

# Disk Diffusion Test Interpretive Criteria and Quality Control Recommendations for Testing Linezolid (U-100766) and Eperezolid (U-100592) with Commercially Prepared Reagents

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**Two new oxazolidinones were tested to determine interpretive susceptibility testing criteria for MIC and disk diffusion methods. Commercial lots of linezolid (formerly U-100766) and eperezolid (formerly U-100592) disks containing 30 µg of drug were tested against 728 isolates of bacteria with defined mechanisms of resistance. Results from linezolid were highlighted because of its choice for clinical development. By using preliminary pharmacokinetic data, a tentative susceptibility breakpoint of ≤4 µg/ml was selected. Corresponding breakpoint zone diameters for linezolid were ≥21 mm (≤4 µg/ml) for susceptibility and ≤17 mm (≥16 µg/ml) for resistance. Regression statistics demonstrated a high correlation coefficient ( $r \geq 0.98$ ), and absolute categorical agreement between methods was obtained, when staphylococci and enterococci were tested with the cited criteria. When *Streptococcus* spp. (including *S. pneumoniae*) were tested, only the susceptibility breakpoint was suggested. Quality control (QC) guidelines for linezolid disk diffusion tests were established by a multilaboratory trial as follows: 27 to 31 mm for *Staphylococcus aureus* ATCC 25923 and 28 to 34 mm for *S. pneumoniae* ATCC 49619. More than 95% of all QC results were within these proposed ranges. Although not advanced to clinical trials, eperezolid demonstrated potency comparable to that of linezolid and had identical interpretive testing criteria. These preliminary interpretive criteria and QC limits (accepted by the National Committee for Clinical Laboratory Standards) should be applied to linezolid tests during the clinical-trial phases of oxazolidinone drug development in order to ensure test accuracy and reproducibility.**

Emerging resistance among gram-positive organisms, coupled with their increasing prevalence in serious clinical infections, has prompted the development of compounds specifically directed at the treatment of these pathogens (1, 4, 11). The recent, rapid spread of vancomycin resistance among enterococci, the continued isolation of methicillin-resistant staphylococci in many medical centers, and the increasing frequency of multiply resistant pneumococci and viridans group streptococci have left very few therapeutic options available for many community-acquired and nosocomial infections (3, 4). Dissemination of vancomycin resistance among gram-positive bacteria other than enterococci has been realized with the recent isolation from patients of streptococcal strains that were resistant to vancomycin (17). The possibility of further dissemination of glycopeptide resistance to other more virulent and clinically significant gram-positive pathogens would require that effective therapies be available to circumvent this potential problem.

The oxazolidinone class of antimicrobial agents inhibits bacterial protein synthesis in a way that is unique, which suggests a promising alternative to the currently available agents (5, 6). Oxazolidinones offer potential use against gram-positive organisms, including strains that are resistant to currently prescribed drugs (1, 2, 18). Two newer oxazolidinone antimicrobial candidates, linezolid (U-100766) and eperezolid (U-100592), have been shown to possess excellent in vitro and in vivo activity against strains of staphylococci, enterococci,

streptococci, and mycobacteria (1, 8–10, 16, 20). These compounds possess oral bioavailability, are clinically well tolerated by humans, and produce peak concentrations in serum that exceed the MIC at which 90% of the isolates are inhibited ( $MIC_{90}$ ) for targeted pathogens, including species tested in this study (15). Among the candidate drugs in the class, linezolid has been advanced to phase II clinical-trial status (see Fig. 1).

In this study, 728 isolates of gram-positive and gram-negative bacteria were analyzed by broth microdilution and disk diffusion methods (13, 14) with commercially prepared disks of linezolid and eperezolid. Disk zone criteria are compared for accuracy by using previously recommended MIC breakpoint criteria (8), and disk zone diameter criteria for susceptibility are suggested in this study. Quality control (QC) zone diameter ranges for two gram-positive organisms are also suggested by using a multicenter study (14) to determine the appropriate QC ranges for linezolid and eperezolid.

## MATERIALS AND METHODS

**Bacterial isolates.** A recent collection of clinical isolates cultured from patient specimens was retrieved from banked cryovials (Anti-Infectives Research Center, Iowa City, Iowa), providing a total of 728 isolates of gram-positive and gram-negative species for this investigation. Gram-positive strains represented species from three genera (*Streptococcus*, *Staphylococcus*, and *Enterococcus*), as well as a small number of *Bacillus* species strains (six strains). The streptococcal component included the following: viridans group species (118 strains); beta-hemolytic streptococci, including group A (25 strains), group B (30 strains), group C (9 strains), group F (5 strains), and group G (5 strains); and 110 strains of *Streptococcus pneumoniae*. The penicillin susceptibility of the alpha-hemolytic streptococci, including pneumococci, was adjusted to represent the contemporary clinical occurrence found in our geographic region. Penicillin MICs indicating resistance or intermediate susceptibility were obtained for 55% of the viridans group strains and 42% of the *S. pneumoniae* strains; the majority of these results were within the intermediate-susceptibility category. Staphylococcal spe-

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cies included oxacillin-susceptible (97 strains) and -resistant (53 strains) *Staphylococcus aureus*, oxacillin-susceptible (30 strains) and -resistant (28 strains) *S. epidermidis*, and 70 strains from eight other commonly encountered coagulase-negative staphylococcal species. The enterococcal collection of 56 isolates consisted of six species represented by *Enterococcus faecalis* and *E. faecium*, the two most commonly isolated species. Vancomycin-resistant strains of *E. faecalis* and *E. faecium* were included in this investigation and consisted of 11 strains with *vanA* and 16 strains with *vanB*. Although the oxazolidinones have limited activity against most gram-negative organisms, a selected set of these species was included in order to provide a drug-resistant population that was used for statistical susceptibility test analysis. These organisms consisted of 76 isolates, including *Enterobacteriaceae* species, *Acinetobacter* spp., *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and a small number of *Moraxella catarrhalis* isolates.

QC strains, obtained from the American Type Culture Collection (Rockville, Md.), included *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 25923 and 29213, *Escherichia coli* ATCC 25922 and 35218, *E. faecalis* ATCC 29212, and *P. aeruginosa* ATCC 27853.

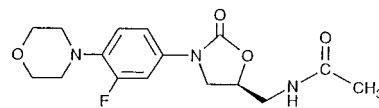
**Susceptibility test methods.** MICs were determined by using a semi-automated inoculator to deliver a standard organism suspension into the broth microdilution tray wells, which contained a range of 12 twofold dilutions for each of the tested oxazolidinones. The drugs were diluted in Mueller-Hinton (MH) broth for all staphylococci and enterococci, and in MH broth supplemented with 3 to 5% lysed defibrinated horse blood to facilitate the growth of streptococci. The MIC was defined as the lowest concentration of antibiotic which clearly inhibited visible growth of an organism in the test panels (Prepared Media Laboratory, Tualatin, Oreg.). Disk inhibitory zone diameters were measured on MH agar, which was supplemented with 5% sheep blood when streptococcal species were tested. Zone diameters were read with a digital caliper, and all results were rounded to the nearest whole millimeter for analysis.

Both tests were performed concurrently, on the same day, by using methods recommended by the National Committee for Clinical Laboratory Standards (NCCLS); the standard organism suspension was applied to MH agar plates with a cotton swab and was allowed to dry before the antimicrobial disks were applied to the surface. The remainder of the inoculum was diluted to initially seed each microdilution plate well with approximately  $5 \times 10^5$  CFU/ml. Incubation periods of 16 to 20 h for gram-negative species and 20 to 24 h for gram-positive species provided sufficient time for growth by both methods (12, 13).

**Disk diffusion QC trial.** The five laboratories participating in the QC trial were the University of Massachusetts Medical Center (Worcester, Mass.), Barnes Hospital (St. Louis, Mo.), Michigan State University (East Lansing, Mich.), MRL Pharmaceutical Services Laboratory (Franklin, Tenn.), and our laboratory. All five laboratories tested two lots of media. One lot (Difco Laboratories, Detroit, Mich.) was arbitrarily assigned as the common reagents to be used at all five study sites. In addition, five different lots of media were distributed as unique lots, one to each of the five sites (14). Two strains, *S. pneumoniae* ATCC 49619 and *S. aureus* ATCC 29523, were analyzed in the disk diffusion QC trial. For each of the QC strains, each laboratory made 10 separate inoculum replicates that were applied to the common lot of media and 20 inoculum replicates that were applied to its unique lot of media, by using methods described previously (12, 13). One linezolid disk and one eperezolid disk (30 µg) from each of the two lots were applied to each plate, along with a vancomycin disk (30 µg), which was used as an internal QC. These tests provided a total of 100 disk diffusion zone diameter results for the common media and a total of 200 disk zone diameter results for all unique-medium lots for both QC strains tested against the two oxazolidinone compounds (14).

**Antimicrobial powders and disk reagents.** Linezolid (U-100766) and eperezolid (U-100595) antimicrobial standard powders were obtained from Pharmacia and Upjohn, Inc. (Kalamazoo, Mich.). Two disk lots from different manufacturers, Difco Laboratories and Becton Dickinson Microbiology Systems (BDMS) (Cockeysville, Md.), were commercially prepared for each of these compounds for comparative assessment with broth microdilution MIC test results. Disk diffusion QC studies required an additional six MH lots (Difco; BDMS; Accumedia, Cockeysville, Md.) for purposes of evaluating potential variations in agar lots. Two lots of disks (30 µg) for both oxazolidinone compounds were provided to each of the participants, and the MH agar lots were prepared by a common manufacturer (Prepared Media Laboratory, Wilsonville, Oreg.).

**Data analysis.** Zone diameter QC ranges were determined by first calculating the overall median value (in millimeters) of all combined laboratory results for each control strain. The range was adjusted by applying the median method (14) or until the zone diameter ranges incorporated  $\geq 95\%$  of all test values. Regression analysis for comparison of disk diffusion results to broth microdilution test results was performed by the least-squares method adapted to the computer. All results presented graphically represent the Difco disk lot only, since results of an analysis of the BDMS disk lot did not significantly vary from these results. Disk diffusion errors were defined as very major (false susceptible), major (false resistant), or minor (when one test result was intermediate and the other result was susceptible or resistant) (14). Error was minimized to  $\leq 1.5\%$  for the very major category.



Linezolid

FIG. 1. Structure of linezolid (formerly U-100766).

## RESULTS

Linezolid (Fig. 1) is a chemical analog of lead compounds synthesized in the early development of the oxazolidinone class of antimicrobial agents. The morpholinyl and fluorine substitutions on the aromatic ring increase the in vitro and in vivo activities of linezolid against gram-positive pathogens compared to those of earlier compounds (1, 2, 5, 7, 18, 20).

The scattergram of linezolid MICs versus zone diameters (30-µg disks) for 416 staphylococci and enterococci, as well as for selected gram-negative species isolates, is shown in Fig. 2. The numbers shown at high MICs and small zone diameters represent isolates of gram-negative bacilli, indicating the inactivity of linezolid, for the most part, against these species (MICs,  $\geq 64$  µg/ml; zone diameters,  $\leq 10$  mm). The five organisms for which the linezolid MIC was 4 µg/ml were *M. catarrhalis*. Susceptibility testing results for gram-positive species were distributed in the lower right portion of Fig. 2. The suggested susceptibility breakpoint criteria for MIC and disk diffusion tests (a disk zone diameter of  $\geq 21$  mm or a MIC of  $\leq 4$  µg/ml for susceptibility, and a disk zone diameter of  $\leq 17$  mm or a MIC of  $\geq 16$  µg/ml for resistance) indicate that all organisms were accurately categorized. Results between these values (1 log<sub>2</sub> dilution apart) would be deemed intermediate in susceptibility to linezolid. These proposed breakpoint criteria could also be utilized in the testing of eperezolid, due to the similar activities of these two oxazolidinones against these tested species (data not shown). The correlations between MIC and zone diameter results were quite high for both oxazolidinones (correlation coefficients of  $\geq 0.98$ ) (Fig. 2).

Figure 3 provides a comparison of linezolid MICs with zones of inhibition around 30-µg disks in testing against 202 strains of beta-hemolytic and viridans group streptococci. A single susceptibility breakpoint, the same as that suggested for staphylococci and *Enterococcus* spp. (Fig. 2), was proposed for linezolid tested against these species. MICs of  $>1$  µg/ml were obtained for only three of these strains, and zone diameter results of  $\leq 25$  mm were obtained for only two strains. Figure 4 similarly illustrates the distribution of MICs and zone diameters for 110 *S. pneumoniae* isolates. As suggested for the other streptococcal tests, a single breakpoint criterion was proposed for pneumococci. These breakpoint criteria would also be appropriate for testing of eperezolid against all streptococci (data not shown).

Intermethod error rates between linezolid or eperezolid test results obtained by the commercially prepared 30-µg disk method and those obtained by the NCCLS broth microdilution method (12, 13) were analyzed for three gram-positive species groups. No error was produced due to the monomodal, susceptible nature of streptococci, staphylococci, and enterococci vis-à-vis the oxazolidinones used in this study and earlier investigations (6, 8–11, 20). No minor errors for streptococci were detected, since no intermediate-susceptibility category was proposed for these organisms. It would be prudent to have nonsusceptible streptococci tested by a reference laboratory to confirm results and/or identification of the organisms. When the clinical responses of strains for which oxazolidinone MICs

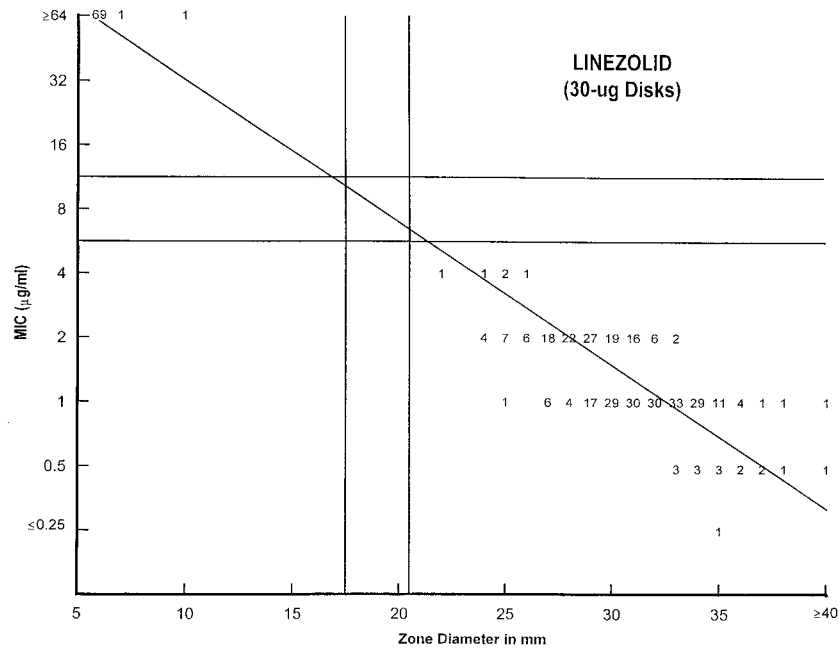


FIG. 2. Scattergram comparing the linezolid MIC with zones of inhibition around commercially prepared 30- $\mu\text{g}$  disks tested against staphylococci, enterococci, and selected gram-negative species (416 strains). The regression formula was  $y = -0.22x + 16.2$ , and the correlation coefficient ( $r$ ) was 0.98. Numbers of isolates for which the indicated MICs and zone diameters were obtained are shown. Solid vertical and horizontal lines indicate proposed interpretive breakpoint criteria (susceptibility breakpoint,  $\leq 4 \mu\text{g/ml}$  or  $\geq 21 \text{ mm}$ ).

are elevated are known, the breakpoint and/or the categories should be redefined.

Linezolid disk diffusion QC results from the multicenter trial (14) are found in Table 1. Variations in zone diameters from each study site on the unique medium only ranged from 4 to 5 mm for the control, *S. pneumoniae*, and from 4 to 6 mm for *S. aureus*. Interlaboratory comparisons for the unique and common lots of media showed no significant variation when *S. aureus* was tested, as reflected in the median value calculations from each site, which ranged from 28 to 30 mm. Greater variation in results among the laboratories was observed when *S. pneumoniae* was tested with the unique and common lots of media, as can be demonstrated by the wider range of median calculations with this organism (28 to 34 mm). Two laboratories contributed most to the observed variation in median values. Laboratory B produced slightly wider zone diameters, while laboratory E had a number of smaller zone diameters. The combined common-medium lot results were not significantly different from any of the unique-medium lot results for either QC strain, except for laboratory E and *S. pneumoniae*. Additionally, no significant intralaboratory differences were noted between the two linezolid disk lots (mean zone comparisons) used by any of the testing sites. From these results (Table 1), statistical analyses were used to propose disk diffusion QC ranges (14). When *S. pneumoniae* ATCC 49619 was tested against 30- $\mu\text{g}$  disks of linezolid on MH agar supplemented with 5% sheep blood, a QC zone diameter range of 28 to 34 mm was suggested. This 7-mm range incorporated 95.3% of all generated results and was consistent with ranges currently found for this organism in the NCCLS tables (12). A 5-mm range of 27 to 31 mm, which included 95.7% of all results, was suggested when *S. aureus* ATCC 25923 was tested on MH agar. All results that did not fall within these proposed ranges were within 1 or 2 mm of the zone diameter range limits for both QC strains.

QC ranges were also determined for eperzolid with *S. aureus* ATCC 25923 and *S. pneumoniae* ATCC 49619 (data not shown). Very little variation in results was observed when eperzolid was tested against *S. aureus*, as median values ranged only from 26 to 28 mm on both the unique- and common-medium lots. Analysis suggests that a QC range of 25 to 30 mm would be appropriate for testing of *S. aureus* ATCC 25923 on MH agar with 30- $\mu\text{g}$  eperzolid disks. Site variation was also observed

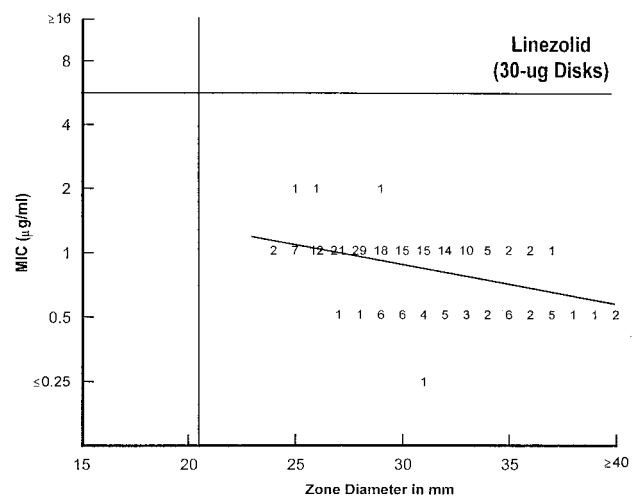


FIG. 3. Scattergram comparing linezolid MIC results with zones of inhibition around 30- $\mu\text{g}$  disks tested against viridans group and beta-hemolytic streptococci (202 strains). The regression equation was  $y = -0.07x + 10.8$ , and the correlation coefficient ( $r$ ) was 0.48. Solid vertical and horizontal lines indicate proposed interpretive breakpoint criteria (susceptibility breakpoint,  $\leq 4 \mu\text{g/ml}$  or  $\geq 21 \text{ mm}$ ).

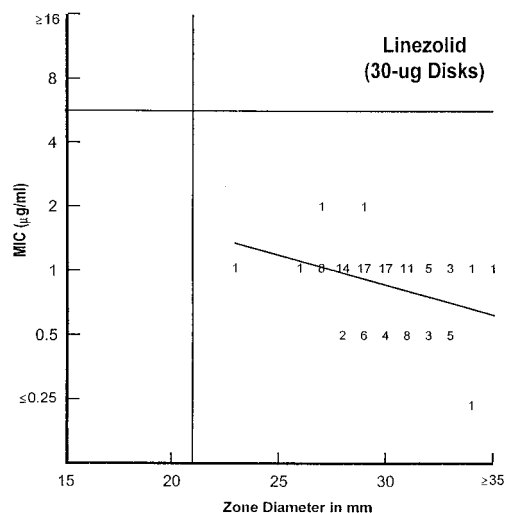


FIG. 4. Scattergram comparing the linezolid MIC with zones of inhibition around 30-µg disks tested against *S. pneumoniae* (110 strains). The regression equation was  $y = -0.09x + 11.4$  ( $r = 0.35$ ). Solid vertical and horizontal lines indicate proposed interpretive breakpoint criteria (susceptibility breakpoint,  $\leq 4$  µg/ml or  $\geq 21$  mm).

when eperezolid was tested against *S. pneumoniae* (median zone diameters, 28 to 34 mm). The same two sites that produced the variations observed with linezolid and this QC strain contributed to the variations with eperezolid disks. Analysis of

TABLE 1. Linezolid (U-100766) disk diffusion QC trial results from five laboratories<sup>a</sup>

Organism	Zone diam (mm)	No. of occurrences					Total (cumulative %)	
		In unique lot, by laboratory						In common lot
		A	B	C	D	E		
<i>S. pneumoniae</i> <sup>b</sup>	27	0	0	0	0	2	0	2 (0.7)
	28	5	0	0	0	30	0	35 (12.3)
	29	9	0	3	0	6	1	19 (18.7)
	30	10	0	13	9	1	22	55 (37.0)
	31	10	0	14	16	1	21	62 (57.7)
	32	6	1	10	13	0	26	56 (76.3)
	33	0	15	0	2	0	17	34 (87.7)
	34	0	17	0	0	0	8	25 (96.0)
	35	0	7	0	0	0	4	11 (99.7)
	36	0	0	0	0	0	1	1 (100.0)
<i>S. aureus</i> <sup>c</sup>	26	1	0	6	0	0	3	10 (3.3)
	27	5	0	13	1	0	11	30 (13.3)
	28	11	6	16	6	6	19	64 (34.7)
	29	19	17	5	4	10	38	93 (96.7)
	30	4	13	0	18	22	18	75 (90.7)
	31	0	4	0	10	2	9	25 (99.0)
	32	0	0	0	1	0	2	3 (100.0)

<sup>a</sup> QC trials were conducted with common and unique MH agar lots and with the organisms *S. pneumoniae* ATCC 49619 and *S. aureus* ATCC 25923 (12-14).

<sup>b</sup> MH agar was supplemented with 5% sheep blood for testing with *S. pneumoniae*. The median zone diameters (in millimeters) for the unique lots were 30.0 for laboratory A, 34.0 for laboratory B, 31.0 for laboratories C and D, and 28.0 for laboratory E; for the common lot, the median zone diameter was 32.0 mm. The proposed range of 28 to 34 mm includes 95.3% of the total results.

<sup>c</sup> In tests with *S. aureus*, the median zone diameters (in millimeters) for the unique lots were 29.0 for laboratories A and B, 28.0 for laboratory C, and 30.0 for laboratories D and E; for the common lot, the median zone diameter was 29.0 mm. The proposed range of 27 to 31 mm includes 95.7% of the total results.

these results suggest a QC range of 28 to 35 mm in testing of 30-µg eperezolid disks against *S. pneumoniae* ATCC 49619 on MH agar supplemented with 5% sheep blood.

The QC ranges for the MIC testing method for linezolid and eperezolid have been previously reported by Worth et al. (19). The modal MICs of linezolid for *S. pneumoniae* ATCC 49619 and *S. aureus* ATCC 29213 were 1 and 2 µg/ml, respectively.

DISCUSSION

With the advent of increasing populations of resistant gram-positive bacteria (3, 4, 17), new compounds such as linezolid and eperezolid have been rapidly developed and evaluated to determine their role as possible alternative therapeutic agents (1, 6, 8-11, 15, 16, 20). Both compounds possess excellent potential in terms of potency and spectrum for the treatment of oxacillin-susceptible and -resistant strains of staphylococci, penicillin-nonsusceptible streptococci, and vancomycin-resistant enterococci (6, 8-11, 20). Linezolid has been selected as the clinical candidate for further human investigation (16a). This compound has activity similar to those of currently available agents directed against gram-positive species such as vancomycin, but it also demonstrates potency against strains that have developed resistances over the last few years.

In this study, linezolid and eperezolid were confirmed to possess excellent and nearly equal activity against all tested gram-positive strains, including multiply resistant strains. The main focus of this study, however, was to suggest tentative disk diffusion and MIC breakpoint criteria for susceptibility, as well as QC guidelines for the most relevant disk diffusion test control strains. Previously suggested MIC (susceptibility breakpoint, 4 µg/ml) and disk diffusion breakpoint criteria for various disk potencies (30 µg) provided the best discrimination (8), and the criteria suggested in this study have been validated by using commercial disk lots and the preliminary pharmacokinetic results (15, 16a). Furthermore, the QC results suggested in this study for linezolid testing have been accepted by the NCCLS (January 1997) for publication in the next edition of M7 and M2 tables (12, 13). QC ranges for linezolid were produced for the *S. pneumoniae* ATCC 49619 and *S. aureus* ATCC 25923 strains by using a multicenter trial design conforming to the currently recommended NCCLS guideline (14), and these ranges should be utilized when linezolid becomes clinically available or when it is used during phase III clinical investigations.

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