**Susceptibility**	**No. of Pathogens**	**No. of Pathogens Eradicated[a]**	**% Eradicated[a]**	**No. of Patients**	**No. of Patients Cured[b]**	**% Cured[b]**
***Haemophilus* spp.**	S (≥ 22 mm)	164	157	96	164	150	92
	R (< 22 mm)	1	1	100	1	1	100
S. pneumoniae	R (≤ 15 mm)	0	--	--	0	--	--
	I (16-18 mm)	0	--	--	0	--	--
	S (≥ 19 mm)	100	91	91	100	91	91
Streptococcus* spp other than *S. pneumoniae	R (≤ 15 mm)	3	3	100	3	3	100
	I (16-18 mm)	3	1	33	3	3	100
	S (≥ 19 mm)	154	130	85	154	136	88
M. catarhalis	R (≤ 14 mm)	0	--	--	0	--	--
	I (15-17 mm)	0	--	--	0	--	--
	S (≥ 18 mm)	58	55	95	58	53	91
N. gonorrhoeae	R (≤ 33 mm)	2	2	100	2	2	100
	I (34-36 mm)	0	--	--	0	--	--
	S (≥ 37 mm)	23	23	100	23	21	91
S. aureus	R (≤ 14 mm)	7	4	57	7	7	100
	I (15-17 mm)	17	12	70	17	15	88
	S (≥ 18 mm)	305	253	83	305	279	91
Staphylococcus* spp. other than *S. aureus	R (≤ 14 mm)	15	13	87	15	14	93
	I (15-17 mm)	9	7	78	9	7	78
	S (≥ 18 mm)	201	180	90	201	185	92
***Enterococcus* spp.**	R (≤ 14 mm)	11	7	64	11	9	82
	I (15-17 mm)	7	7	100	7	7	100
	S (≥ 18 mm)	98	85	87	98	92	94
***Enterobacteriaceae* spp.[c]**	R (≤ 14 mm)	28	18	64	28	22	79
	I (15-17 mm)	10	6	60	10	6	60
	S (≥ 18 mm)	560	503	89	560	508	91
Gram-negative nonfermenters[d]	R (≤ 14 mm)	9	7	78	9	9	100
	I (15-17 mm)	10	6	60	10	9	90
	S (≥ 18 mm)	100	67	67	100	85	85

[a] Including eradicated and presumed eradicated pathogens
[b] Including cured and improved patients
[c] Excluding all *Acinetobacter* spp., *Pseudomonas* spp., and *S. maltophilia*
[d] Includes all *Acinetobacter* spp., *Pseudomonas* spp. and *S. maltophilia*

Figure **19.** Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm)

Neisseria gonorrhea (n=66)

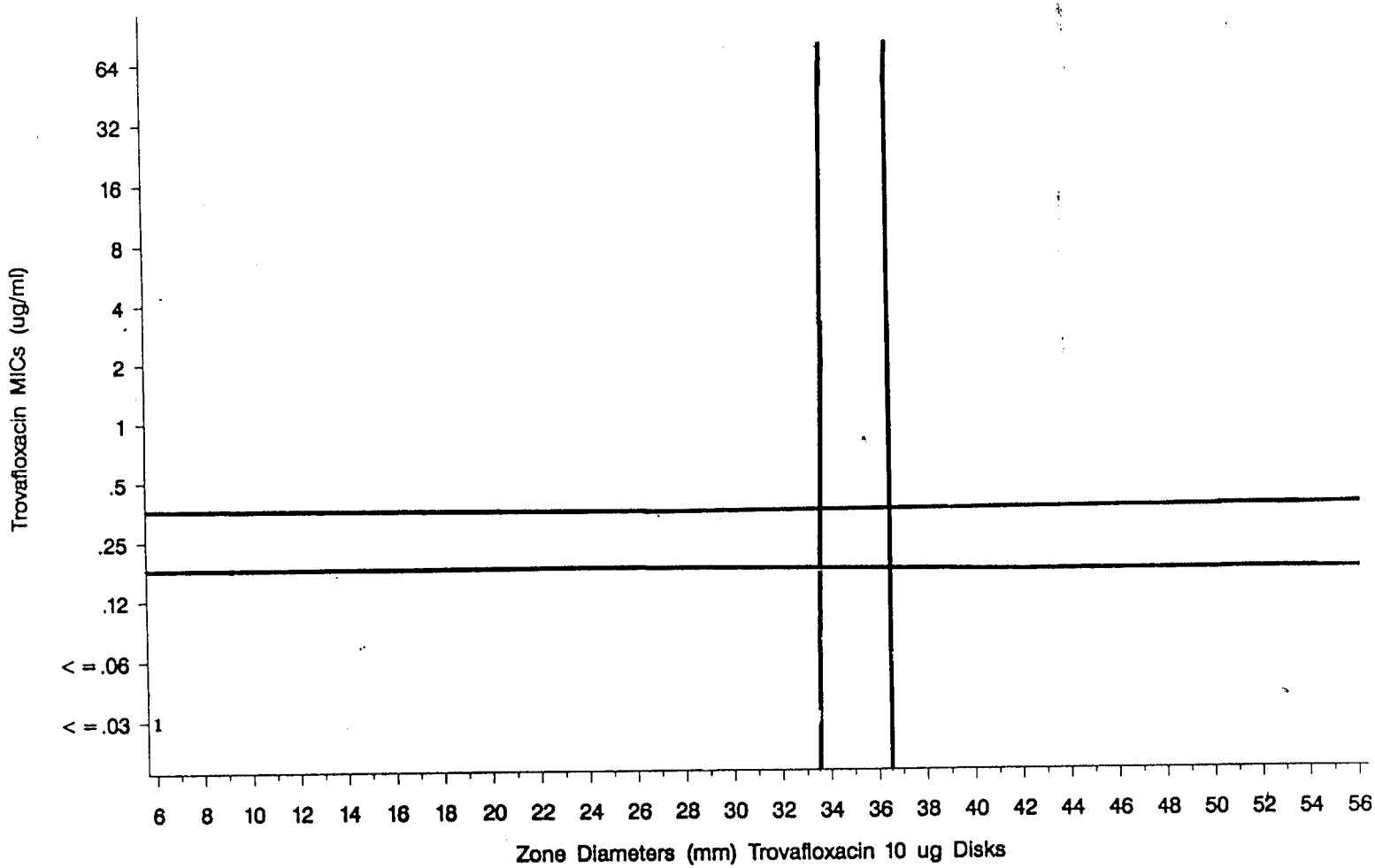
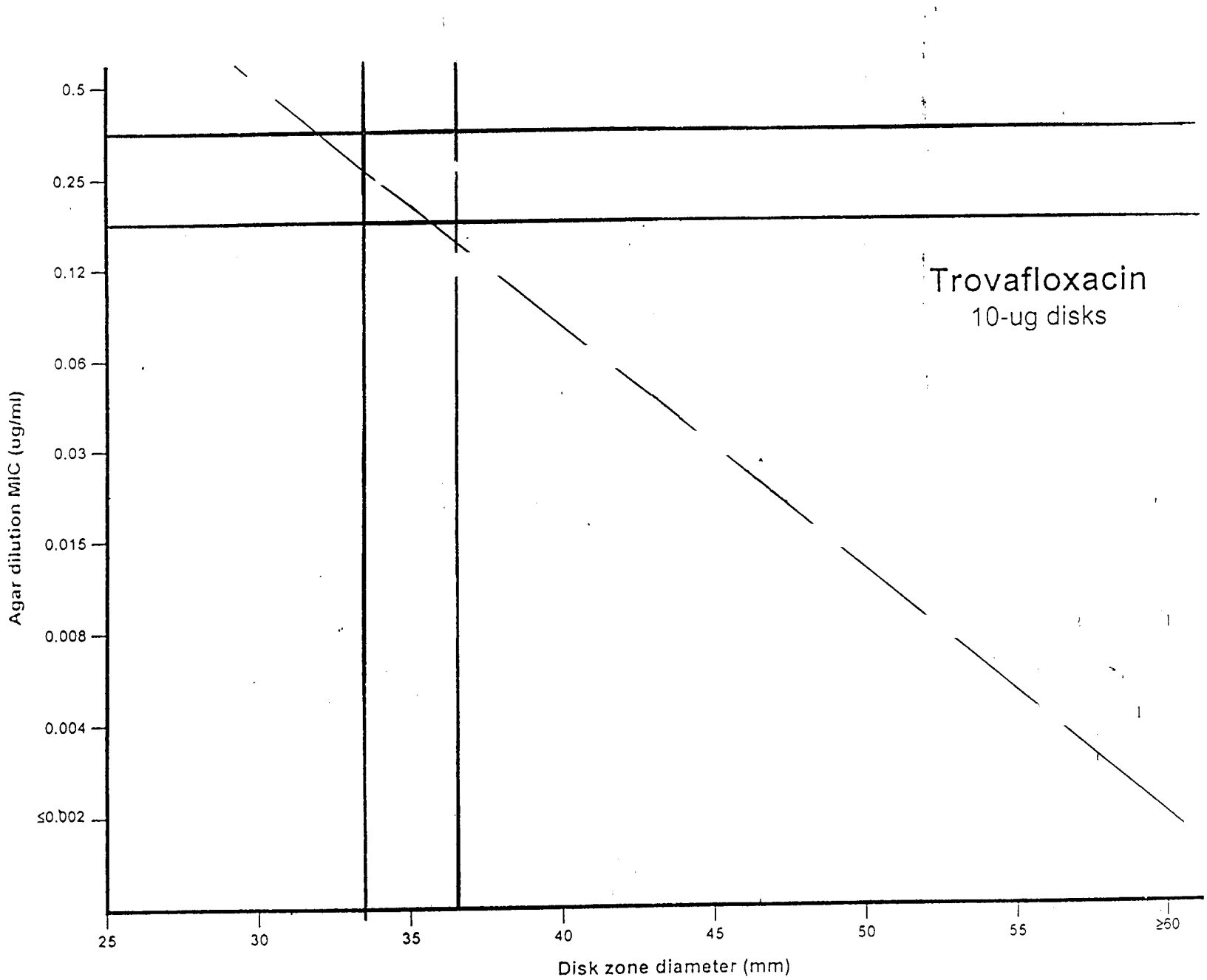


Figure 20. Scattergram of 150 gonococcal isolates including 50 strains from ciprofloxacin/ofloxacin therapy failures,



8. Discussion of Disk Diffusion Interpretive Breakpoints for Non-Fastidious Aerobic Organisms

Figures 21 to 23 are scattergrams for clinical isolates of all non-fastidious aerobic organisms obtained during the clinical trials. In this section the sponsor has included all the isolates regard less of the clinical outcome. When one compares the U.S./Canada strains (Figure 21) with the non-U.S./Canada strains (Figure 22) it becomes evident that there is not much difference between the susceptibility patterns of the two groups. Therefore, one may combine the data from the U.S. and non-U.S. studies (Figure 23) and using the error rate-bound method determine the disk diffusion breakpoints based on MIC breakpoints of ≤ 1 , 2.0, and ≥ 4.0 µg/mL for susceptible, intermediate and resistant, respectively.

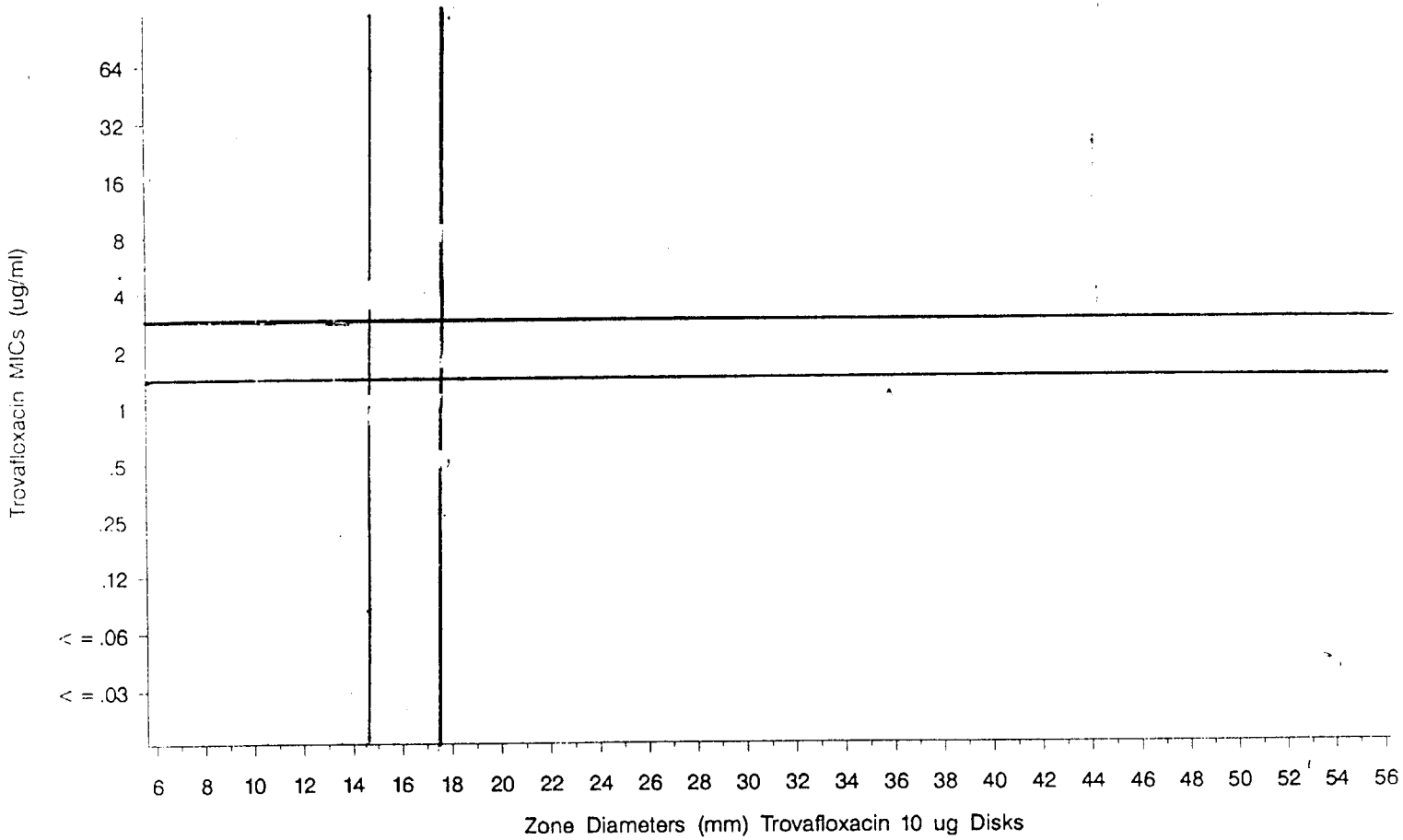
Using the error rate-bound method the disk diffusion susceptible, intermediate, and resistant breakpoints should be set at ≥ 18, , and ≤ 14 mm, respectively. This would result in an acceptable very major and major and minor error rates of 0.36%, 0.36%, and 3.4%, respectively.

If one considers MIC breakpoints of ≤ 2 , 4.0, and ≥ 8.0 µg/mL for susceptible, intermediate and resistant, respectively, using the error rate-bound method the disk diffusion susceptible, intermediate, and resistant breakpoints should be set at ≥ 17, and ≤ 13 mm, respectively. This would result in an acceptable very major and major and minor error rates of 0.17%, 0.54%, and 3.6%, respectively (See Figures 24-26 and addendum by Dr. Albert Sheldon)

Table 26 show overall trends in the data demonstrating that the above disk diffusion interpretive breakpoint serves as good predictors of therapeutic outcome for non-fastidious aerobic organisms. There is a direct correlation between a susceptible disk diffusion result and both bacterial eradication and clinical cure rates. As seen in Table 26, for *Moraxella catarrhalis,* susceptible disk diffusion result correspond with 95% bacterial eradication and 91% clinical cure rates; for *Staphylococcus aureus,* susceptible disk diffusion result correspond with 83% bacterial eradication and 91% clinical cure rates; for staphylococci other than *S. aureus*, susceptible disk diffusion result correspond with 90% bacterial eradication and 92% clinical cure rates; for *Enterococcus* spp., susceptible disk diffusion result correspond with 87% bacterial eradication and 94% clinical cure rates; for Enterobacteriaceae spp., susceptible disk diffusion result correspond with 89% bacterial eradication and 91% clinical cure rates; and for gram-negative non-fermenters, susceptible disk diffusion result correspond with 67% bacterial eradication and 85% clinical cure rates.

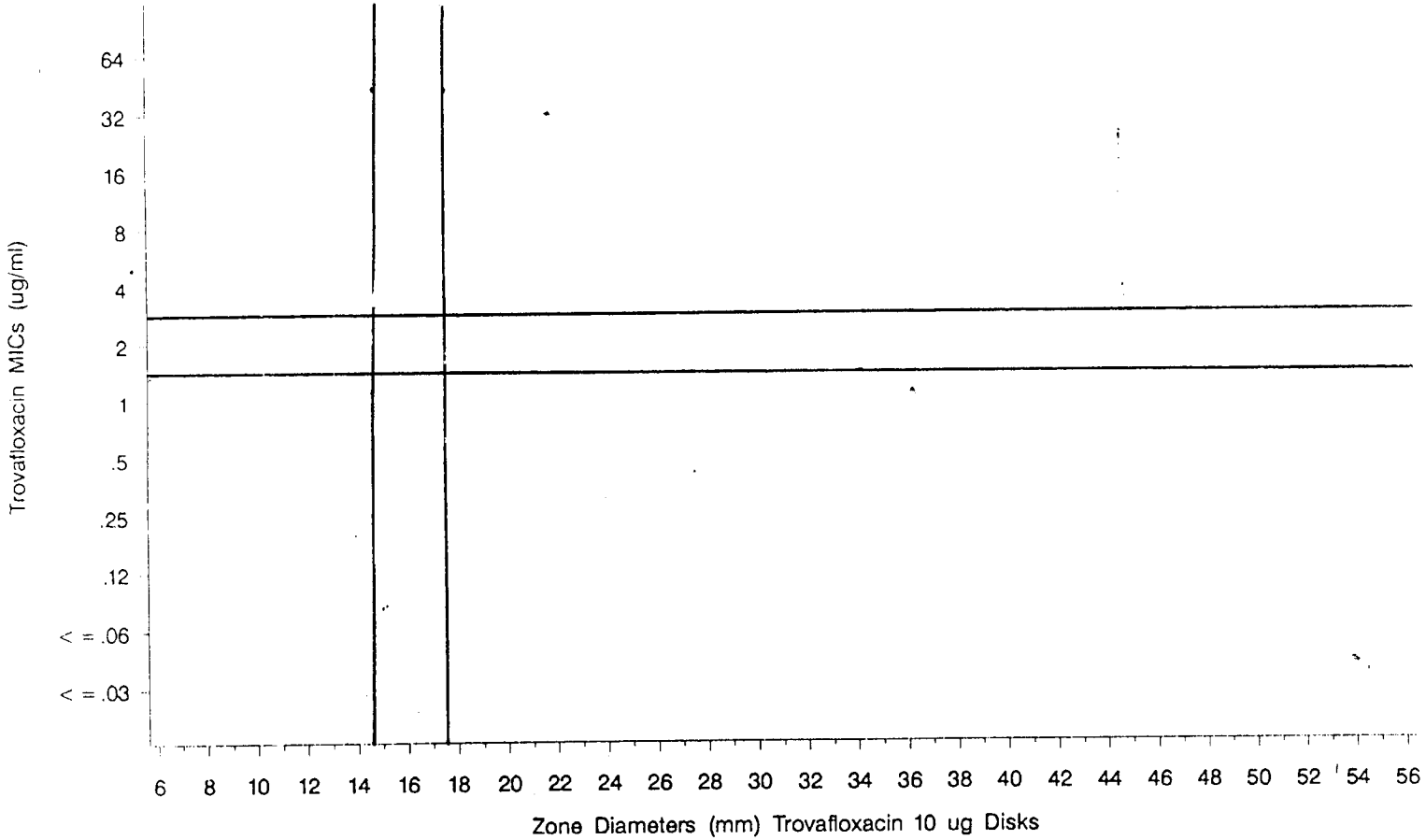
Figure **21.** Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) USA/Canada

All Staph spps, all Enterococcal spps, all Enterobacteriacae and all gram negative nonfermenters (n=2282)



Very Major Errors = 3 (0.13% of Total or 2.94% of 67 Resistant Strains)
Major Errors = 5 (0.22% of Total or 0.23% of 2175 Susceptible Strains)
Minor Errors = 42 (1.84% of Total or 1.93% of 2175 Susceptible Strains)

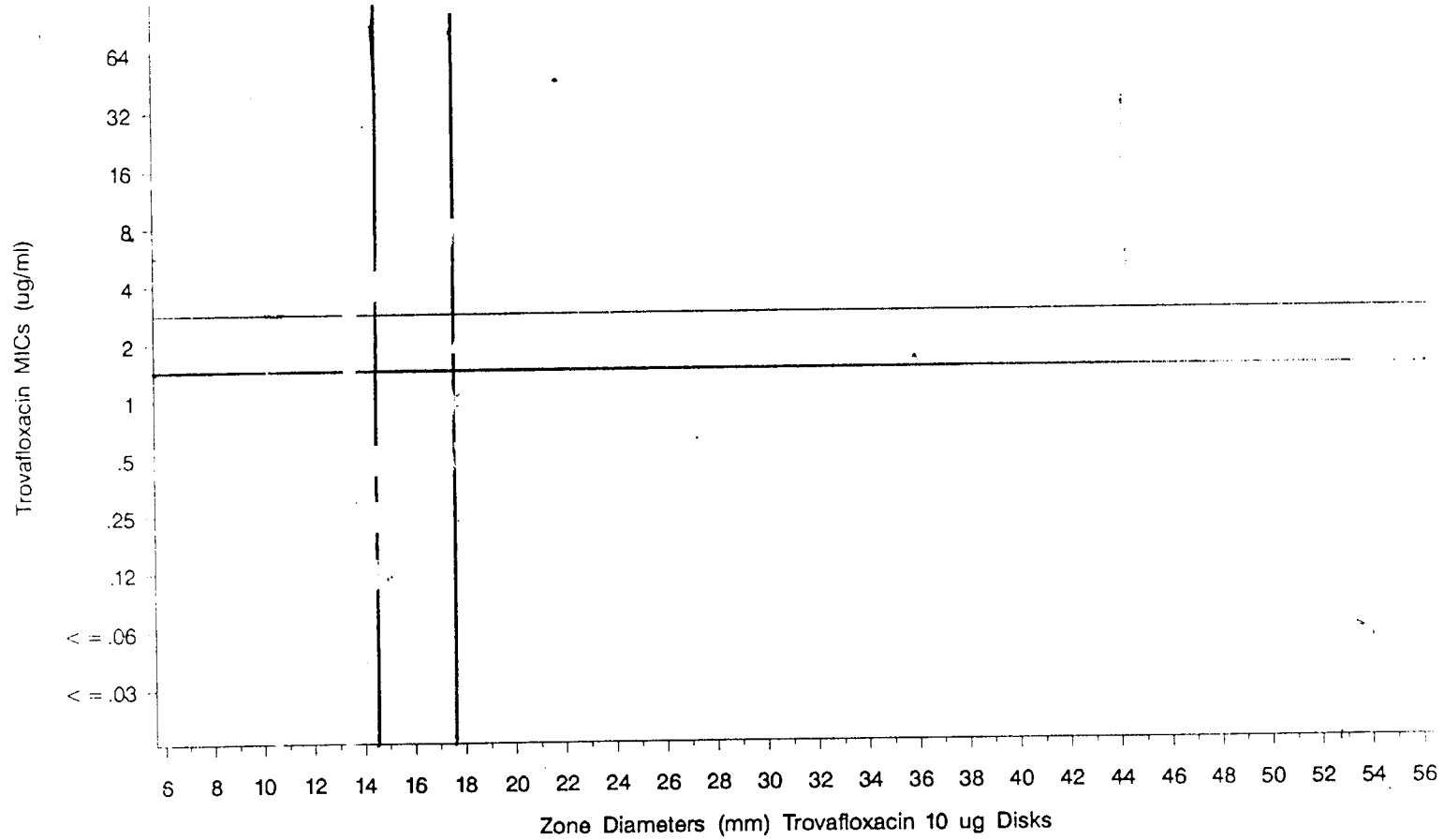
Figure **22.** Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) Non – USA/Canada
All Staph spps, all Enterococcal spps, all Enterobacteriacae and all gram negative nonfermenters (n=1071)



Very Major Errors=3 (0.28% of Total or 3.45% of 37 Resistant Strains)
Major Errors=3 (0.28% of Total or 0.29% of 1022 Susceptible Strains)
Minor Errors=13 (1.21% of Total or 1.27% of 1022 Susceptible Strains)

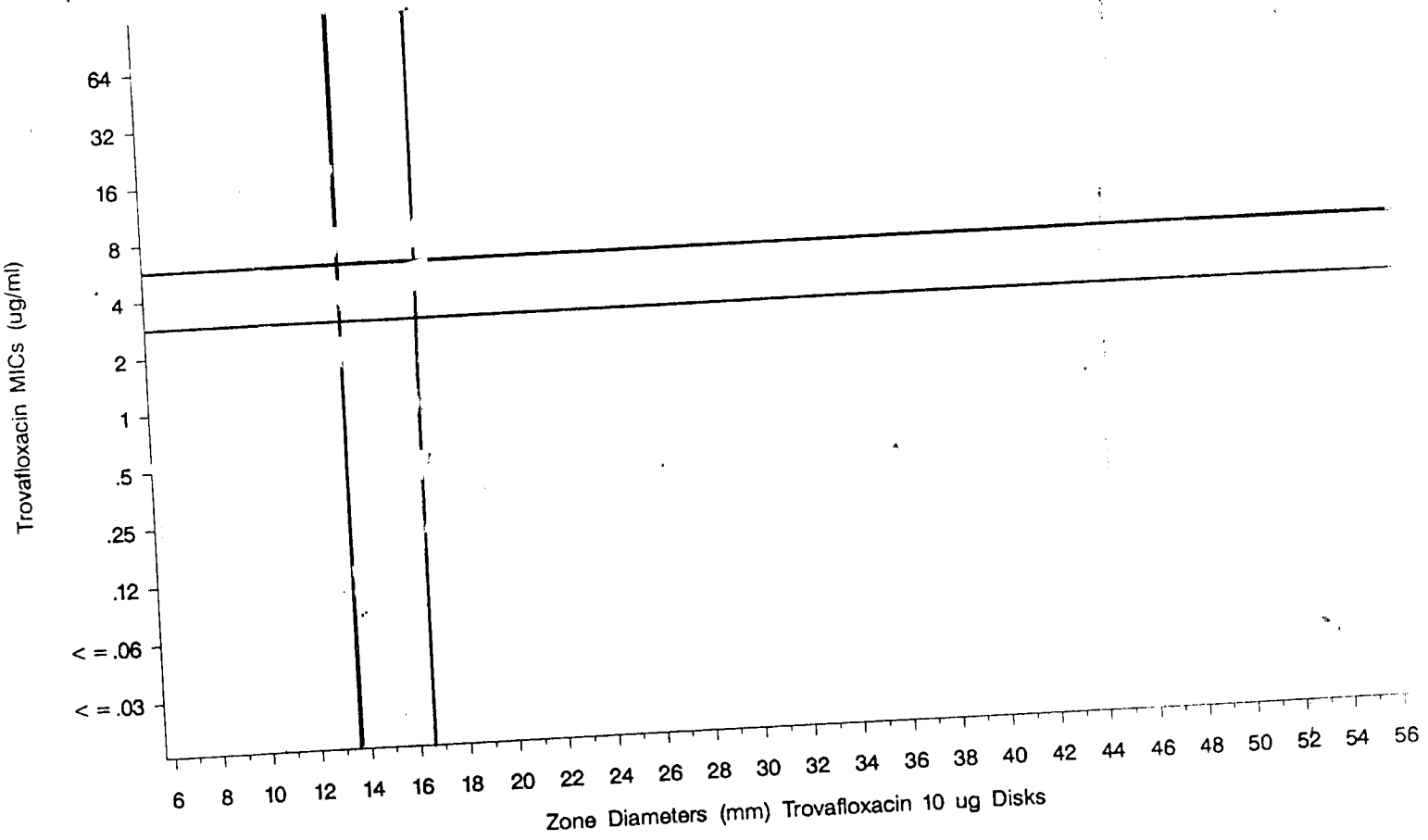
Figure 23. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm)

All Staph spps, all Enterococcal spps, all Enterobacteriacae and all gram negative nonfermenters (n=3353)



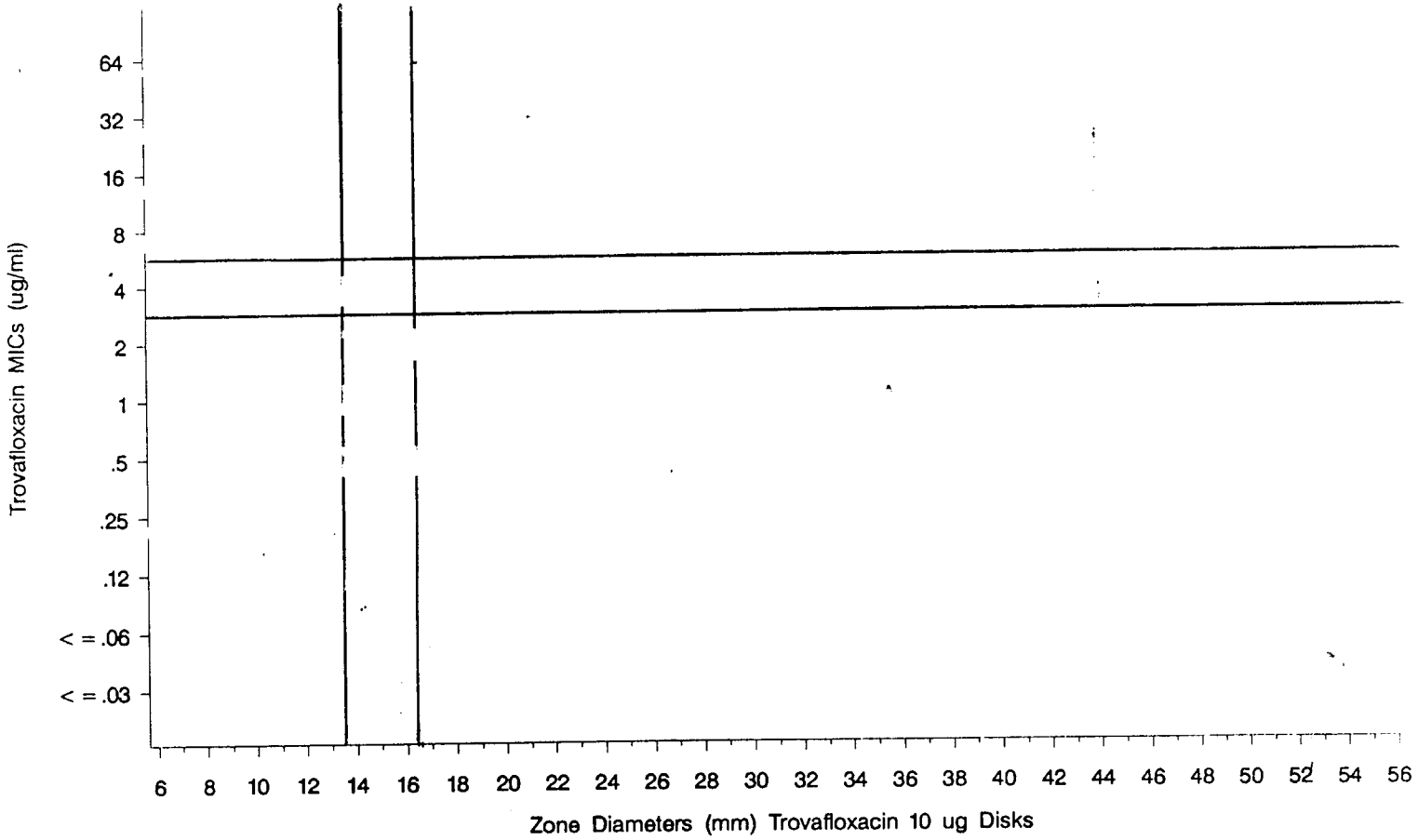
Very Major Errors = 6 (0.18% of Total or 3.10% of 104 Resistant Strains)
Major Errors = 8 (0.24% of Total or 0.25% of 3197 Susceptible Strains)
Minor Errors = 55 (1.64% of Total or 1.72% of 3197 Susceptible Strains)

Figure 24. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) USA/Canada
All Staph spps, all Enterococcal spps, all Enterobacteriacae and all gram negative nonfermenters (n=2282)



Very Major Errors = 3 (0.13% of Total or 2.94% of 67 Resistant Strains)
Major Errors = 5 (0.22% of Total or 0.23% of 2175 Susceptible Strains)
Minor Errors = 42 (1.84% of Total or 1.93% of 2175 Susceptible Strains)

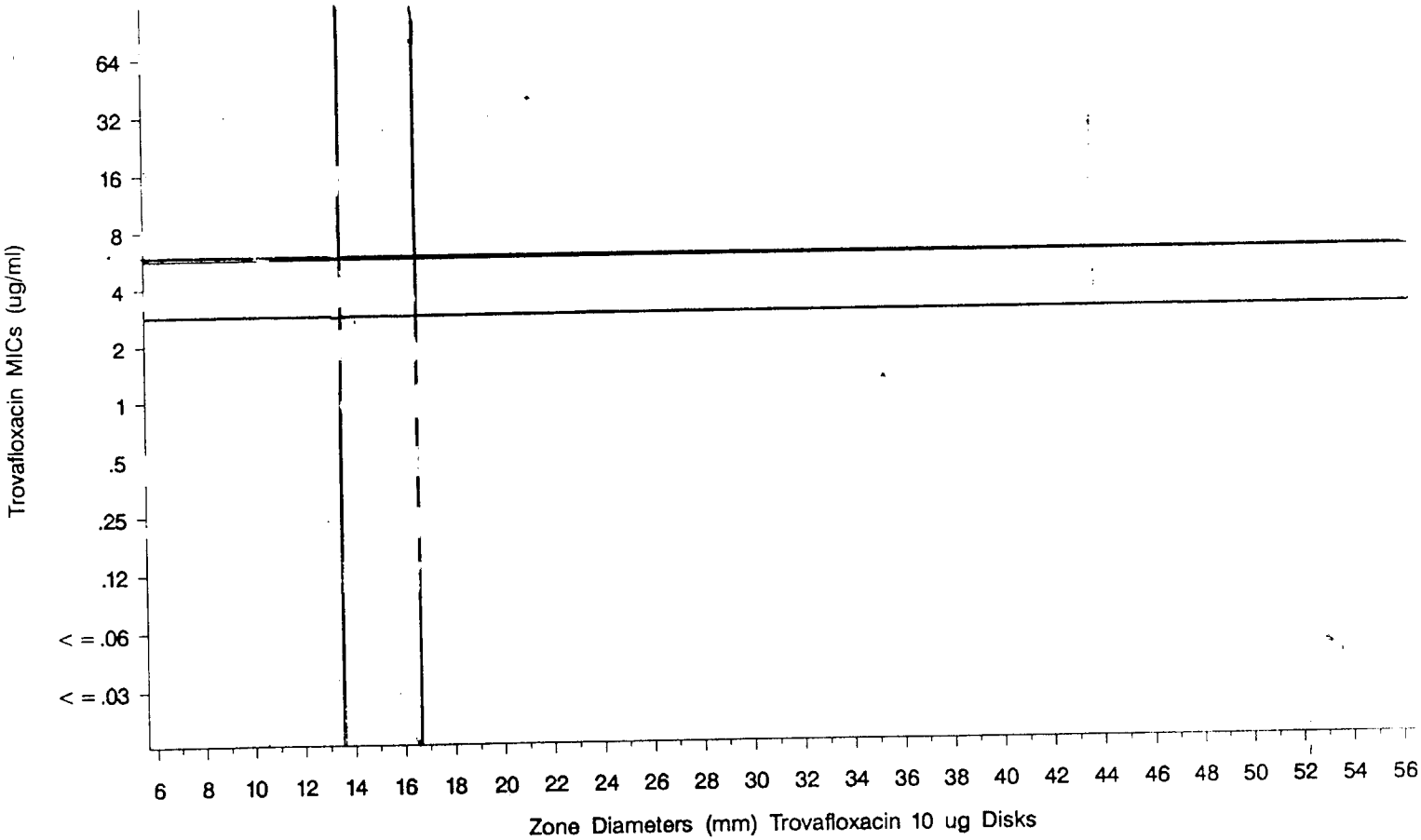
Figure 25. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm) Non – USA/Canada
All Staph spps, all Enterococcal spps, all Enterobacteriacae and all gram negative nonfermenters (n = 1071)



Very Major Errors = 3 (0.28% of Total or 3.45% of 37 Resistant Strains)
Major Errors = 3 (0.28% of Total or 0.29% of 1022 Susceptible Strains)
Minor Errors = 13 (1.21% of Total or 1.27% of 1022 Susceptible Strains)

Figure 26. Trovafloxacin MICs (ug/ml) vs Zone Diameter (mm)

All Staph spps, all Enterococcal spps, all Enterobacteriacae and all gram negative nonfermenters (n=3353)



Very Major Errors = 6 (0.18% of Total or 3.10% of 104 Resistant Strains)
Major Errors = 8 (0.24% of Total or 0.25% of 3197 Susceptible Strains)
Minor Errors = 55 (1.64% of Total or 1.72% of 3197 Susceptible Strains)