Primary Efficacy Outcome

The Clinical Success rates for the pooled MITT population from Studies 9801 and 9901 were 75.8% in the daptomycin group and 76.2% in the comparator group (95% CI: -5.7, 5.0) (see Table 40). The results indicate that daptomycin at 4 mg/kg q24h for 7 to 14 days is clinically and statistically non-inferior to the comparator agents for the treatment of cSSSI.

Table 40: Primary efficacy endpoint: Sponsor-Defined Clinical Outcome, Primary Comparative cSSSI Studies (MITT population)

	Pooled cSSSI 9801 + 9901				
	Daptomycin (N=422)		Comparator[a] (N=467)		
Clinical Response	n	%	n	%	95% CI[b]
Clinical Success	320	(75.8%)	356	(76.2%)	(-5.7, 5.0)
Cure	173	(41.0%)	195	(41.8%)	
Clinical Improvement	147	(34.8%)	161	(34.5%)	
Clinical Failure	102	(24.2%)	111	(23.8%)	
Clinical Failure	64	(15.2%)	66	(14.1%)	
Nonevaluable	38	(9.0%)	45	(9.6%)	

a. Vancomycin 1 g q12h or semi-synthetic penicillin (oxacillin, nafcillin, cloxacillin, or flucloxacillin) 4 to 14 grams daily in equal divided doses.
b. 95% confidence interval around the difference in success rate (Comparator Daptomycin) using the normal approximation to the binomial distribution. For combined protocols, the confidence interval is calculated stratifying on protocol.

Clinical Success Rates by Pathogen

Clinical Success rates by pathogen for the ME population (Table 41) were similar to those of the MITT population (Table 42) when these rates for daptomycin were assessed against all comparators. Tables showing data for clinical success rates for both populations comparing daptomycin to either semi-synthetic penicillins or vancomycin are not shown here but can be found in Microbiology Section 8.6.10 as tables 8-16, 8-17, 10-59, and 10-60.

Table 41: Sponsor Defined Clinical Success Rates by Pathogen (ME population: Daptomycin arm versus Comparator arm) for comparative cSSSI studies at test-of-cure[a]

Pathogen[b]	Daptomycin		Comparator[c]		95% CI[d]
Staphylococcus aureus (all)	222/265	(83.8%)	240/285	(84.2%)	(-5.8, 6.7)
Staphylococcus aureus (MSSA)[d]	176/208	(84.6%)	185/216	(85.6%)	(-5.9, 7.9)
Staphylococcus aureus (MRSA)[d]	21/30	(70.0%)	27/39	(69.2%)	(-23.1, 21.6)
Streptococcus pyogenes	80/87	(92.0%)	82/94	(87.2%)	(-13.7, 4.3)
Streptococcus agalactiae	24/28	(85.7%)	22/31	(71.0%)	(-35.7, 6.2)
Streptococcus dysgalactiae equisimilis	9/10	(90.0%)	9/11	(81.8%)	(-38.2, 21.8)
Viridans Streptococci Group	15/22	(68.2%)	27/32	(84.4%)	(-7.5, 39.8)
Enterococcus faecalis (all)	27/39	(69.2%)	41/54	(75.9%)	(-12.1, 25.5)
Enterococcus faecalis (VSE)[d]	25/36	(69.4%)	39/52	(75.0%)	(-13.9, 25.0)

a. Based on the Sponsor-Defined Clinical Outcome.
b. Only pathogens for which an indication is being sought are shown.
c. Semi-synthetic penicillin (oxacillin, nafcillin, cloxacillin, or flucloxacillin).
d. Susceptibility determinations were made only for Central Lab isolates.
e. Seven subjects in the pooled ME population were initially treated with semi-synthetic penicillins and had MRSA

isolated as a baseline pathogen. Six of these subjects were then switched to vancomycin; five of these were clinical successes. The remaining subject was continued on semi-synthetic penicillin and was a clinical success.

Table 42: Clinical Success Rates by Pathogen, Primary Comparative cSSSI Studies: Pooled Analysis (MITT population)

Pathogen[b]	Daptomycin		Comparator[c]		95% CI[d]
	n/N	(%)	n/N	(%)	
Staphylococcus aureus (all)	223/299	(74.6%)	241/320	(75.3%)	(-6.2, 7.7)
Staphylococcus aureus (MSSA)[e]	177/227	(78.0%)	185/237	(78.1%)	(-7.6, 7.8)
Staphylococcus aureus (MRSA)[e]	21/39	(53.8%)	27/46	(58.7%)	(-16.7, 26.4)
Streptococcus pyogenes	81/92	(88.0%)	82/103	(79.6%)	(-18.9, 2.0)
Streptococcus agalactiae	24/30	(80.0%)	23/39	(59.0%)	(-42.5, 0.5)
Streptococcus dysgalactiae equisimilis	9/13	(69.2%)	9/12	(75.0%)	(-30.0, 41.6)
Viridans Streptococci Group	15/23	(65.2%)	27/32	(84.4%)	(-4.5, 42.8)
Enterococcus faecalis (all)	27/45	(60.0%)	42/61	(68.9%)	(-10.0, 27.7)
Enterococcus faecalis (VSE)[e]	25/41	(61.0%)	40/56	(71.4%)	(-9.0, 29.9)

a. Based on the Sponsor-Defined Clinical Outcome.
b. Only pathogens for which an indication is being sought are shown.
c. Semi-synthetic penicillin (oxacillin, nafcillin, cloxacillin, or flucloxacillin) or vancomycin.
d. 95% confidence interval around the difference in success rate (Comparator Daptomycin) using the normal approximation to the binomial distribution. For combined protocols, the C.I. is calculated stratifying on protocol.
e. Restricted to Infecting Pathogens with susceptibility testing performed at the Central Laboratory

Reviewer's comments: In both populations, the clinical success rates for daptomycin and comparators were very similar for *Staphylococcus aureus* including MSSA and MSRA. Daptomycin was less effective (≥5% lower clinical success rate) than semi-synthetic penicillins against MRSA.

Overall, clinical success rates of daptomycin for the treatment of *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus dysgalactiae equisimilis* were rather superior (≥5% higher clinical success rate) to comparators. However, clinical success rates of daptomycin for the treatment of viridans streptococci were lower overall to comparators. Daptomycin seemed more successful against viridans streptococci than semi-synthetic penicillins.

Overall, clinical success rates of daptomycin for the treatment of *Enterococcus faecalis*, including VSE, were lower than comparators. This was due to the observation that clinical success rates of daptomycin were superior to vancomycin but inferior to that for semi-synthetic penicillins.

Pathogen Eradication Rates

Pathogen eradication rates by pathogen and treatment group for the pooled ME population is shown in Table 43 and for the MITT population in Table 44. Pathogen eradication rates were comparable for the two populations. Additional data for pathogen eradication rates for both populations comparing daptomycin to either semi-synthetic penicillins or vancomycin are not shown here but can be found in Microbiology Section 8.6.1 as Tables 8-19, 8-20, 10-62, and 10-63.

Table 43: Eradication Rates By Pathogen and Treatment Group For The Primary Comparative cSSSI Studies: Pooled Analysis (ME population)

Pathogen[a]	Daptomycin		Comparators[b]		95% CI[c]
	nN	(%)	nN	(%)	
Staphylococcus aureus (all)	186/265	(70.2%)	211/285	(74.0%)	(-3.8,11.5)
Staphylococcus aureus (MSSA)[d]	148/208	(71.2%)	161/216	(74.5%)	(-5.3,12.0)
Staphylococcus aureus (MRSA)[d]	15/30	(50.0%)	23/39	(59.0%)	(-15.1,33.1)
Streptococcus pyogenes	77/87	(88.5%)	74/94	(78.7%)	(-20.6,1.1)
Streptococcus agalactiae	22/28	(78.6%)	19/31	(61.3%)	(-40.7,6.1)
Streptococcus dysgalactiae equisimilis	9/10	(90.0%)	9/11	(81.8%)	(-38.2,21.8)
Viridans Streptococci Group	17/25	(68.0%)	28/38	(73.7%)	(-17.8,29.2)
Enterococcus faecalis (all)	25/39	(64.1%)	35/54	(64.8%)	(-19.4,20.8)
Enterococcus faecalis (VSE)[d]	23/36	(63.9%)	33/52	(63.5%)	(-21.3,20.4)

a. Only pathogens for which an indication is being sought are shown.
b. Semi-synthetic penicillin (oxacillin, nafcillin, cloxacillin, or flucloxacillin) or vancomycin.
c. 95% confidence interval around the difference in success rate (Comparator Daptomycin) using the normal approximation to the binomial distribution. For combined protocols, the C.I. is calculated stratifying on protocol.
d. Restricted to Infecting Pathogens with susceptibility testing performed at the Central Laboratory.

Table 44: Eradication Rates By Pathogen and Treatment Group for the Primary Comparative cSSSI Studies: Pooled Analysis (MITT population)

Pathogen[a]	Daptomycin		Comparator[b]		95% CI[c]
	n/N	(%)	n/N	(%)	
Staphylococcus aureus (all)	186/299	(62.2%)	211/320	(65.9%)	(-4.0,11.4)
Staphylococcus aureus (MSSA)[d]	148/227	(65.2%)	161/237	(67.9%)	(-6.0,11.5)
Staphylococcus aureus (MRSA)[d]	15/39	(38.5%)	23/46	(50.0%)	(-9.9,33.0)
Streptococcus pyogenes	77/92	(83.7%)	74/103	(71.8%)	(-23.6,-0.1)
Streptococcus agalactiae	22/30	(73.3%)	19/39	(48.7%)	(-47.4,-1.9)
Streptococcus dysgalactiae equisimilis	9/13	(69.2%)	9/12	(75.0%)	(-30.0,41.6)
Viridans Streptococci Group	17/26	(65.4%)	28/38	(73.7%)	(-15.2,31.8)
Enterococcus faecalis (all)	25/45	(55.6%)	35/61	(57.4%)	(-17.7,21.3)
Enterococcus faecalis (VSE)[d]	23/41	(56.1%)	33/56	(58.9%)	(-17.5,23.2)

a. Only pathogens for which an indication is being sought are shown.
b. Semi-synthetic penicillin (oxacillin, nafcillin, cloxacillin, or flucloxacillin) or vancomycin.
c. 95% confidence interval around the difference in success rate (Comparator Daptomycin) using the normal approximation to the binomial distribution. For combined protocols, the C.I. is calculated stratifying on protocol.
d. Restricted to Infecting Pathogens with susceptibility testing performed at the Central Laboratory.

Reviewer's comments: In the ME population, the pathogen eradication rates for daptomycin and comparator were similar for *Staphylococcus aureus* however, daptomycin was less effective (9% lower pathogen eradication rate) comparator against MRSA. In the MITT population, the pathogen eradication rate among MRSA was significantly lower (11.5%) for daptomycin versus comparator.

Overall, pathogen eradication rates of daptomycin for the treatment of *Streptococcus pyogenes* and *Streptococcus agalactiae* were significantly superior to comparators. Daptomycin had higher eradication rates in both the ME and MITT populations (9.8% and 11.9% higher, respectively) against *Streptococcus pyogenes.*

Again, daptomycin had higher eradication rates in both the ME and MITT populations (17.3% and 24.6% higher, respectively) against *Streptococcus agalactiae*. However, pathogen eradication rates of daptomycin for the treatment of viridans streptococci and *Streptococcus dysgalactiae equisimilis* were lower overall to comparators. Eradication rates in both the ME and MITT populations were lower for daptomycin versus comparators (5.7% and 8.3% lower, respectively) against viridans streptococci. However, against *Streptococcus dysgalactiae equisimilis,* the eradication rate in the ME population was 8.2% higher against comparator while the eradication rate in the MITT population was 5.8% lower for daptomycin versus comparators. The disagreement in eradication rates between the two populations is odd but may be partially explained by particularly low numbers of isolates.

Overall, pathogen eradication rates of daptomycin for the treatment of *Enterococcus faecalis*, including VSE, were similar to comparators. This was due to the observation that pathogen eradication rates of daptomycin were somewhat superior to vancomycin but somewhat inferior to that of semi-synthetic penicillins.

Clinical success rates and pathogen eradication rates of daptomycin versus comparators for the various pathogens paralleled one another with two exceptions. First, pathogen eradication rates for daptomycin versus comparators was somewhat lower for MRSA than clinical success rates. Thus it seems, daptomycin may have a similar clinical success rate for the treatment of MRSA as compared to comparators but the drug will not be as effective in eradicating the pathogen as the comparator drugs. The second exception is that daptomycin has a comparable rate of eradicating *E. faecalis* as do the comparator drugs despite the fact that the comparator drugs seem to be more successful clinically.

Overall, compared to subjects infected with a single pathogen, subjects infected with two pathogens had lower success rates (see Table 45); the clinical success rates for those subjects were similar for daptomycin (70.1%) and comparator (67.5%). The most prevalent combination of dual infecting pathogens was *S. pyogenes* and *S. aureus*, which was found in 48 subjects in each treatment group in the pooled MITT population (see Table 10-64 of the Microbiology Section). Among these subjects, the clinical success rates were higher in the daptomycin group than in comparator (81.3% vs. 68.8%, respectively); the individual pathogen eradication rates against *S. aureus* were 66.7% and 54.2%, respectively, and against *S. pyogenes,* 77.1% and 62.5%.

Table 45: Clinical Success Rates[a] by Number of Infecting Gram-Positive Pathogens at Baseline, Primary Comparative cSSSI Studies: Pooled analysis. (MITT population)

Number of Infecting Gram-Positive Pathogens at Baseline	Daptomycin n/N	Daptomycin (%)	Comparator[a] n/N	Comparator[a] (%)
One Pathogen	250/322	(77.6)	269/342	(78.7)
Two Pathogens	68/97	(70.1)	79/117	(67.5)
Three Pathogens	2/3	(66.7)	8/8	(100.0)
All MITT Subjects	320/422	(75.8)	356/467	(76.2)

a. Using Sponsor-Defined Clinical Outcome
b. Semi-synthetic penicillin (oxacillin, nafcillin, cloxacillin, or flucloxacillin) or vancomycin.

The overall *in vitro* daptomycin susceptibility of all pathogens from the MITT populations of trials DAP-SST-9801 and DAP-SST-9901 is shown in Table 46. Overall, the two trials yielded MIC_{50} and MIC_{90} values that were within one doubling dilution. The maximum MIC values in DAP-SST-9901 for *E. faecalis* (MIC = 8 µg/ml), and *S. aureus* MRSA (MIC = 2 µg/ml) were more than one doubling dilution higher than the corresponding combined MIC_{90} values of 2 and 0.5 µg/ml, respectively.

Table 46: *In vitro* susceptibility to daptomycin of Infecting Pathogens at Baseline, Primary Comparative cSSSI Studies[a] (MITT population)

Pathogen[b]	N	Daptomycin Susceptibility (µg/mL)			
		Minimum	Maximum	MIC_{50}	MIC_{90}
Enterococcus faecalis (VSE)					
DAP-SST-9801	54			1	2
DAP-SST-9901	43			2	2
Combined	97			1	2
Staphylococcus aureus (MRSA)					
DAP-SST-9801	69			0.25	0.5
DAP-SST-9901	16			0.5	1
Combined	85			0.25	0.5
Staphylococcus aureus (MSSA)					
DAP-SST-9801	200			0.25	0.5
DAP-SST-9901	264			0.25	0.25
Combined	464			0.25	0.5
Staphylococcus aureus (total)					
DAP-SST-9801	269			0.25	0.5
DAP-SST-9901	280			0.25	0.25
Combined	549			0.25	0.5
Streptococcus agalactiae					
DAP-SST-9801	37			0.25	0.25
DAP-SST-9901	27			0.25	0.25
Combined	64			0.25	0.25
Streptococcus dysgalactiae equisimilis					
DAP-SST-9801	13			=0.03	0.06
DAP-SST-9901	10			0.06	0.06
Combined	23			0.06	0.06
Streptococcus pyogenes					
DAP-SST-9801	61			=0.03	0.06
DAP-SST-9901	114			=0.03	0.06
Combined	175			=0.03	0.06
Viridans Streptococci Group[c]					
DAP-SST-9801	29			0.5	0.5
DAP-SST-9901	28			0.5	1
Combined	57			0.5	1

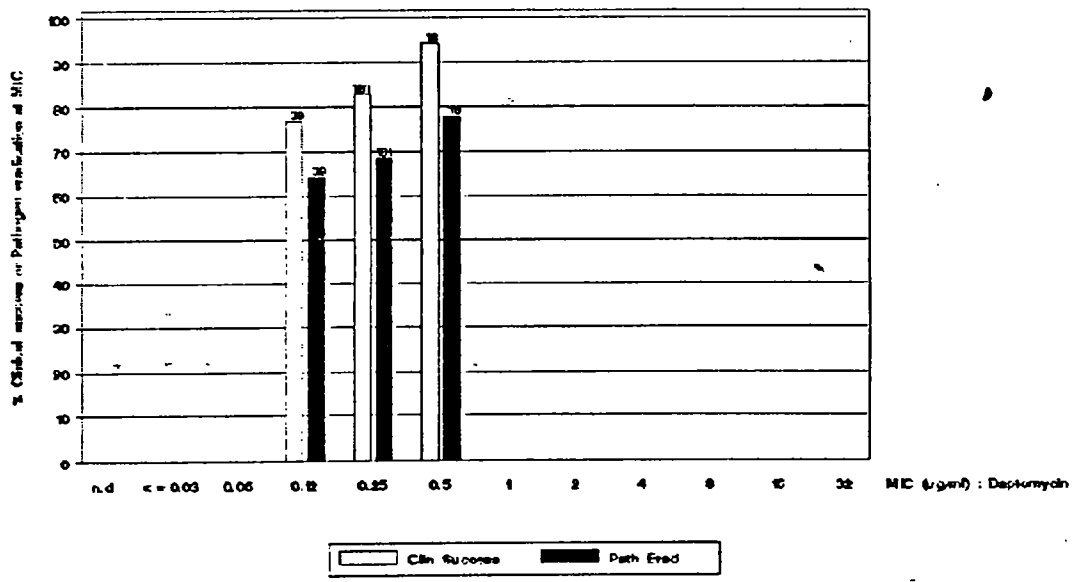
a. Restricted to Infecting Pathogens with susceptibility testing performed at the Central Laboratory.
b. Only pathogens for which an indication is being sought are shown; all geographic regions combined.
c. Three isolates were not tested by the Central Lab for susceptibility to daptomycin and are not included in this analysis.

A summary of clinical success and pathogen eradication rates by daptomycin MIC value for staphylolcocci, streptococci and *Enterococcus faecalis* can be found in Tables 8-23, 8-24, 8-25 and 8-26 of the Microbiology Section 8.6.14. These data are visually reflected in Figures 6, 8 and 10, which can found below.

The listing of daptomycin MIC values with clinical success and pathogen eradication for all *S. aureus* in the ME population at TOC is shown in Table 8-23 and Figure 6. The daptomycin MIC values ranged from 0.12 to 0.5 µg/ml in the daptomycin-treated subjects, and from 0.12 to 2 µg/ml in the comparator treated subjects. The Applicant states that "There was no correlation in the clinical success rate or pathogen eradication rate compared to MIC value for *S. aureus* (see Figure 6)". Figure 7 shows that the distribution of *S. aureus* MIC values for the daptomycin pooled treatment group isolates was similar to distribution for the combined SECURE surveillance isolates from skin.

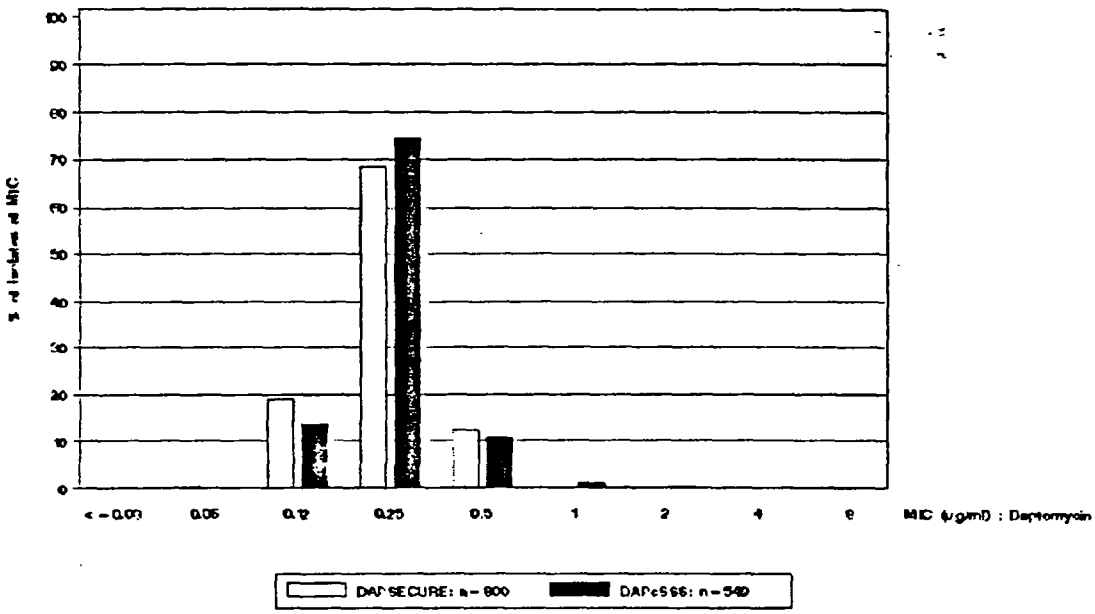
> ***Reviewer's comments:*** In fact, there seemed to be a trend as the clinical success rate and pathogen eradication rate increased compared to MIC value. MICs for both MSSA and MRSA were restricted to a range of 3 dilutions. Most isolates in both the clinical and surveillance studies demonstrated a MIC of 0.25µg/ml.

Figure 6: Bar chart[a] of percentage of clinical success and pathogen eradication at each daptomycin MIC for *Staphylococcus aureus* (total) from comparative cSSSI studies (ME subpopulation; Central Lab isolates; daptomycin-treated subjects)



[a] The number above each bar represents the number of subjects at the MIC (for clinical success) or the number of isolates at the MIC (for pathogen eradication)

Figure 7: Bar chart of percentage of isolates at each daptomycin MIC for *Staphylococcus aureus* (total) from comparative cSSSI studies [a] and isolates isolated from skin or skin structures from the SECURE surveillance studies



a All Baseline pathogens from subjects in the ITT subpopulation are included

The listing of daptomycin MIC values with clinical success and pathogen eradication for individual baseline *Streptococcus* spp. in the ME population at TOC is shown in Table 47 and the grouping of all baseline *Streptococcus* spp. into a single group is shown in Table 8-25. The daptomycin MIC values ranged from =0.03 to 1.0 µg/ml in the daptomycin and comparator treated subjects. There was no correlation in the clinical success rate or pathogen eradication rate compared to MIC value for *Streptococcus* spp. (see Figure 8). The majority of the isolates were *S. pyogenes*, which had a narrow MIC range (0.03 to 0.06 µg/ml). The broadest MIC range was observed in the viridans Streptococci group with a MIC range from 0.06 to 1 µg/ml. *S. pyogenes* was the most common streptococcal baseline pathogen. The distribution of MIC values in the combined SECURE surveillance studies for *S. pyogenes* and all of the *Streptococcus* spp. from skin or all sources were similar to the MIC values obtained in DAP-SST-9801 and DAP-SST-9901 (see Figure 9).

> ***Reviewer's comments:*** It should be noted that according to the data in Figure 9, more clinical isolates have lower MIC values than the surveillance isolates.

Table 47: Clinical Success Rates[a] and Pathogen Eradication Rates For Streptococcus Spp. by Daptomycin MIC of Infecting Pathogen at Baseline, Primary Comparative cSSSI Studies: Pooled Analysis (ME population)

Baseline Infecting Pathogen[b]	Daptomycin MIC (µg/ml)	Daptomycin Clinical Success		Daptomycin Pathogen Eradication		Comparator[c] Clinical Success		Comparator[c] Pathogen Eradication	
		n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Streptococcus agalactiae	0.06	---	---	---	---	1/1	(100.0%)	0/1	(0.0%)
	0.12	8/10	(80.0%)	7/10	(70.0%)	8/9	(88.9%)	6/9	(66.7%)
	0.25	13/15	(86.7%)	12/15	(80.0%)	13/19	(68.4%)	13/19	(68.4%)
	0.5	1/1	(100.0%)	1/1	(100.0%)	---	---	---	---
Streptococcus dysgalactiae equisimilis	≤0.03	4/4	(100.0%)	4/4	(100.0%)	4/4	(100.0%)	4/4	(100.0%)
	0.06	5/5	(100.0%)	5/5	(100.0%)	3/5	(60.0%)	3/5	(60.0%)
	0.12	---	---	---	---	---	---	---	---
	0.25	---	---	---	---	---	---	---	---
	0.5	---	---	---	---	1/1	(100.0%)	1/1	(100.0%)
Streptococcus pyogenes	≤0.03	59/64	(92.2%)	57/64	(89.1%)	67/75	(89.3%)	60/75	(80.0%)
	0.06	14/15	(93.3%)	13/15	(86.7%)	8/10	(80.0%)	7/10	(70.0%)
Viridans Streptococci Group[d]	ND[e]	---	---	0/1	(0.0%)	2/2	(100.0%)	2/2	(100.0%)
	0.06	---	---	---	---	---	---	0/1	(0.0%)
	0.12	3/5	(60.0%)	3/5	(60.0%)	---	---	1/1	(100.0%)
	0.25	1/3	(33.3%)	2/4	(50.0%)	7/9	(77.8%)	5/11	(45.5%)
	0.5	6/9	(66.7%)	7/10	(70.0%)	10/12	(83.3%)	12/14	(85.7%)
	1	3/3	(100.0%)	3/3	(100.0%)	6/7	(85.7%)	6/7	(85.7%)

a. Using Sponsor-Defined Clinical Outcome

b. Only Streptococcus spp. for which an indication is being sought are shown in this table; restricted to isolates with susceptibility testing performed at the central laboratory.

c. Semi-synthetic penicillin (oxacillin, nafcillin, cloxacillin, or flucloxacillin) or vancomycin.

d. For the Viridans Streptococci Group, Some subjects had two different Viridans Streptococci Group species at Baseline. N represents the number of subjects at each MIC; each pathogen is shown in the Pathogen Eradication column. The subject s Clinical Outcome is shown only once, assigned to the Baseline pathogen that is the least susceptible to daptomycin.

e. ND, Not determined; the isolates were received by the Central Lab, but the daptomycin MICs were not determined.

Figure 8. Bar chart[a] of percentage of clinical success and pathogen eradication at each daptomycin MIC for all Streptococci species[b,c] from comparative cSSSI studies (ME subpopulation; Central Lab isolates; daptomycin- treated subjects)

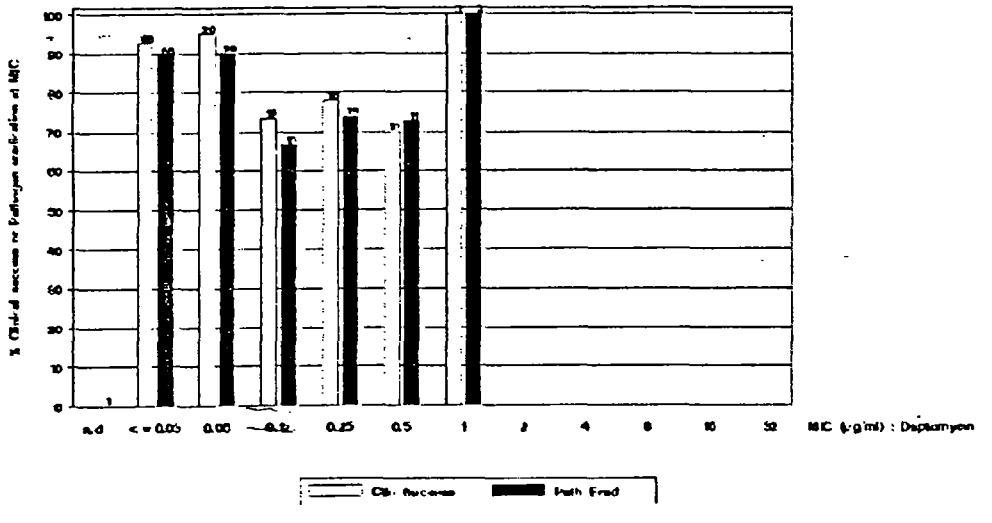
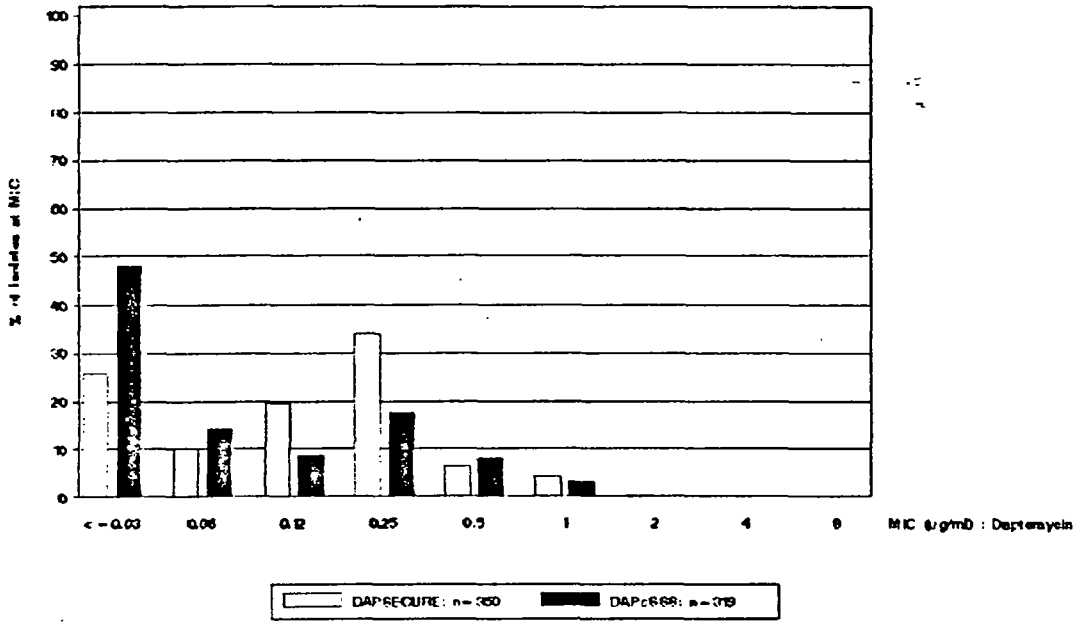


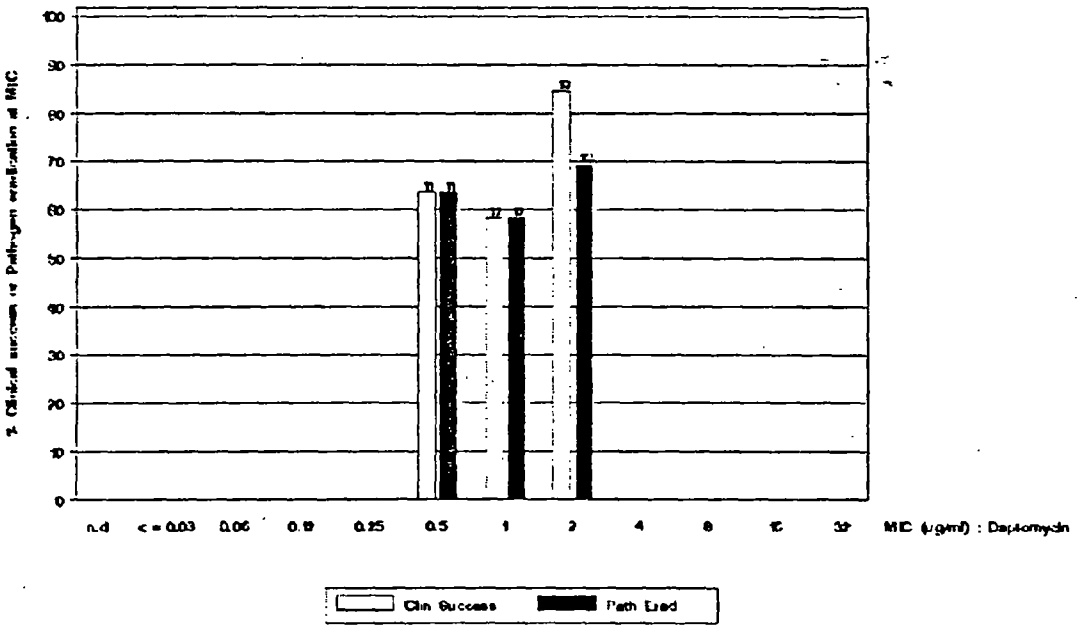
Figure 9: Bar chart of percentage of isolates at each daptomycin MIC for all Streptococci species [a] from comparative cSSSI studies [b, c] and isolates isolated from skin or skin structures from the SECURE surveillance studies



The listing of daptomycin MIC values with clinical success and pathogen eradication for all *E. faecalis* in the ME population at TOC is shown in Table 8-26 of the Microbiology Section. The daptomycin MIC values ranged from 0.5 to 2 µg/ml in the daptomycin-treated subjects, and from 0.12 to 8 µg/ml in the comparator treated subjects. There was no correlation in the clinical success rate or pathogen eradication rate compared to MIC value for *E. faecalis* (see Figure 10). For the daptomycin treated subjects, the *E. faecalis* MIC values were distributed nearly equally over three values (0.5 to 2 µg/ml). The daptomycin clinical success ranged from 58.3% to 84.6%, and the pathogen eradication was from 58.3% to 69.2%. In both cases, the highest success rates were obtained against the *E. faecalis* with the highest MIC value (2 µg/ml). The range of *E. faecalis* MIC values in the daptomycin-treated arm of DAP-SST-9801 and DAP-SST-9901 was slightly narrower than the MIC values produced in the combined SECURE studies, but the overall distribution was similar (see Figure 11).

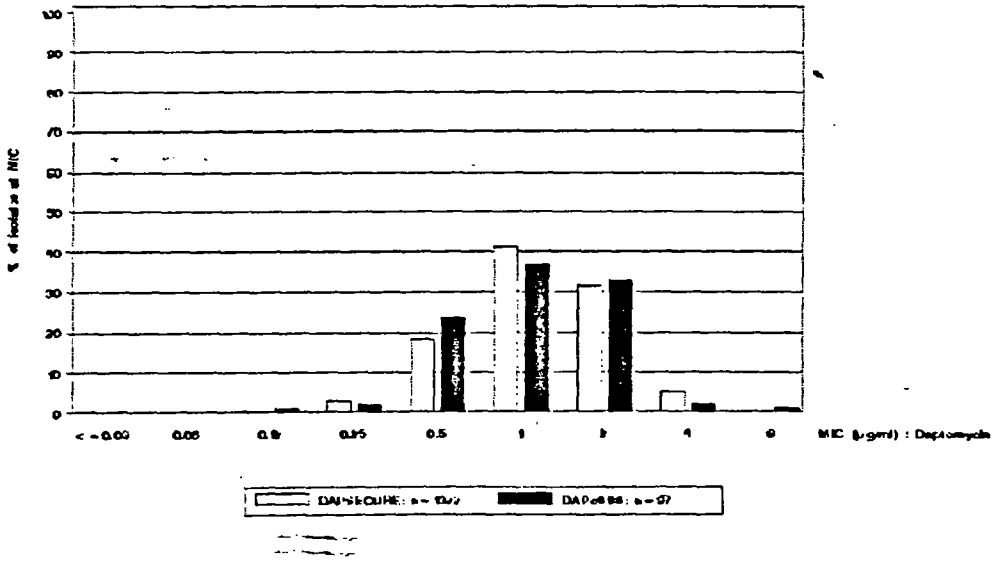
A series of tables containing data examining the correlation of daptomycin zone sizes with clinical success and pathogen eradication has been provided by the Applicant and can be found in Microbiology Section 8.6.15. These tables include Tables 8-27, 8-28, 8-29, 8-30, 10-90 and 10-91.

Figure 10. Bar chart [a] of percentage of clinical success and pathogen eradication at each daptomycin MIC for *Enterococcus faecalis* from comparative cSSSI studies (ME subpopulation; Central Lab isolates; daptomycin-treated subjects)



a The number above each bar represents the number of subjects at the MIC (for clinical success) or the number of isolates at the MIC (for pathogen eradication)

Figure 11: Bar chart of percentage of isolates at each daptomycin MIC for *Enterococcus faecalis* from comparative cSSSI studies [a] and isolates isolated from skin or skin structures from the SECURE surveillance studies



a All Baseline pathogens from subjects in the ITT subpopulation are included

A summary of daptomycin zone sizes correlated with clinical success rates and pathogen eradication rates for MRSA and MSSA in the ME population at TOC can be found in Table 8-27. The zone sizes and clinical success for all *S. aureus* combined are also displayed in Table 10-90. The zone sizes ranged from 16 mm to 25 mm in the daptomycin treated subjects, and from 17 mm to 26 mm in the comparator treated subjects. For MRSA, the daptomycin zone size was from 17 mm to 24 mm. The most prevalent zone sizes for MRSA were 19, 20, and 21 mm (22/30, 73% isolates). The clinical success rate ranged from 57.1% to 87.5% for these three zones, while the pathogen eradication rate ranged from 42.9% to 75.0%. The clinical success rates were 100% and 50% for the 2 smallest zones (17 and 18 mm, respectively), while the pathogen eradication rates were 100% and 25%, respectively. There was not a clear pattern of zone versus clinical outcome for MRSA.

For *S. aureus* MSSA, the most prevalent zone sizes were also 19, 20, and 21 mm (166/208, 80% of isolates). The clinical success rates ranged from 85.3% to 86.8% and the pathogen eradication rates ranged from 66.7% to 73.7% for MSSA of these three zone sizes. For the next three smaller zone sizes (16 - 18 mm), the clinical success rates were 75.0% to 100% (14/18, 78% overall), and the pathogen eradication rates were 69.2% to 100%(13/18, 72% overall). There was not a clear pattern of zone size versus clinical outcome for MSSA. Similar results were obtained with the combined results of MSSA and MRSA (see Table 10-90). The distribution of zone sizes was similar between the combined FOCUS Surveillance studies and clinical studies DAP-SST-9801 and DAP-SST-9901 (see Table 10-38 and Figure 10-27).

The listing of daptomycin zone sizes correlated with clinical success rates and pathogen eradication rates for *S. agalactiae* and *S. pyogenes* in the ME population at TOC is shown in Table 8-28. The *S. agalactiae* zone sizes ranged from 16 mm to 22 mm and the *S. pyogenes* zones ranged from 18 mm to 26 mm for daptomycin treated subjects. For both *S. agalactiae* and *S. pyogenes*, the clinical success and pathogen eradication rates were high for daptomycin treated subjects across all zone sizes. The one zone listing with a lower pathogen eradication rate was *S. agalactiae* 17 mm zone with a pathogen eradication rate of 40% (2/5). This result appeared to be an aberration, as the daptomycin treated pathogen eradication rates were higher for *S. agalactiae* in the zones immediately larger (18 mm) and smaller (16 mm). *S. pyogenes* was the most common *Streptococcus* spp. in trials 9801 and 9901, and daptomycin produced a high clinical success and pathogen eradication rate across all zone sizes. The zone size distribution was similar for the combined SECURE Surveillance studies and trials DAP-SST-9801 and DAP-SST-9901 for *S. pyogenes* (see Figure 10-32,Table 10-45 and Table 10-46) and *S. agalactiae* (see Figure 10-34, and Table 10-48).

The listing of daptomycin zone sizes with clinical success rates and pathogen eradication rates for *S. dysgalactiae* subsp. *Equisimilis (S. dysgalactiae)* and viridans streptococci group in the ME population at TOC is shown in Table 10-91 and Table 8-29. The *S. dysgalactiae* zone sizes ranged from 19 mm to 26 mm, and the viridans streptococci group zones ranged from 16 mm to 28 mm for daptomycin treated subjects. For *S. dysgalactiae*, the clinical success and pathogen eradication rates were 100% for daptomycin treated

subjects across all zone sizes. For the viridans streptococci group, the zone distribution was relatively large and the resulting N for any given zone was =3. The clinical success and pathogen eradication rates were 7/11 (64%) and 8/12 (67%), respectively, against viridans streptococci group with zone sizes =21 mm (the median value). The clinical success and pathogen eradication rates were 6/9 and 7/10 (70%), respectively, for viridans streptococci group with zone sizes =22 mm. Thus, there appeared to be no pattern of viridans streptococci zone size and clinical success or pathogen eradication. The zone size distribution was similar for the combined SECURE Surveillance studies and trials DAP-SST-9801 and DAP-SST-9901 for *S. dysgalactiae equisimilis* (see Figure 10-36, and Table 10-50) and the viridans streptococci group (see Figure 10-38, and Table 10-52).

A summary of the daptomycin-treated subjects who were therapeutic failures was examined for any trend or pattern corresponding to pathogen or MIC value. There was no apparent pattern of clinical failure, microbiologic failure and overall therapeutic failure with daptomycin MIC for *S. aureus*, the streptococci, or *E. faecalis*.

The correlation of daptomycin MIC results, zone size, and clinical outcome for daptomycin treated subjects is shown in the following scattergrams. The scattergrams are presented for *S. aureus*, the streptococci (combined) and *E. faecalis*. For each pathogen group, sets of two scattergrams are presented. The first shows the MIC and zone correlation for the clinical isolates from studies DAP-SST-9801 and DAP-SST-9901 combined. The second graph in each series shows the baseline infecting pathogens from therapeutic failures. The third graph in each series shows the baseline infecting pathogens from therapeutic failures. Therapeutic failures are defined as subjects who were sponsor- defined clinical failures or microbiological failures at TOC. Note that not all scattergrams are shown here and the reader is referred to Microbiology Section 8.6.17 for these scattergrams.

The scattergrams for *S. aureus* (Figures 12, 13, and 14) and the breakout of MRSA and MSSA (Figures 15, 16, 17, 18, 19, and 20) with proposed breakpoint MIC and zone sizes are provided. The MIC zone susceptibility for all *S. aureus* in the two clinical trials (see Figure 13), and the clinical failures (Figure 14) show the correlations. The *S. aureus* in the clinical trials are representative of the isolates encountered in the larger surveillance studies. The SECURE studies did report a small number of *S. aureus* isolates with MIC values of 1 µg/ml, while none were encountered in the clinical trials. For the *S. aureus* from the two clinical trials (see Figure 8-8), there was a narrow MIC zone range from 0.12 to 0.5 µg/ml, with the majority of the isolates at MIC = 0.25 µg/ml. There was a similar narrow distribution of zone sizes from 16 - 25 mm in these isolates. The distribution of *S. aureus* MIC and zone sizes for isolates that were therapeutic failures (Figure 14) was very similar to the overall MIC/zone distribution of *S. aureus* from the clinical studies. There was no clear correlation between MIC/zone distribution and therapeutic failure for *S. aureus* in the clinical trials. With the proposed zone and MIC susceptibility criteria, there was a minor error rate of 0.04% in the combined SECURE surveillance set of isolates and no errors in the cSSSI set of isolates.

Figure 12: Scattergram of daptomycin zone size versus MIC for *Staphylococcus aureus* isolated from skin or skin structures from the SECURE surveillance studies

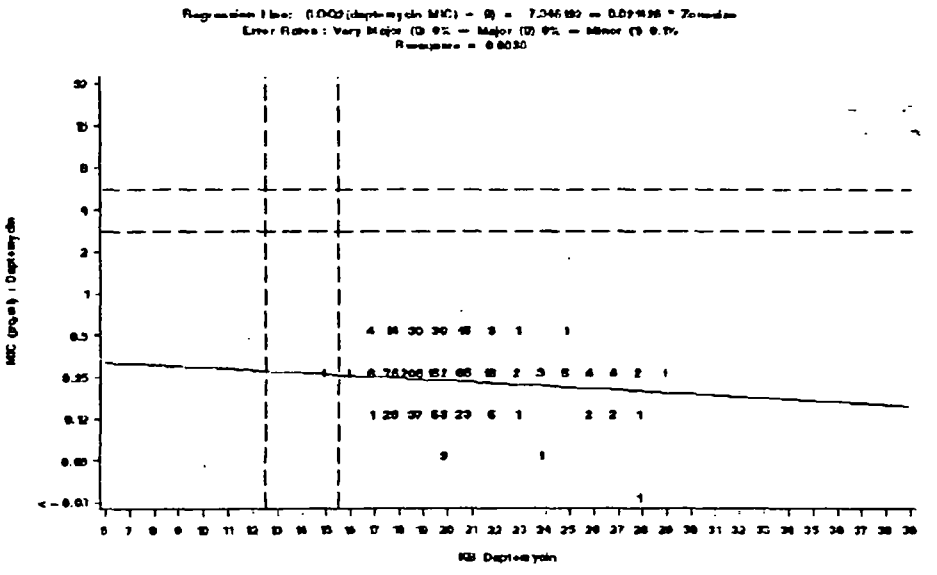


Figure 13. Scattergram of daptomycin zone size versus MIC for *Staphylococcus aureus* (total) from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin- treated subjects)

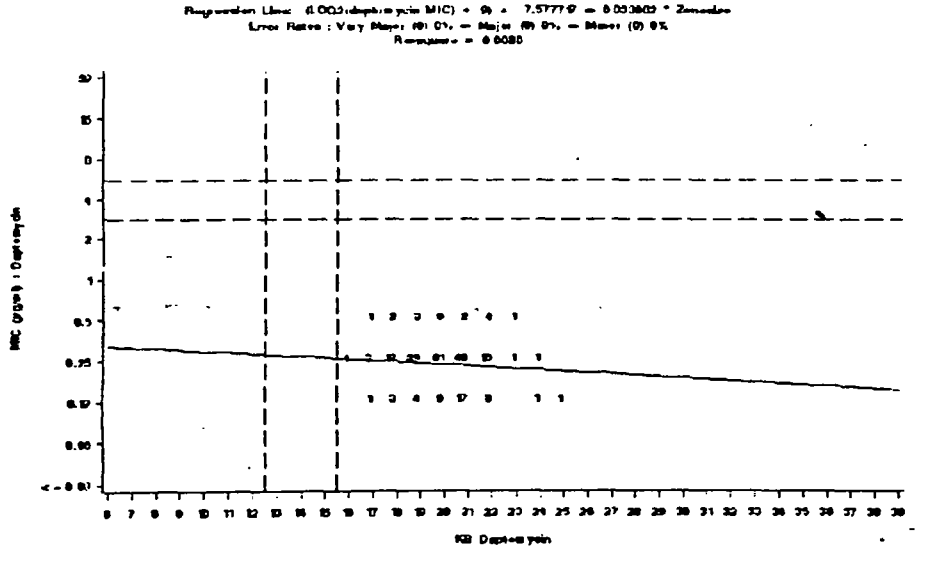


Figure 14. Scattergram of daptomycin zone size versus MIC for *Staphylococcus aureus* (total) from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin- treated subjects who were therapeutic failures)

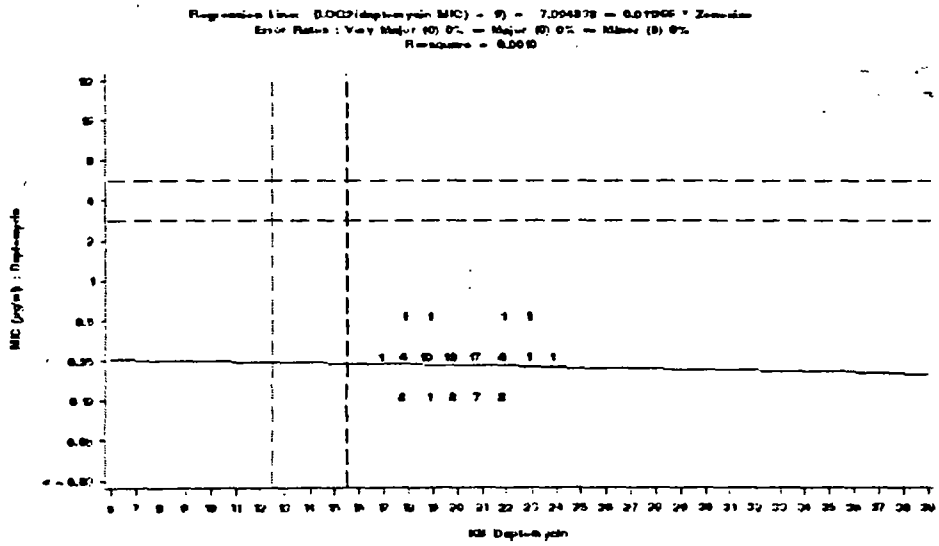


Figure 15: Scattergram of daptomycin zone size versus MIC for *Staphylococcus aureus* (MRSA) isolated from skin or skin structures from the SECURE surveillance studies

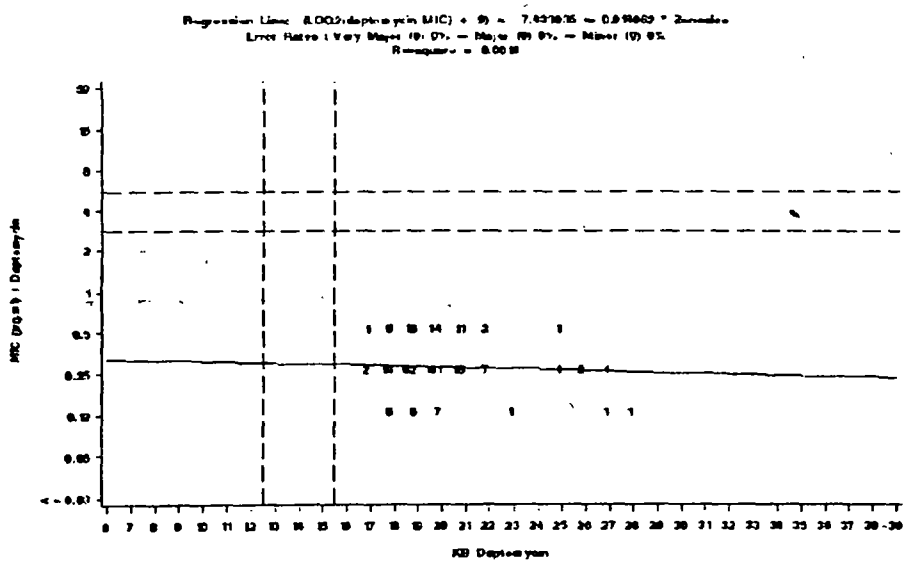


Figure 16: Scattergram of daptomycin zone size versus MIC for *Staphylococcus aureus* (MRSA) from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin-treated subjects)

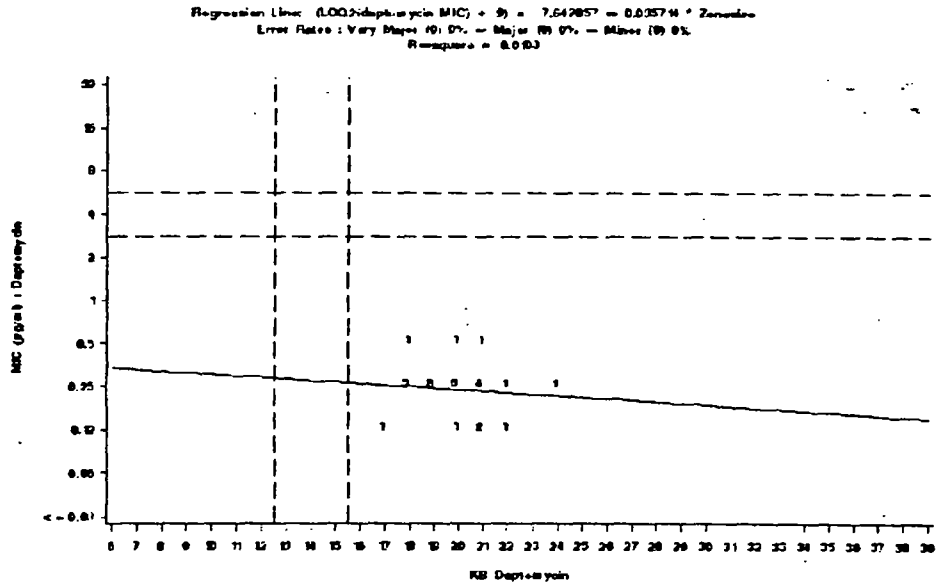


Figure 17: Scattergram of daptomycin zone size versus MIC for *Staphylococcus aureus* (MRSA) from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin-treated subjects who were therapeutic failures)

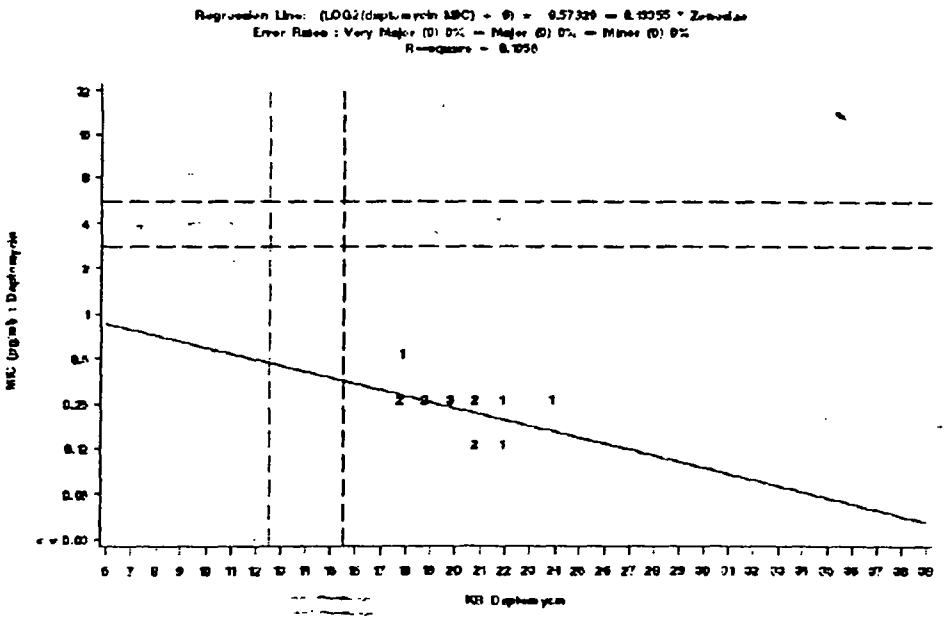


Figure 18: Scattergram of daptomycin zone size versus MIC for *Staphylococcus aureus* (MSSA) isolated from skin or skin structures from the SECURE surveillance studies

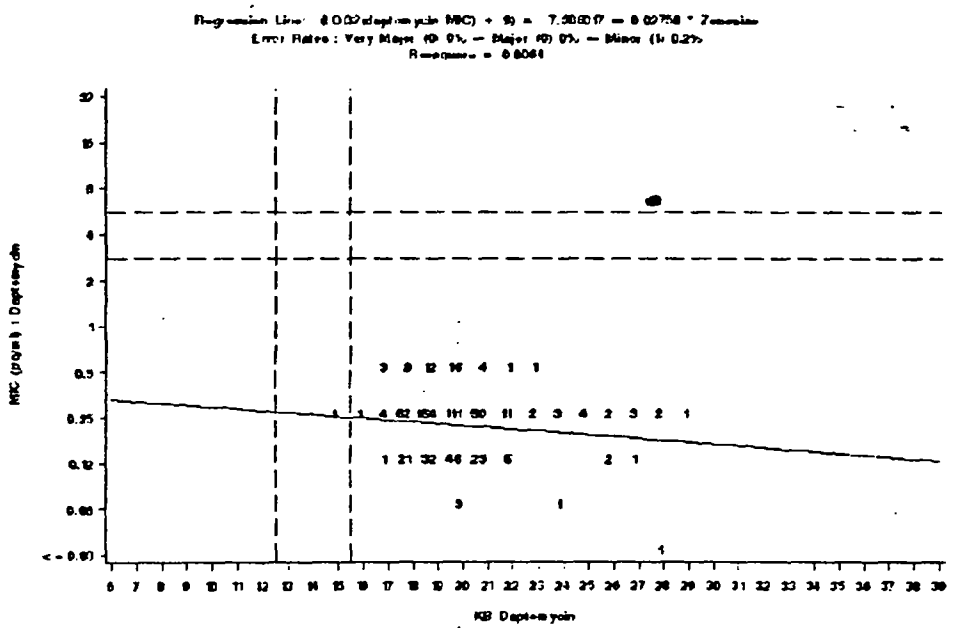


Figure 19: Scattergram of daptomycin zone size versus MIC for *Staphylococcus aureus* (MSSA) from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin-treated subjects)

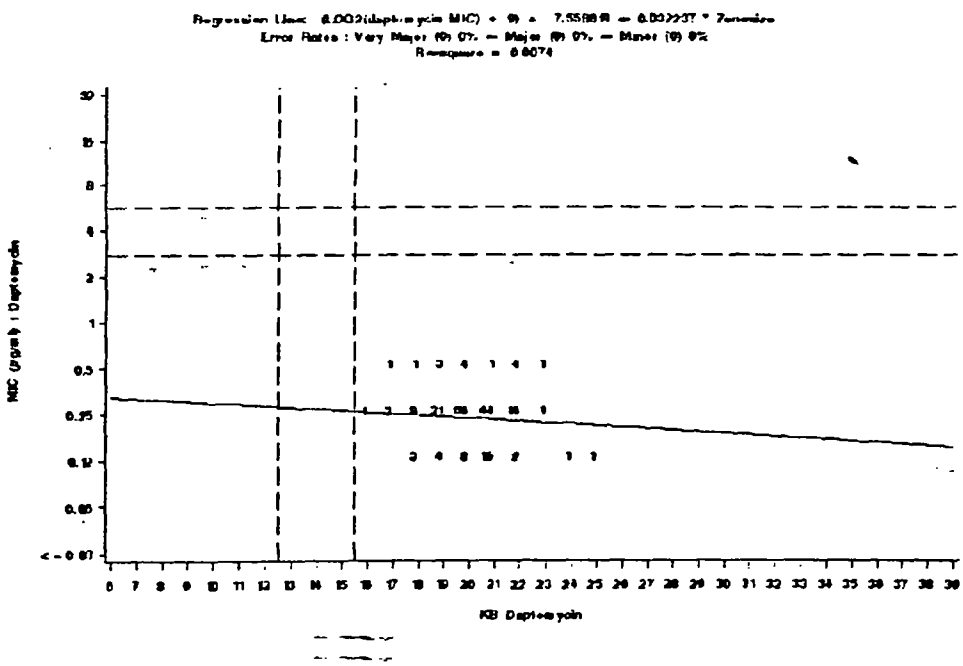
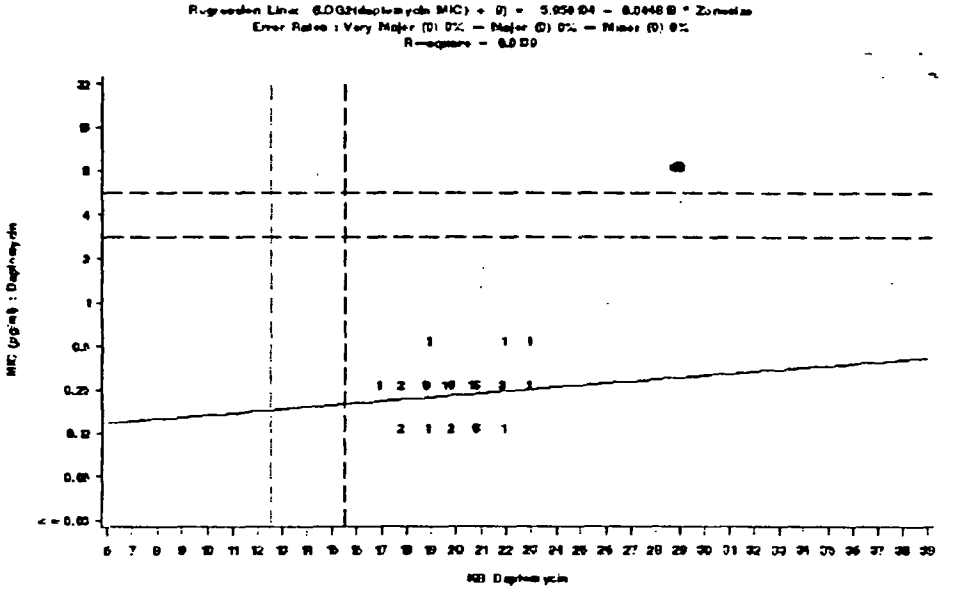


Figure 20: Scattergram of daptomycin zone size versus MIC for *Staphylococcus aureus* (MSSA) from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin-treated subjects who were therapeutic failures)



The MIC/zone correlations for the streptococci are presented both individually and as a single grouping. It is intended to unify the streptococci under one set of breakpoint values for daptomycin. Each of the streptococci will be presented individually, with a unification of all four species presented in the section on breakpoints to follow in Figure 32, Figure 33, and Figure 34.

The MIC and zone sizes for *S. pyogenes* encountered in the two clinical trials DAP-SST-9801 and DAP-SST-9901 were similar to the values determined in the SECURE surveillance studies (Figure 21 and Figure 22). In the clinical trials, the MIC values for *S. pyogenes* were very narrow and ranged from =0.03 to 0.06 µg/ml. The zone distribution of 18 to 26 mm was relatively larger. The correlation and MIC/zone distribution for the few (N = 14) *S. pyogenes* isolates that failed therapy (see Figure 23) is similar to the overall MIC/zone distribution of isolates in the clinical trials and even tended towards the lower MIC value. There was no clear correlation between MIC/zone distribution and therapeutic failure for *S. pyogenes* in the clinical trials.

Figure 21: Scattergram of daptomycin zone size versus MIC for *Streptococcus pyogenes* isolated from skin or skin structures from the SECURE surveillance studies

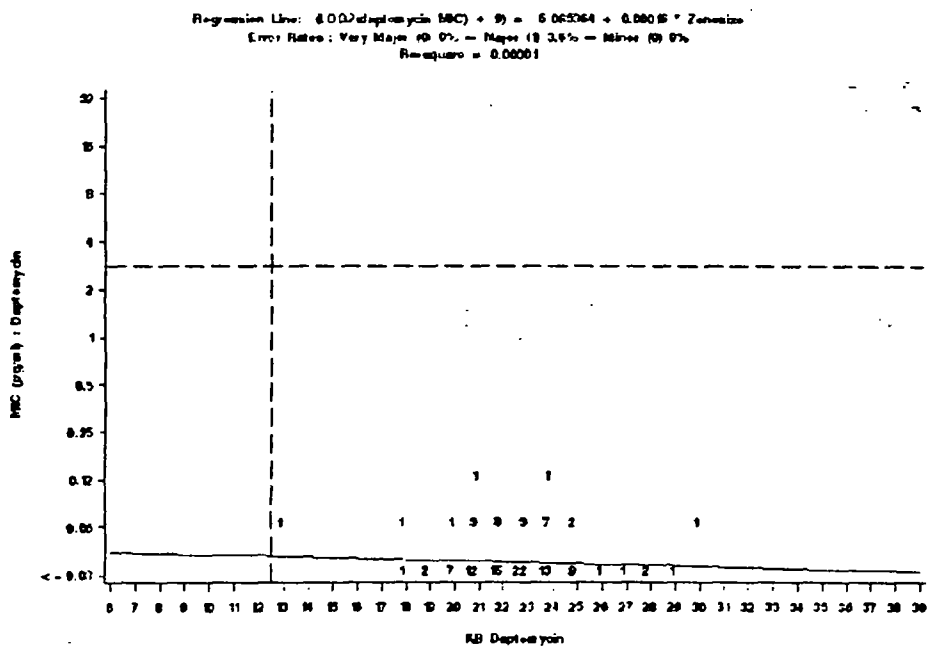


Figure 22: Scattergram of daptomycin zone size versus MIC for *Streptococcus pyogenes* from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin-treated subjects)

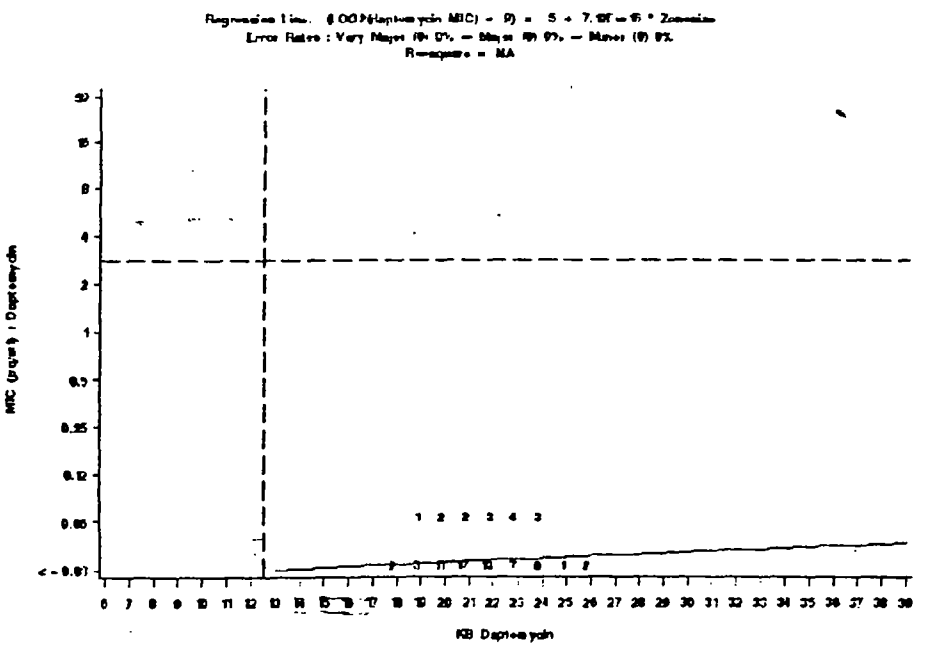
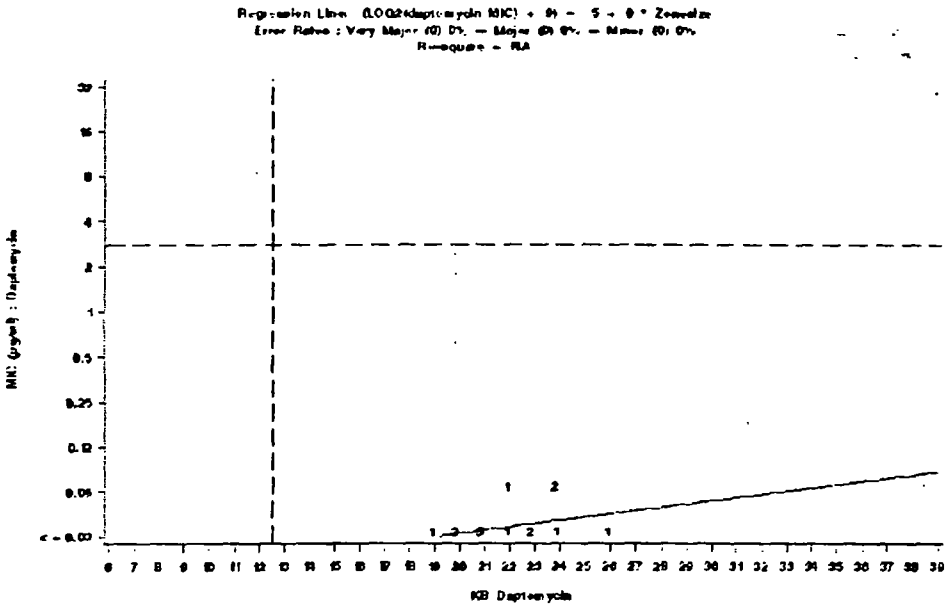


Figure 23: Scattergram of daptomycin zone size versus MIC for *Streptococcus pyogenes* from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin-treated subjects who were therapeutic failures)



The MIC and zone sizes for *S. agalactiae* treated in the two clinical trials DAP-SST-9801 and DAP-SST-9901 were similar to the values determined in the SECURE surveillance studies (Figure 24 and Figure 25). In the clinical trials, the MIC values for *S. agalactiae* were relatively large and ranged from 0.12 to 0.5 µg/ml (see Figure 25). The zone distribution of 16 to 22 mm is also similar to the SECURE studies. The correlation and MIC/zone distribution for the few (N = 7) *S. agalactiae* isolates that failed therapy (see Figure 10-62) is similar to the overall MIC/zone distribution of isolates in DAP-SST-9801 and DAP-SST-9901. For *S. agalactiae*, there was no clear correlation between MIC/zone distribution and therapeutic failure in the clinical trials.

The MIC and zone distribution for *S. dysgalactiae equisimilis* isolates from a separate directed study can be found in Table 10-49 and Table 10-50 (not shown here). This study was not part of the SECURE surveillance, but rather was a retrospective study of MIC distributions against a collection of *S. dysgalactiae.* The MIC and zone sizes for *S. dysgalactiae* encountered in the two clinical trials DAP-SST-9801 and DAP-SST-9901 are shown in Figure 27. In the clinical trials, the MIC values for *S. dysgalactiae* were very narrow and ranged from =0.03 to 0.06 µg/ml. The zone distribution of 19 to 26 mm was relatively larger. There was only one isolate of *S. dysgalactiae* that was a therapeutic failure (Figure 28). Due to the lack of therapeutic failures, it is not possible to draw a correlation between MIC/zone distribution and therapeutic failure in clinical trials.

Figure 24: Scattergram of daptomycin zone size versus MIC for *Streptococcus agalactiae* isolated from skin or skin structures from the SECURE surveillance studies

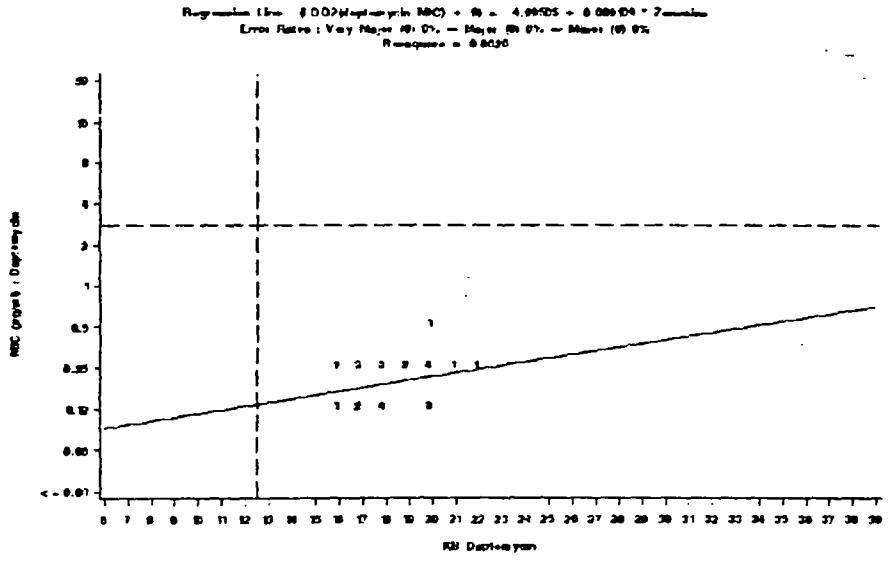


Figure 25: Scattergram of daptomycin zone size versus MIC for *Streptococcus agalactiae* from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin-treated subjects)

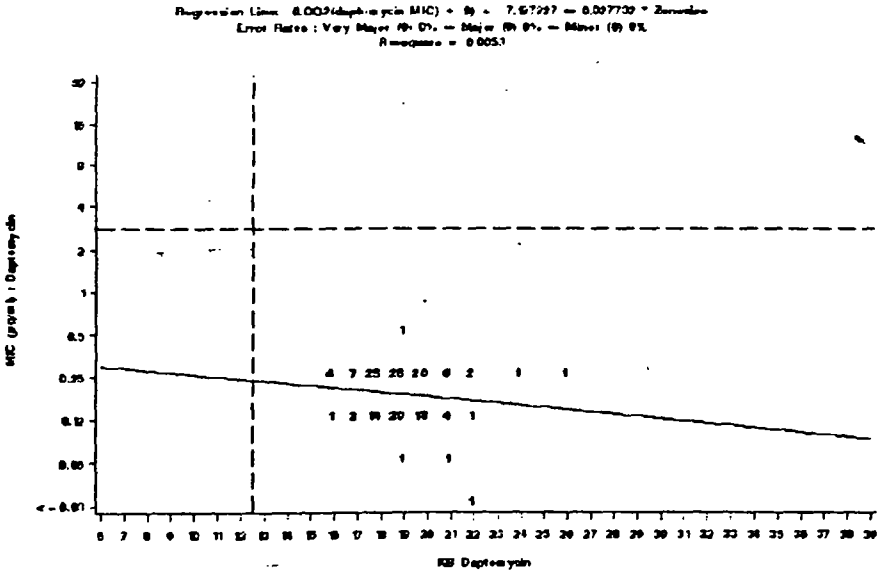


Figure 26: Scattergram of daptomycin zone size versus MIC for *Streptococcus agalactiae* from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin-treated subjects who were therapeutic failures)

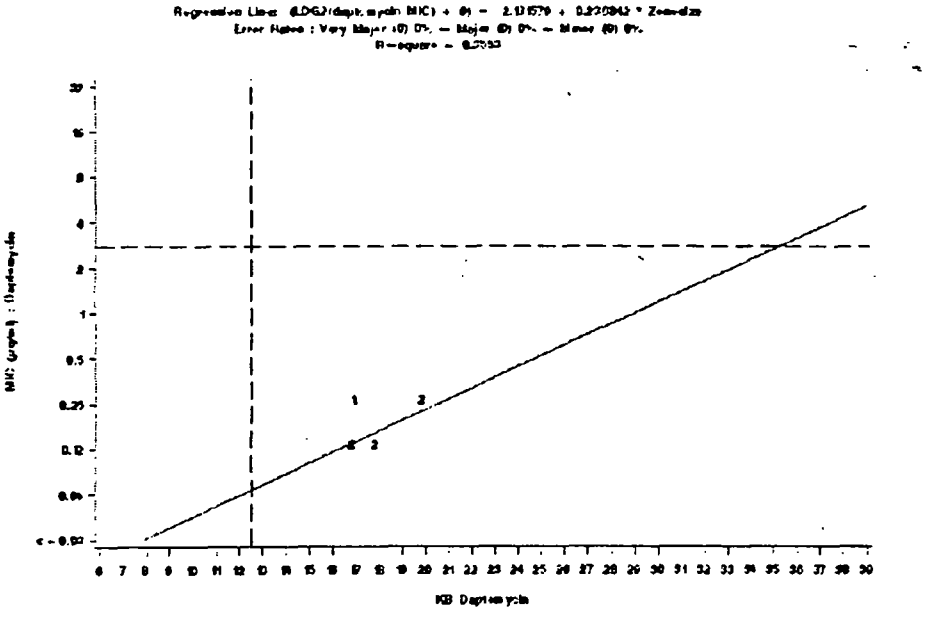


Figure 27: Scattergram of daptomycin zone size versus MIC for *Streptococcus dysgalactiae equisimilis* from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin-treated subjects)

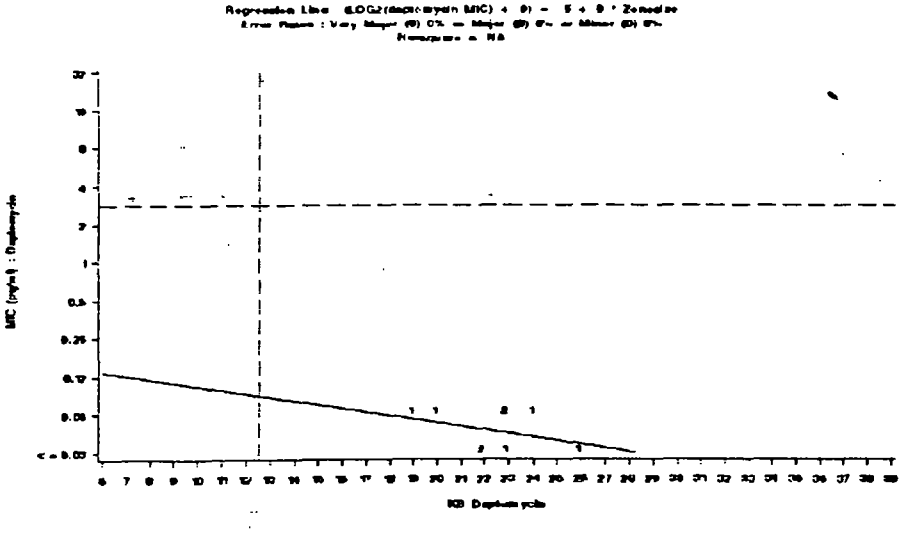
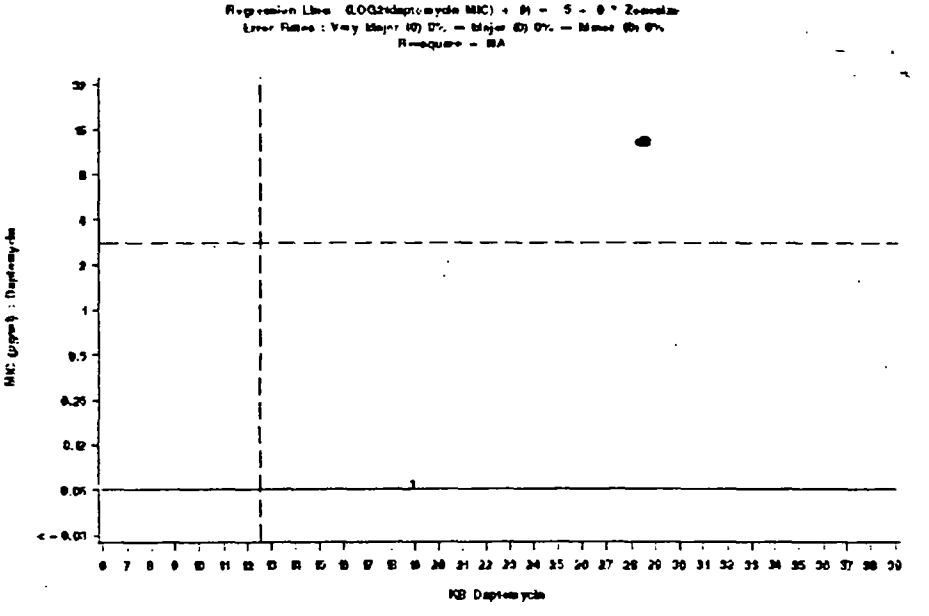


Figure 28: Scattergram of daptomycin zone size versus MIC for *Streptococcus dysgalactiae equisimilis* from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin-treated subjects who were therapeutic failures)



The MIC and zone sizes for viridans streptococci from the two clinical trials DAP-SST-9801 and DAP-SST-9901 were similar to the values determined in the SECURE surveillance studies (Figure 29). In the clinical trials, the MIC values for viridans streptococci were relatively broad and ranged from 0.12 to 1 µg/ml (Figure 30). The daptomycin zone distribution of 16 to 28 mm was the largest for any Gram-positive pathogen the clinical trials. The correlation of MIC/zone distribution for the viridans streptococci isolates that failed therapy (see Figure 31) is similar to the overall MIC/zone distribution of isolates in the clinical trials. There was no clear correlation between MIC/zone distribution and therapeutic failure for viridans streptococci in clinical trials.

The scattergrams for all baseline pathogen streptococci for which an indication is being requested are shown in Figure 32, Figure 33, and Figure 34. The MIC and zone sizes for streptococci from the two clinical trials DAP-SST-9801 and DAP-SST-9901 were similar to the values determined in the SECURE surveillance studies. In the clinical trials, the MIC values for streptococci were relatively broad due to the viridans streptococci group and ranged from =0.03 to 1 µg/ml (see Figure 33). The cumulative daptomycin zone distribution for these streptococci groups was 16 to 28 mm. The correlation of MIC/zone distribution for the streptococci isolates that failed therapy (see Figure 34) is similar to the overall MIC/zone distribution of isolates in clinical trials (see Figure 33). There was no clear correlation between MIC/zone distribution and therapeutic failure for all Streptococcus spp. in clinical trials.

Figure 29: Scattergram of daptomycin zone size versus MIC for Viridans Streptococci Group isolated from skin or skin structures from the SECURE surveillance studies

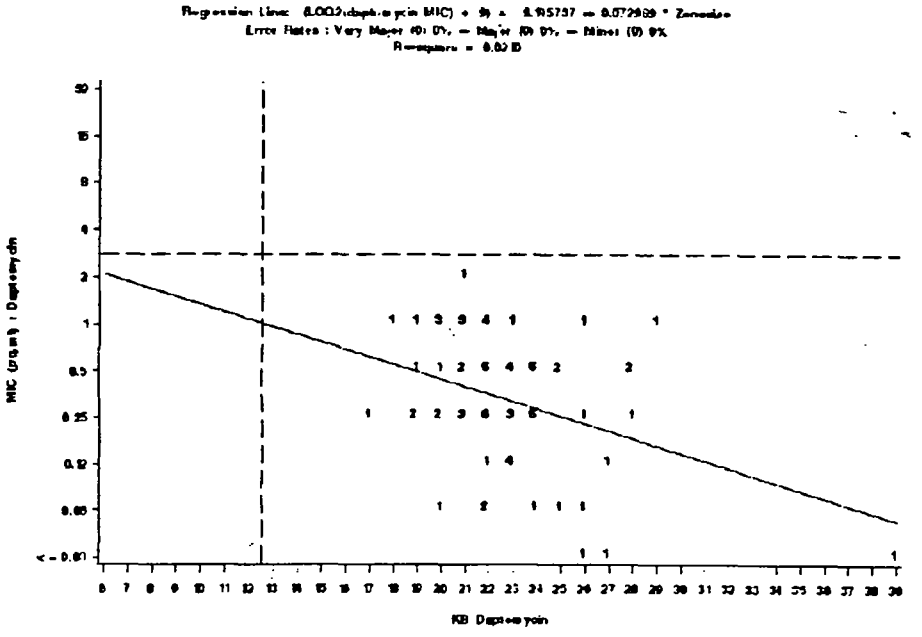
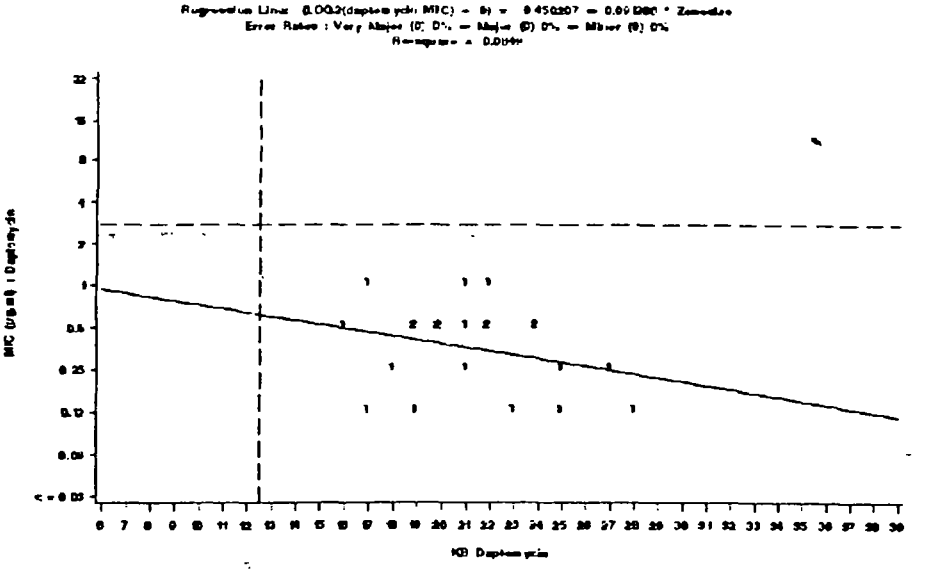
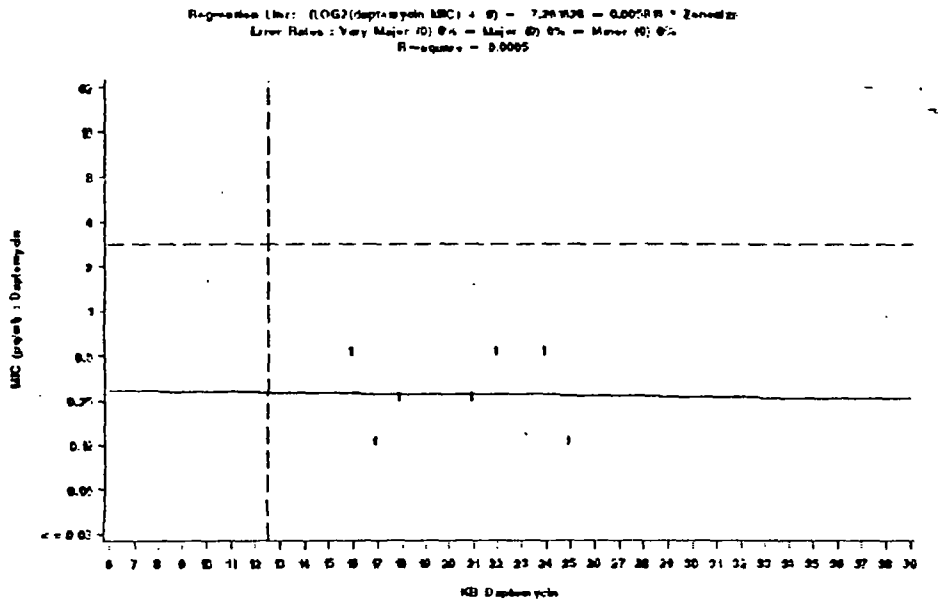


Figure 30: Scattergram of daptomycin zone size versus MIC for Viridans Streptococci Group from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates [a]; daptomycin-treated subjects)



[a] Only those Central Lab isolates tested for susceptibility to daptomycin are included

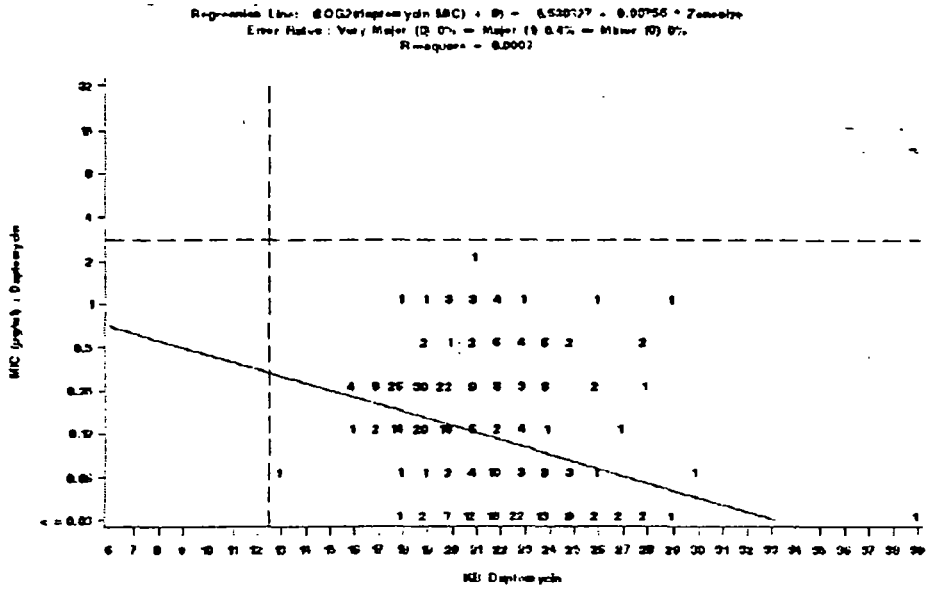
Figure 31: Scattergram of daptomycin zone size versus MIC for Viridans Streptococci Group from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates [a]; daptomycin-treated subjects who were therapeutic failures).



a Only those Central Lab isolates tested for susceptibility to daptomycin are included

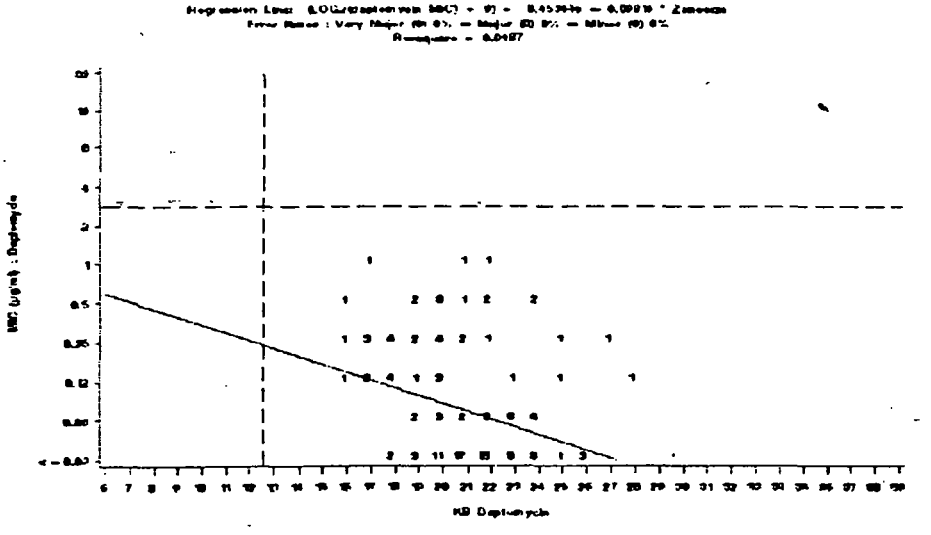
The scattergrams for all baseline pathogen streptococci for which an indication is being requested are shown in Figure 32, Figure 33, and Figure 34. The MIC and zone sizes for streptococci from the two clinical trials DAP-SST-9801 and DAP-SST-9901 were similar to the values determined in the SECURE surveillance studies. In the clinical trials, the MIC values for streptococci were relatively broad due to the viridans streptococci group and ranged from =0.03 to 1 µg/ml (see Figure 33). The cumulative daptomycin zone distribution for these streptococci groups was 16 to 28 mm. The correlation of MIC/zone distribution for the streptococci isolates that failed therapy (see Figure 34) is similar to the overall MIC/zone distribution of isolates in the clinical trials (see Figure 33). There was no clear correlation between MIC/zone distribution and therapeutic failure for all Streptococcus spp. in the clinical trials.

Figure 32: Scattergram of daptomycin zone size versus MIC for *Streptococcus* spp. [a] isolated from skin or skin structures from the SECURE surveillance studies [b]



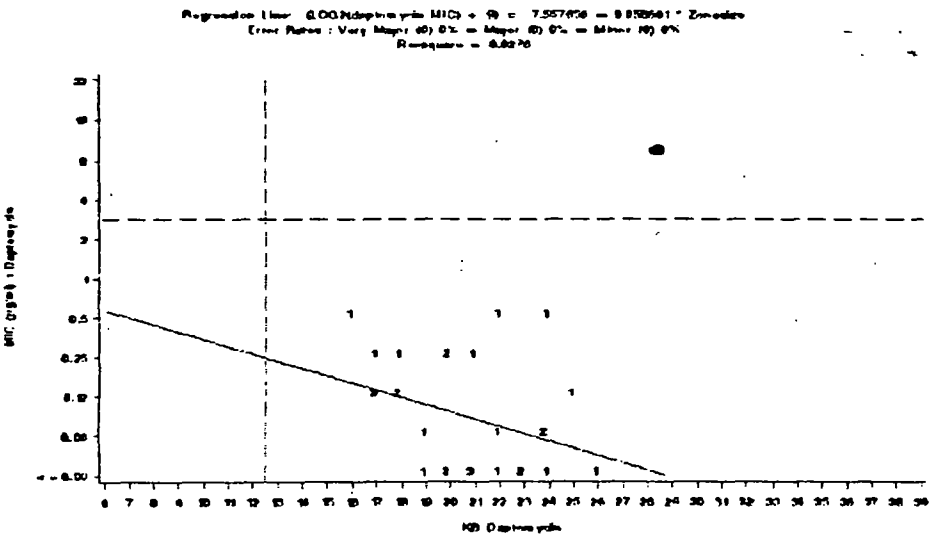
a Only *Streptococcus* species for which an indication is being sought are included.
b There were no isolates of *S. dysgalactiae equisimilis* tested in the SECURE surveillance studies.

Figure 33: Scattergram of daptomycin zone size versus MIC for *Streptococcus* spp. [a] from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates [b]; daptomycin-treated subjects)



a Only *Streptococcus* species for which an indication is being sought are included.
b Only those Central Lab isolates tested for susceptibility to daptomycin are included.

Figure 34: Scattergram of daptomycin zone size versus MIC for *Streptococcus* spp. [a] from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin-treated subjects who were therapeutic failures)



The scattergrams for *E. faecalis* are shown in Figure 35, Figure 36, and Figure 37. The MIC and zone sizes for *E. faecalis* in the two clinical trials DAP-SST-9801 and DAP-SST-9901 were similar to the values determined in the SECURE surveillance studies. However, the SECURE studies yielded 68 skin and skin structure *E. faecalis* isolates of MIC ≥ 4 µg/ml, (see Figure 35) while the clinical trials had no *E. faecalis* with MIC > 2 µg/ml in the daptomycin treated arm. In the clinical trials, the MIC values for *E. faecalis* ranged from 0.5 to 2 µg/ml and the zone distribution of 15 to 22 mm (see Figure 36). The correlation and MIC/zone distribution for the *E. faecalis* isolates that failed therapy (see Figure 37) is similar to the overall MIC/zone distribution of isolates in the clinical trials (Figure 36). For *E. faecalis*, there was no clear correlation between MIC/zone distribution and therapeutic failure in the clinical trials.

Figure 35: Scattergram of daptomycin zone size versus MIC for *Enterococcus faecalis* isolated from skin or skin structures from the SECURE surveillance studies

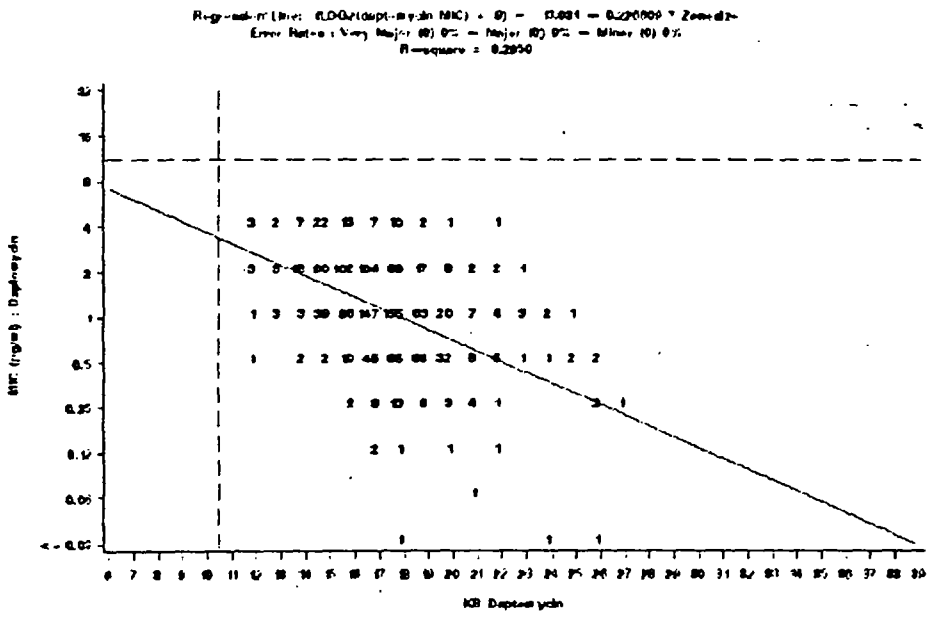


Figure 36: Scattergram of daptomycin zone size versus MIC for *Enterococcus faecalis* from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin-treated subjects)

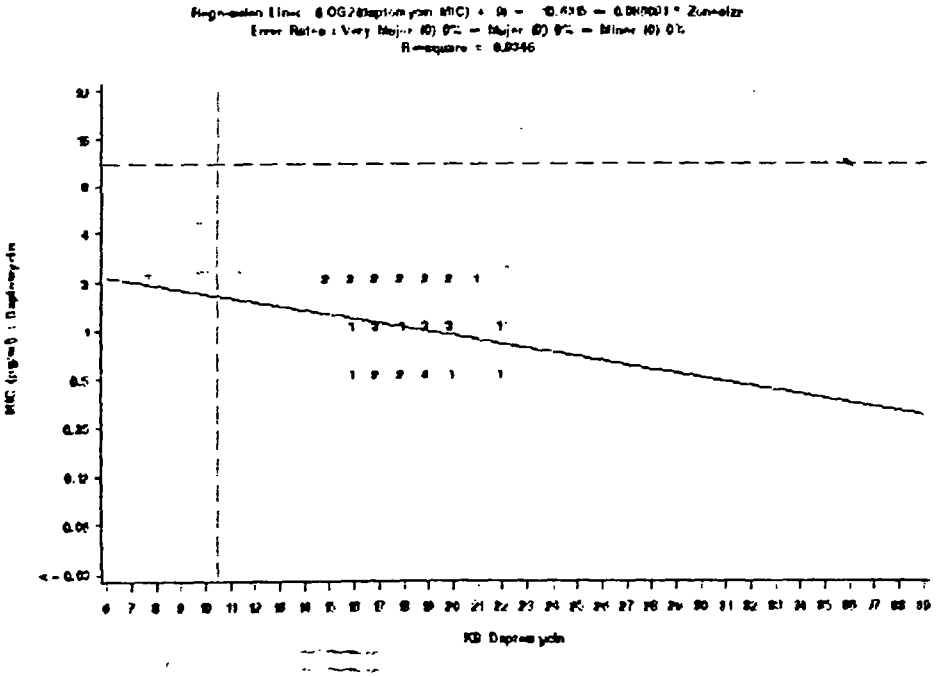


Figure 37: Scattergram of daptomycin zone size versus MIC for *Enterococcus faecalis* from the comparative cSSSI studies (Baseline pathogens; ME subpopulation; Central Lab isolates; daptomycin-treated subjects who were therapeutic failures)

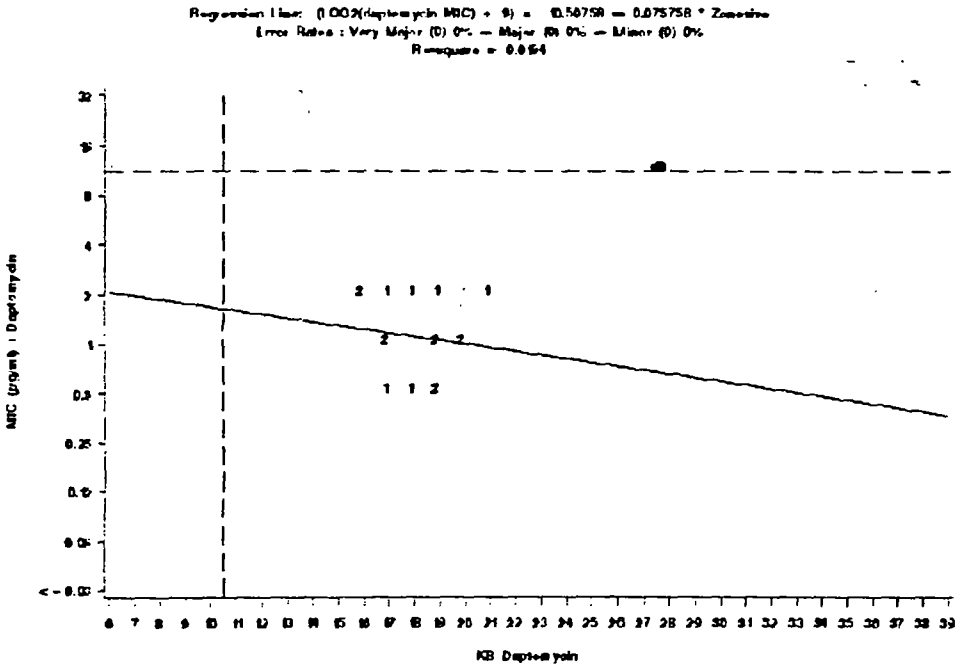


Table 48: Therapeutic failure rates to baseline daptomycin MIC for *Staphylococcus aureus* and *Enterococcus faecalis* (ME subpopulation; Central Lab isolates; daptomycin-treated subjects) at test-of-cure[a] for comparative cSSSI studies

Pathogen	Baseline Daptomycin MIC (µg/ml)	N	Clinical Failures		Microbiological Failures[b]		Therapeutic Failures[c]	
Staphylococcus aureus (MRSA)	0.12	5	1/5	(20.0%)	2/4	(50.0%)	3/5	(60.0%)
	0.25	22	8/22	(36.4%)	3/14	(21.4%)	11/22	(50.0%)
	0.5	3	0/3	(0.0%)	1/3	(33.3%)	1/3	(33.3%)
Staphylococcus aureus (MSSA)	0.12	34	8/34	(23.5%)	3/26	(11.5%)	11/34	(32.4%)
	0.25	159	23/159	(14.5%)	23/136	(16.9%)	46/159	(28.9%)
	0.5	15	1/15	(6.7%)	2/14	(14.3%)	3/15	(20.0%)
Staphylococcus aureus (total)	0.12	39	9/39	(23.1%)	5/30	(16.7%)	14/39	(35.9%)
	0.25	181	31/181	(17.1%)	26/150	(17.3%)	57/181	(31.5%)
	0.5	18	1/18	(5.6%)	3/17	(17.6%)	4/18	(22.2%)
Enterococcus faecalis (VSE)	0.5	11	4/11	(36.4%)	0/7	(0.0%)	4/11	(36.4%)
	1	12	5/12	(41.7%)	1/7	(14.3%)	6/12	(50.0%)
	2	13	2/13	(15.4%)	4/11	(36.4%)	6/13	(46.2%)

a. Test-of-cure analysis was based on data collected from Day 6P to Day 20P.
b. A Microbiological Outcome is assigned only to a pathogen associated with a subject who is a Clinical Success.
c. A Therapeutic Failure is defined as a pathogen associated with a subject that was either a Clinical Failure or a Microbiological Failure.

Table 49: Therapeutic failure rates to baseline daptomycin MIC for *Streptococcus* spp.[a] (ME subpopulation; Central Lab isolates; daptomycin-treated subjects) at test-of-cure[b] for comparative cSSSI studies

Pathogen	Baseline Daptomycin MIC (µg/ml)	N	Clinical Failures		Microbiological Failures[c]		Therapeutic Failures[d]	
Streptococcus agalactiae	0.12	10	2/10	(20.0%)	2/8	(25.0%)	4/10	(40.0%)
	0.25	15	2/15	(13.3%)	1/13	(7.7%)	3/15	(20.0%)
	0.5	1	0/1	(0.0%)	0/1	(0.0%)	0/1	(0.0%)
Streptococcus dysgalactiae equisimilis	≤0.03	4	0/4	(0.0%)	0/4	(0.0%)	0/4	(0.0%)
	0.06	5	0/5	(0.0%)	1/5	(20.0%)	1/5	(20.0%)
Streptococcus pyogenes	≤0.03	64	5/64	(7.8%)	6/59	(10.2%)	11/64	(17.2%)
	0.06	15	1/15	(6.7%)	2/14	(14.3%)	3/15	(20.0%)
Viridans Streptococci Group[e]	0.12	5	2/5	(40.0%)	0/3	(0.0%)	2/5	(40.0%)
	0.25	3	2/3	(66.7%)	0/1	(0.0%)	2/3	(66.7%)
	0.5	9	3/9	(33.3%)	0/6	(0.0%)	3/9	(33.3%)
	1	3	0/3	(0.0%)	0/3	(0.0%)	0/3	(0.0%)
All Streptococci[e]	≤0.03	68	5/68	(7.4%)	6/63	(9.5%)	11/68	(16.2%)
	0.06	20	1/20	(5.0%)	3/19	(15.8%)	4/20	(20.0%)
	0.12	15	4/15	(26.7%)	2/11	(18.2%)	6/15	(40.0%)
	0.25	18	4/18	(22.2%)	1/14	(7.1%)	5/18	(27.8%)
	0.5	10	3/10	(30.0%)	0/7	(0.0%)	3/10	(30.0%)
	1	3	0/3	(0.0%)	0/3	(0.0%)	0/3	(0.0%)

a. Only *Streptococcus* spp. for which an indication is being sought are included in this analysis.
b. Test-of-cure analysis was based on data collected from Day 6P to Day 20P.
c. A Microbiological Outcome is assigned only to a pathogen associated with a subject who is a Clinical Success.
d. A Therapeutic Failure is defined as a pathogen associated with a subject that was either a Clinical Failure or a Microbiological Failure.
e. Some subjects had two different infecting pathogens from this grouping at Baseline. The subject s outcome is shown only once, assigned to the Baseline pathogen that is the least susceptible to daptomycin.

Reviewer's comments: The therapeutic failure rates for MRSA and *Enterococcus faecalis* were rather high at ≥40% for most of the daptomycin MICs (see Table 48). Table 49 shows the therapeutical failure rates to daptomycin MIC for all *Streptococcus* spp. tested. Note the high therapeutic failure rates (≥30%) for *Streptococcus agalactiae* (MIC=0.12 µg/ml) and for Viridans Streptococci (MIC=0.12-0.5 µg/ml).

ESTABLISHMENT OF *IN VITRO* SUSCEPTIBILITY TESTING INTERPRETIVE CRITERIA

Interpretive criteria for *in vitro* susceptibility testing are presented for three sets of organisms:

- *S. aureus* including both MSSA and MRSA.
- Streptococci, representing the most prevalent species encountered in DAP-SST-9801 and DAP-SST-9901, specifically *S. agalactiae, S. dysgalactiae equisimilis, S. pyogenes,* and the viridans streptococci group, which consists of *S. anginosus, S. mitis, S. oralis, S. sanguis, S. salivarius, S. intermedius, S. constellatus, S. mutans,* and *S. bovis.*
- *E. faecalis* (vancomycin susceptible isolates only)

The susceptibility criterion for each of the three pathogen groupings is based on:

- Surveillance results and clinical susceptibilities
- Pharmacodynamics in animals
- Human pharmacokinetics
- Monte Carlo analysis (human pharmacokinetics and surveillance variables applied to a pharmacodynamic standard)
- Clinical results and failure analysis

Breakpoint discussion for *Staphylococcus aureus*

In surveillance studies, the overwhelming majority of *S. aureus* isolates fall in the MIC range of 0.12 to 0.5 µg/ml. There are a few isolates in both the SECURE studies and the cSSSI clinical trials with MIC values of 1 or 2 µg/ml (see Microbiology section 8.6.19.1). Overall, the distributions of the MIC values for *S. aureus* were similar between the two clinical trials and the SECURE surveillance studies. The MIC distribution profiles for *S. aureus* are unimodal, with no distinct secondary population. The MIC distributions of *S. aureus* MRSA and MSSA are similar, with MIC_{50} values of 0.25 µg/ml, and MIC_{90} values of 0.25 to 0.5 µg/ml. While the daptomycin MIC_{90} value for *S. aureus* was 0.5 µg/ml in the two SECURE studies, two smaller studies reported daptomycin MIC_{90} values of 1 µg/ml [16, 77]. A total of eight studies including five surveillance [66, 67, 69, 70, 74] and three retrospective [16, 63, 77] collections of *S. aureus* observed daptomycin values of 1 µg/ml. The frequency of *S. aureus* isolates with MIC values of 1 µg/ml was 4.9% (153/3092) in these combined eight studies. *In vitro* studies of GISA isolates have confirmed the potency and bactericidal activity of daptomycin, but these isolates did include a higher proportion with MIC of 2 µg/ml as well as several isolates with MIC of 4 and 8 µg/ml. Thus, surveillance studies have shown that the majority of *S. aureus* isolates are of MIC values =0.5 µg/ml, with a unimodal distribution curve extending to 2 µg/ml. Studies of special population of *S. aureus* (GISAs) have produced MIC values up to 8 µg/ml. One clinical isolate of *S. aureus* from the Lilly study AVAM has shown an increase in MIC from 0.5 µg/ml to 12.5 µg/ml. Daptomycin potency against the two VRSA isolates was =1 µg/ml.

Pharmacodynamic analysis of daptomycin efficacy against *S. aureus* is available from three laboratories that used somewhat different methodologies. Dandekar *et al.* [45] using an MRSA strain determined an AUC/MIC ratio of 11.9 to 18.4 of free daptomycin was needed for efficacy as measured by 80% of maximal effect (see Table 30). Since daptomycin in approximately 90% serum bound across species, this represents a total AUC/MIC ratio of 119 to 184. A study by Louie *et al* [46] showed an AUC/MIC ratio of 43.4 for a static effect. While this value was a total AUC, the MIC value (1 µg/ml) used in the calculation was determined in 100% serum for the *S. aureus*, which typically causes a 4x increase in daptomycin MIC value (see Table 6-14 of the Microbiology Section). Therefore, the AUC/MIC ratio required adjustment to avoid setting too lenient a standard. Consequently, taking the most stringent approach and using a MIC value of 0.25 µg/ml for *S. aureus* in the calculation increases the required AUC/MIC ratio four fold to 174. A third study using standard methodology in a neutropenic mouse model yielded a mean AUC/MIC ratio of 438 for a static effect against *S. aureus* (see Table 29).

Therefore, the AUC/MIC ratios for daptomycin efficacy against *S. aureus* from these three studies calculated based on total AUC and standard MIC values measured in broth using NCCLS methodology are:

- 184 (Dandekar *et al*) [45]
- 176 (Louie *et al*) [46]
- 438 (Legget *et al*) [42]

The dose of daptomycin being submitted for registration is 4 mg/kg q24h. This dose produces a mean (SD) AUC of 494 ± 75 µg x hr/ml (see Table 8-11 of the Microbiology Section). The AUC mean and standard deviation were utilized in Monte Carlo simulations.

Applying the pharmacodynamic parameters with human pharmacokinetics, an AUC of 494 µg x hr/ml will support a susceptibility criterion of 2 µg/ml for *S. aureus* by the Dandekar and Louie studies, which had AUC/MIC requirements of 176 and 184, respectively, for efficacy. The Legget study (AUC/MIC for efficacy = 438) supports a criterion of 1 µg/ml.

As presented above (see Section 7.8.2), a Monte Carlo analysis was performed on potential efficacy against *S. aureus*, using the MIC values of the *S. aureus* isolates in the SECURE study, and the human AUC values obtained in the phase study DAP-00-02 as variables, applied to an AUC/MIC criterion of 184 for efficacy against *S. aureus*. This Monte Carlo analysis yielded a > 99.9% probability of efficacy against *S. aureus*. The Monte Carlo analysis was reapplied against a theoretical population of *S. aureus* with uniform MIC values of 2 µg/ml, 4 µg/ml, and 8 µg/ml [48]. These analyses supported a breakpoint of 2 µg/ml for daptomycin against *S. aureus*. In that simulation, there was a probability of 94.97% for daptomycin achieving the required pharmacodynamic criteria for efficacy against a population of *S. aureus* of MIC = 2 µg/ml. Probabilities of efficacy were less than 10% against *S. aureus* of MIC values =4 µg/ml.

In the clinical trials, the efficacy of daptomycin against *S. aureus* (both methicillin-susceptible and resistant) was clinically and statistically comparable to that of comparator antibiotics. *S. aureus* up to a MIC value of 0.5 µg/ml were treated in the clinical trial by daptomycin. The limited data on resistance has shown one clinical *S. aureus* isolate with a MIC value of 12.5 µg/ml, as well as laboratory isolates with the same MIC range.

An MIC value of 2 µg/ml is proposed by the Applicant as susceptible; an MIC value of 4 µg/ml is proposed as a buffer to be designated as intermediate; and 8 µg/ml is proposed as resistant (see Table 50). The corresponding zone sizes for these MIC values are =16 mm = susceptible, 13 to 15 mm = intermediate, =12 mm = resistant. The supporting data is summarized as follows:

- Surveillance studies have shown a unimodal distribution curve with MIC_{50} and MIC_{90} value of 0.25 to 0.5 µg/ml, with isolates up to 2 µg/ml. Other studies have reported MIC_{90} values of 1 µg/ml.
- Studies of select populations of GISAs have shown a greater number of MIC = 2 µg/ml isolates. Daptomycin maintains bactericidal activity against these isolates.
- Pharmacodynamic analysis supports a susceptibility criteria of 2 µg/ml in 2/3 studies; the third study supported a susceptibility criteria of 1 µg/ml.

•Monte Carlo analysis supports a susceptibility criteria of 2 µg/ml as a probability of 95% was obtained for achieving pharmacodynamic efficacy criteria against a population of *S. aureus* MIC = 2 µg/ml.
•Clinical efficacy of daptomycin showed no pattern of decreased clinical success or pathogen eradication with increasing MIC to 0.5 µg/ml, the least susceptible baseline *S. aureus* isolate in the daptomycin treated subjects.
•There is very limited experience with *S. aureus* isolates of reduced susceptibility.

A single subject from an early Lilly study produced one *S. aureus* isolate with a daptomycin MIC of 12.5 µg/ml.

The application of these susceptibility criteria to *S. aureus* isolates from the surveillance study, the combined clinical trials, and the therapeutic failures from the clinical trials is shown in Figure 12, Figure 13, and Figure 14, respectively.

Table 50: Proposed daptomycin susceptibility criteria for *S. aureus*

Pathogen	MIC (µg/ml)			Disk diffusion zone diameters (mm)		
	S	I	R	S	I	R
Staphylococcus aureus MSSA + MRSA	≤2	4	≥8	≥16	13-15	≤12

Reviewer's comments: The susceptibility criterion for each of the three pathogen groupings is based on:

- *In vitro* spectrum of activity including surveillance results, clinical susceptibilities, comparison studies with other antimicrobials and MICs of organisms having characterized resistance genes.
- *In vivo* animal studies including mouse septicemia studies, pharmacodynamics in animals and Monte Carlo analysis (human pharmacokinetics and surveillance variables applied to a pharmacodynamic standard).
- Clinical results and failure analysis.

Based upon the data presented by the Applicant, this Reviewer proposes that a ***MIC value of 1 µg/ml*** be set as the breakpoint for susceptibility for *Staphylococcus aureus*. This proposal is based upon the previously mentioned factors.

In vitro spectrum of activity (Table 5) and surveillance studies (Figure 7 and Table 11) have shown unimodal distribution curves with MIC_{90} values of 0.25 to 0.5 µg/ml with only a few isolates having a MIC of 1 µg/ml. These isolates were oxacillin sensitive and resistant CNS isolates obtained in the US. *In vitro* comparison studies (Table 12) where daptomycin was compared with other agents e.g. vancomycin, teicoplainin, linezolid, Q/D and penicillin demonstrated that no MICs exceeded 1 µg/ml (MSSA, MRSA-methicillin resistance not specified and VRSA) except GISA isolates ranging up to 2 µg/ml. Among organisms having characterized resistance genes, MIC_{90}s never exceeded 0.5 µg/ml (Table 16). As indicated in the MIC vs zone size scattergrams for the surveillance studies and the

clinical studies, (Figures 12-20), no isolates were found having a MIC_{90} value greater than 0.5 µg/ml.

In vivo animal studies, particularly pharmacodynamic and pharmacokinetic studies presented conflicting data. In a neutropenic mouse thigh model, a MIC = 0.5 µg/ml achieved a static response with a AUC/MIC of 438. In the mouse septicemia model, MICs of 0.5 to 2.0 µg/ml were associated with a 50% survival rate for MRSA (table 39). However, 2/3 pharmacodynamic studies supported a susceptibility criterion of 2 µg/ml while the third study supported a susceptibility criterion of 1 µg/ml. Since daptomycin is considered a new molecular entity (NME) and one study supports a susceptibility criterion of 1 µg/ml, it would be more prudent to err on the side of caution and accept a breakpoint closer to the lower value. The initial Monte Carlo analysis supported a susceptibility criterion of 2 µg/ml at a probability of 95% was obtained for achieving a pharmacodynamic efficacy criterion against a population of *S. aureus* in which the AUC/MIC of 184. However, if the AUC/MIC of 484 is used in the simulation, a criterion of 1 µg/ml is supported. As a result, the pharmacokinetic data were de-emphasized in the determination of the breakpoints.

Clinical studies (Figure 6) and have shown unimodal distribution curves with MIC_{90} values of 0.25 to 0.5 µg/ml. Clinical efficacy of daptomycin and comparators showed low rates of clinical success (see Tables 41 and 42) and pathogen eradication for MRSA (see Tables 43 and 44); however, in both populations, the clinical success rates for daptomycin and comparators were very similar for *Staphylococcus aureus* including MSSA and MRSA. Daptomycin was somewhat less effective (≥5% lower clinical success rate) than semi-synthetic penicillins against MRSA but that may be due in part to low numbers of isolates. In both populations, the pathogen eradication rates for daptomycin and comparators were very similar for *Staphylococcus aureus* including MSSA and MRSA. Daptomycin was somewhat less effective (≥5% lower pathogen eradication rate) than semi-synthetic penicillins against MRSA but that may be due in part to low numbers of isolates. In addition, therapeutic failure was high for MRSA (see Table 48). As indicated in the MIC vs zone size scattergrams for the clinical studies, (Figures 12-20), no isolates were found having a MIC_{90} value greater than 0.5 µg/ml.

Considering all the data presented, this Reviewer has set the breakpoint at 1 µg/ml. This value is one dilution greater than 0.5 µg/ml and thus should cover >99% of all isolates tested as well as any possible testing errors. There is very limited experience with resistant *S. aureus* isolates, therefore it is not possible to set intermediate or resistant breakpoints.

Breakpoint discussion for *Streptococcus* spp.

In surveillance studies, the overwhelming majority of *Streptococcus* spp. isolates fall in the MIC range of 0.03 to 0.5 µg/ml. There are several isolates in both the SECURE studies and the cSSSI clinical trials with MIC values of 1 µg/ml. These isolates are primarily from the viridans streptococci group. The MIC distributions for the *S. pyogenes, S. agalactiae, S. dysgalactiae equisimilis* and the viridans streptococci group were all similar. Overall, the distributions of the MIC values for these streptococci were similar between the two clinical trials and the SECURE surveillance studies. The MIC distribution profiles for the

streptococci are unimodal, with no distinct secondary population. The surveillance studies have shown that the majority of *Streptococcus* spp. isolates are of MIC values =0.5 µg/ml, with a unimodal distribution curve extending to 1 µg/ml.

Pharmacodynamic analysis of daptomycin efficacy against the streptococci is available from one study. An AUC/MIC ratio of 160 total daptomycin was needed for efficacy as measured by a static effect in neutropenic mice (see Table 29). This method used standard NCCLS methodology for calculation of MIC values, and determined total daptomycin concentration to produce efficacy in a neutropenic mouse thigh model.

The dose of daptomycin being submitted for registration is 4 mg/kg. This dose produces a mean AUC value of 494 ± 75 µg x hr/ml (see Table 8-11 of the Microbiology Section). The AUC mean and variability was utilized in Monte Carlo simulations. Applying the pharmacodynamic parameters with human pharmacodynamics, the AUC value of 494 µg x hr/ml will support a susceptibility criteria of 2 µg/ml for the streptococci.

Monte Carlo analysis was performed on potential efficacy against *Streptococcus* spp. The MIC values of the *S. pyogenes, S. agalactiae, S. dysgalactiae equisimilis* and viridans streptococci group isolates in the SECURE study and the human AUC values obtained in the phase I study DAP-00-02 were used as variables applied to the pharmacodynamic standards for efficacy against *Streptococcus* spp. Using this Monte Carlo analysis, a 99.9% probability of obtaining the AUC/MIC criteria (160) for efficacy against these streptococci was calculated (see Figure 10-5 of the Microbiology Section). The Monte Carlo analysis was reapplied against a theoretical uniform population of *Streptococcus* spp. with set MIC values of 2 µg/ml, and 4µg /ml [48]. This analysis supported a breakpoint of 2 µg/ml for daptomycin against *Streptococcus* spp. (other than *S. pneumoniae*). In this Monte Carlo simulation, a probability of 99.9% was calculated for daptomycin achieving the required pharmacodynamic criteria for efficacy against a population of *Streptococcus* spp. of MIC = 2 µg/ml (see Table 8-17 of the Microbiology Section).

In the clinical trials, daptomycin produced efficacy equal to that of comparators against *S. pyogenes, S. agalactiae, Streptococcus dysgalactiae equisimilis,* and the viridans streptococci group consisting of *S. anginosus, S. mitis, S. oralis, S. sanguis, S. salivarius, S. intermedius, S. constellatus, S. mutans*, and *S. bovis* up to a MIC value of 1.0 µg/ml. There has been no observed increase in MIC value or resistance in the streptococci, either in the clinic or in the laboratory.

An MIC of 2 µg/ml is proposed as susceptible; an MIC of =4 µg/ml is requested as a non-susceptible designation, to reflect the lack of observed resistance. The corresponding zone sizes for these MIC values are =13 mm = susceptible, =12 mm non-susceptible (see Table 51). The supporting data for the streptococci susceptibility criteria is summarized as follows:

- Surveillance studies have shown a unimodal distribution curve with MIC_{50} and MIC_{90} values =0.5 µg/ml, with MIC values up to 2 µg/ml.
- Pharmacodynamic analysis supports a susceptibility criterion of 2 µg/ml.

•Monte Carlo analysis supports a susceptibility criterion of 2 µg/ml. A probability of 99.9% was calculated for daptomycin to meet pharmacodynamic criteria for efficacy against *Streptococcus* spp.
•Clinical efficacy of daptomycin showed no pattern of decreased clinical success or pathogen eradication with increasing MIC to 1.0 µg/ml, the least susceptible baseline *Streptococcus* isolate in the daptomycin treated subjects.
•There is no observed resistance or significant increase in MIC value for the streptococci against daptomycin.

Table 51. Proposed daptomycin susceptibility criteria for *Streptococcus* spp. other than *S. pneumoniae*

Pathogen	MIC (µg/ml)			Disk diffusion zone diameters (mm)		
	S	I	R	S	I	R
Streptococcus spp. other than *S. pneumoniae*[a]	≤ 2b	(b)	(b)	≥13	(b)	(b)

a. *S. pyogenes*, *S. agalactiae*, *Streptococcus dysgalactiae equisimilis*, viridans streptococci group consists of *S. anginosus*, *S. mitis*, *S. oralis*, *S. sanguis*, *S. salivarius*, *S. intermedius*, *S. constellatus*, *S. mutans*, *S. bovis*.
b. The current absence of data on resistant strains precludes defining any categories other than Susceptible. Strains yielding test results suggestive of a non-susceptible category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

Reviewer's comments: Based upon the data presented by the Applicant, this Reviewer proposes that a ***MIC value of 1 µg/ml*** be set as the breakpoint for susceptibility. This proposal is based upon the previously mentioned factors.

In vitro spectrum of activity (Table 5) and surveillance studies (Table 11) have shown a unimodal distribution curve with MIC_{50} and MIC_{90} values =0.5 µg/ml, with MIC values up to 2 µg/ml. Surveillance studies and *in vitro* comparison studies with other antimicrobials (Table 14) demonstrate MIC_{90} s of 0.25 µg/ml or less for *S. pyogenes*, *S. agalactiae*, and *Streptococcus dysgalactiae equisimilis* with the MIC range never exceeding 1 µg/ml except viridans Streptococci. Among organisms having characterized resistance genes (Table 17), the MIC_{90} values never exceeded 0.25 µg/ml except some strains of *S. mitis* and *S. sanguis*. As indicated in the MIC vs zone size scattergrams, no isolates were found having a MIC_{90} value greater than 0.5 µg/ml; one dilution greater than this value would be the 1 µg/ml breakpoint.

In vivo animal studies including pharmacodynamic and pharmacokinetic studies provided inappropriate data. Data from neutropenic mouse thigh model (Tables 29 and 30) show that a MIC of 0.25 µg/ml achieved static response with an AUC/MIC of 160. In a mouse septicemia model (Table 39), a MIC of 0.06 µg/ml was associated with a 50% survival. The Monte Carlo analysis supported a susceptibility criterion of 2 µg/ml that gave a 99.9% probability of achieving a AUC/MIC ration of 160. Pharmacodynamic analysis supports a susceptibility criterion of 2 µg/ml. However, most of these *in vivo* and pharmacokinetic data were obtained using *Streptococcus pneumoniae*. This organism is not a causative agent of complicated skin and skin structure syndrome and thus, the use of this organism is inappropriate. As a result, these data were deemed unsuitable for determination of the breakpoint.

Clinical studies indicated that the MIC_{90} values ranged from 0.06 µg/ml to 0.5 µg/ml except viridans Streptococci which had MIC_{90} values ranged from 0.06 µg/ml to 1 µg/ml (Table 46). As indicated in the MIC vs zone size scattergrams, no isolates were found having a MIC_{90} value greater than 0.5 µg/ml. Clinical efficacy of daptomycin showed low rates of clinical success (see Tables 42 and 43) and pathogen eradication (see Tables 43 and 44) for viridans streptococci. Overall, clinical success rates of daptomycin for the treatment of *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus dysgalactiae equisimilis* were somewhat superior (≥5% higher clinical success rate) to comparators. However, clinical success rates of daptomycin for the treatment of viridans streptococci were lower overall to comparators. Daptomycin seemed more successful against viridans streptococci than semi-synthetic penicillins. Overall, pathogen eradication rates of daptomycin for the treatment of *Streptococcus pyogenes* and *Streptococcus agalactiae* were somewhat superior (≥5% higher clinical success rate) to comparators. However, pathogen eradication rates of daptomycin for the treatment of viridans streptococci and *Streptococcus dysgalactiae equisimilis* were lower overall to comparators. However, daptomycin seemed more successful against viridans streptococci than semi-synthetic penicillins. In addition, therapeutic failure was high for viridans streptococci (see Table 49) and thus, this organism should be eliminated from the first list of the Microbiology Section of the Package Insert.

There is no observed resistance or significant increase in MIC value for the streptococci against daptomycin. Due to the lack of resistant isolates, it is not possible to set intermediate or resistant breakpoints.

Breakpoint discussion for *Enterococcus faecalis*

In the surveillance studies, the majority of *E. faecalis* isolates fall in the MIC range of 0.25 to 4 µg/ml. MIC_{90} value was 4 µg/ml. Across both surveillance studies and the clinical trials, there were two isolates with MIC values of 8 µg/ml. Overall, the distributions of the MIC values for *E. faecalis* were similar between the two clinical trials and the SECURE surveillance studies. The MIC distribution profiles for *E. faecalis* are unimodal, with no distinct secondary population. One *E. faecalis* isolate from trial DAP-RRC-9804 demonstrated an increase in daptomycin MIC from 0.5 to 32 µg/ml. Thus, overall, the majority of *E. faecalis* isolates have a MIC of =0.4 µg/ml, with a unimodal distribution curve extending to 8 µg/ml.

Pharmacodynamic analysis of daptomycin efficacy against *E. faecalis* is available from three different studies. Based on the study by Dandekar, the AUC/MIC ratio (total plasma daptomycin) of 48 to 132 [96] was needed for efficacy. The Dandekar study used one VSE and one VRE isolate of *E. faecalis*. A second study by Alder *et al* calculated a total AUC/MIC ratio of 43 for efficacy in a murine renal infection with *E. faecalis* (Figure 7-2 of the Microbiology Section). A third study by Andes and Craig using standard technology in a neutropenic mouse model yielded a mean AUC/MIC ratio of 0.94 to 1.67 for a static effect against *E. faecalis*.

The dose of daptomycin being submitted for registration is 4 mg/kg. This dose produces a mean AUC value of 494 ± 75 µg x hr/ml. The AUC mean and variability was utilized in

Monte Carlo simulations.

In direct application of pharmacodynamic parameters to human pharmacodynamics, the AUC value of 494 µg x hr/ml will support a susceptibility criterion of 4 or 8 µg/ml for *E. faecalis* by the AUC/MIC requirements from the Dandekar and Louie studies of 176 to 184 for efficacy. Therefore, the Dandekar *et al* would support a susceptibility criteria of 4 or 8 µg/ml, the Alder *et al.* studies would support a susceptibility criteria of 8 µg/ml, while the Legget study supports a criteria of > 16 µg/ml.

As described in Section 7.8.2, an analysis was performed on potential efficacy against the *E. faecalis* using the MIC distribution values of the isolates and the human AUC values and distribution obtained in the DAP-00-02 phase I studies as variables applied to the pharmacodynamic standards for efficacy against *E. faecalis*. Based on an AUC/MIC requirement of 132 for efficacy, daptomycin successfully achieved the criteria for efficacy with a 96.9% frequency against the distribution of *E. faecalis* in 10,000 simulated cases. This standard of an AUC/MIC ratio of 132 was the most stringent criteria. The Monte Carlo analysis was reapplied against a theoretical uniform population of *E. faecalis* with set MIC values of 8 µg/ml, and 16 µg/ml [99]. In this analysis, the AUC/MIC criterion of 48 was used as the most representative standard for efficacy against *E. faecalis*. In this Monte Carlo simulation, a probability of 96.2% was calculated for daptomycin achieving the required pharmacodynamic criteria for efficacy against a population of *E. faecalis* of MIC = 8 µg/ml. Probabilities of efficacy were less than 5% against *E. faecalis* of MIC values =16 µg/ml.

In the clinical trials, daptomycin produced efficacy equal to that of comparators against *E. faecalis*. Isolates of *E. faecalis* up to a MIC value of 2.0 µg/ml were treated in the clinical trial by daptomycin. Surveillance studies have demonstrated a unimodal *E. faecalis* MIC distribution curve with MIC_{90} values up to 4 µg/ml and a range up to 8 µg/ml in surveillance populations. Pharmacodynamic and Monte Carlo analysis support a breakpoint of 8 µg/ml for daptomycin against *E. faecalis*. The limited data on resistance has shown one clinical *E. faecalis* isolate with a MIC value of 16 to 32 µg/ml, as well as laboratory isolates with the same MIC range. Therefore, a MIC value of 16 µg/ml is requested as a resistant designation. The corresponding zone sizes for these MIC values are 11 mm = susceptible and 10 mm = resistant (see Table 52). The supporting data is summarized as follows:

- Surveillance studies have shown a unimodal distribution curve with MIC_{50} and MIC_{90} value of 2 to 4 µg/ml, with isolates up to 8 µg/ml.
- Pharmacodynamic analysis supports a susceptibility criteria of 8 µg/ml in 3/4 studies; the fourth calculation supported a susceptibility criteria of 4 µg/ml.
- Monte Carlo analysis supports a susceptibility criterion of 8 µg/ml. A 96.2% probability was calculated for daptomycin attaining the pharmacodynamic efficacy criteria of AUC/MIC =48 against *E. faecalis*.
- Clinical efficacy of daptomycin showed no pattern of decreased clinical success or
- pathogen eradication with increasing MIC to 2 µg/ml, the least susceptible baseline *E. faecalis* isolate in the daptomycin treated subjects.

- There is very limited experience with *E. faecalis* isolates of reduced susceptibility. A single subject from the DAP-RRC-9804 study produced one *E. faecalis* isolate with a daptomycin MIC of 16 to 32 µg/ml.

The application of these susceptibility criteria to *E. faecalis* isolates from the SECURE surveillance study, the combined clinical trials, and the therapeutic failures from the clinical trials is shown in Figure 8-13, Figure 8-14, Figure 8-15 respectively.

Table 52: Proposed daptomycin susceptibility criteria for *E. faecalis*

Pathogen	MIC (µg/ml)			Disk diffusion zone diameters (mm)		
	S	I	R	S	I	R
Enterococcus faecalis (vancomycin susceptible only)	≤ 8	--	≥ 16	≥11	--	≤ 10

Reviewer's comments: Based upon the data presented by the Applicant, this Reviewer proposes that a **MIC value of 4 µg/*ml*** be set as the break point for *Enterococcus faecalis*. This proposal is based upon the previously mentioned factors.

In vitro spectrum of activity (Table 5) and surveillance studies have shown a unimodal distribution curve with MIC_{50} and MIC_{90} values of 2 to 4 µg/ml, with isolates up to 8 µg/ml. The majority of isolates had MIC_{90} values of 2 µg/ml or less. *In vitro* comparison studies with other antimicrobials (Table 15) showed that no MICs exceeded 2 µg/ml that were vancomycin sensitive or intermediate. Vancomycin resistant and vancomycin resistance not specified isolates did not exceed 4 µg/ml. Among organisms having characterized resistance genes (Table 18), MIC_{90} values never exceeded 2 µg/ml except some strains with high level gentamicin resistance. As indicated in the MIC vs zone size scattergrams, few isolates were found having a MIC_{90} value greater than 4 µg/ml.

In vivo animal studies, particularly pharmacodynamic and pharmacokinetic studies presented confusing data. Due to difficulty in achieving an active enterococcal infection of thigh tissue, daptomycin efficacy against *Enterococcus faecalis* was studied in a murine model of renal infection. Here, a MIC of 1 µg/ml (VSE) and 2 µg/ml (VRE) achieved a static response with an AUC/MIC of 132 and 48, respectively. In a mouse septicemia model (Table 39), a MIC of 2.5 µg/ml for VRE was associated with a 50% survival rate. Pharmacodynamic analysis supports a susceptibility criterion of 8 µg/ml in 3/4 studies; the fourth calculation supported a susceptibility criterion of 4 µg/ml. Since one study supports a susceptibility criterion of 4 µg/ml, it would be more prudent to err on the side of caution and accept this breakpoint. Monte Carlo analysis supports a susceptibility criterion of 1 µg/ml. A 99.9% probability was calculated for daptomycin attaining the pharmacodynamic efficacy criteria of AUC/MIC =132 against *E. faecalis*. Here the investigators used an immunocompetent mouse renal model as opposed to the neutropenic mouse thigh model. As the drug concentration would be higher in the kidney than the thigh yet the kidney is will perfused, it is uncertain what the impact of using the different model will affect the data. As a result, the usefulness of the data for the generation of a breakpoint is limited and was de-emphasized by this Reviewer.

In the clinical studies, a MIC_{90} value of 2 µg/ml was obtained for VSE (Table 46). No clinical failures were seen in isolates having a MIC greater than 2 µg/ml. As indicated in the MIC vs zone size scattergrams, few isolates were found having a MIC_{90} value greater than 4 µg/ml. Clinical efficacy of daptomycin showed no pattern of decreased clinical success or pathogen eradication with increasing MIC to 2 µg/ml, the least susceptible baseline *E. faecalis* isolate in the daptomycin treated subjects. Clinical success rates (see Tables 41 and 42) and pathogen eradication rates (see Tables 43 and 44) were low. Overall, clinical success rates of daptomycin for the treatment of *Enterococcus faecalis*, including VSE, were lower than comparators. This was due to the observation that clinical success rates of daptomycin were somewhat superior to vancomycin but somewhat inferior to that for semi-synthetic penicillins. Overall, pathogen eradication rates of daptomycin for the treatment of *Enterococcus faecalis*, including VSE, were similar to comparators. This was due to the observation that pathogen eradication rates of daptomycin were somewhat superior to vancomycin but somewhat inferior to that of semi-synthetic penicillins. Therapeutic failure was high for *E. faecalis* (see Table 49).

There is very limited experience with *E. faecalis* isolates of reduced susceptibility. A single subject from the DAP-RRC-9804 study produced one *E. faecalis* isolate with a daptomycin MIC of 16 to 32 µg/ml.

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15 pages redacted from this section of the approval package consisted of draft labeling

Peter Coderre
Microbiology Reviewer

Cc: Original NDA No. xxx-xxx
Microbiologist, HFD-520
File name: N21572_RD#2.doc

Smicro/ATSheldon
RD#1 initialed 6/10/03, RD#2 initialed 8/27/03 ATS; Final initialed 8//03ATS

DepDir/LGavrilovich

Cc: Original NDA # 21-572
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-520/Smicro/ATSheldon
HFD-520/Micro
HFD-520/MO/
HFD-520/Pharm/
HFD-520/Chem/
HFD-520/CSO/
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Peter Coderre
9/5/03 01:39:18 PM
MICROBIOLOGIST

Albert Sheldon
9/5/03 01:44:44 PM
MICROBIOLOGIST

Lillian Gavrilovich
9/10/03 04:48:13 PM
MEDICAL OFFICER

Product Quality Microbiology Review
Review for HFD-520

29 MAY 2003

NDA: 21-572

Drug Product Name
Proprietary: Cidecin
Non-proprietary: Daptomycin for injection
Drug Product Priority Classification: P

Review Number: 1

Subject of this Review
Submission Date: 19 December 2002
Receipt Date: 20 December 2002
Consult Date: 12 February 2003
Date Assigned for Review: 25 March 2003

Submission History (for amendments only)
Date(s) of Previous Submission(s): N/A
Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor
Name: Cubist Pharmaceuticals
Address: 65 Hayden Ave., Lexington, MA 02421
Representative: David Schubert
Telephone: 781-860-8455

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:** Abbott Laboratories
Hospital Products Division
1776 N. Centennial Drive
McPherson, KS 67460

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile Lyophilized powder in a single-use 10 mL glass vial for intravenous administration, 250 and 500 mg/vial

5. **METHOD(S) OF STERILIZATION:**

6. **PHARMACOLOGICAL CATEGORY:** Antibiotic

B. **SUPPORTING/RELATED DOCUMENTS:** Amendment to NDA 21-572 BC dated 12 May 2003

C. **REMARKS:** N/A

filename: 21572.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – This submission is recommended for approval on the basis of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is —

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – The drug product is — using a validated manufacturing process. The drug product presents a minimal risk from the standpoint of product quality microbiology.

III. Administrative

A. Reviewer's Signature /S/

B. Endorsement Block
Bryan S. Riley, Ph.D. (Microbiology Reviewer)
Peter H. Cooney, Ph.D. (Microbiology Supervisor)

C. CC Block
N/A

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pages of trade

secret and/or

confidential

commercial

information

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS – N/A

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

[redacted]

TO *(Division/Office)*:
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Bonnie Dunn, and Raquel Peat

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2/12/2003		21-572	000	Electronic submission on 12/19/02

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Daptomycin for Injection	Priority (6 months)	Antibiotics	Before April 2003

NAME OF FIRM:

[redacted]

[redacted]

- ■ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

[redacted]

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

[redacted]

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

[redacted]

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

[redacted]

- ☐ CLINICAL
- ☐ PRECLINICAL

[redacted]

Please evaluate the microbiologic issues in sterility section of drug product in this new NDA. This is a full EDR submission.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Zi-Qiang Gu, Ph.D.	■ DFS ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Bryan Riley
6/16/03 09:04:43 AM
MICROBIOLOGIST

Peter Cooney
6/16/03 02:33:27 PM
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