

**FDA Briefing Package**  
**Anti-Infective Drugs Advisory Committee**  
**68<sup>th</sup> Meeting**  
**March 24, 2000**

**New Drug Applications 21-130, 21-131, 21-132**  
**Zyvox™ (linezolid)**

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## **I. Summary of Selected Preclinical Information**

### **Chemistry**

- Totally synthetic
- Belongs to oxazolidinone class of antimicrobials

### **Mechanism of Action**

- Inhibits protein synthesis by action at novel site on 23S ribosomal RNA

### **Pharmacokinetics/Pharmacodynamics**

- Parenteral and oral administration achieve nearly equivalent serum concentrations
- Two major metabolites have no antibacterial activity
- Key pharmacodynamic parameter - amount of time serum concentration exceeds the MIC
- Mouse thigh model with *S. pneumoniae* showed efficacy achieved when concentration maintained above MIC for 40% of dosing interval
- Approximately 31% protein bound
- 600 mg bid dose - maximum peak plasma concentration [ $\sim 15 \mu\text{g/mL}$  (IV);  $21 \mu\text{g/mL}$  (oral)] occurs within 1 to 2 hours
- 600 mg bid dose -  $C_{\min} \sim 3.68 \mu\text{g/mL}$  (iv);  $\sim 6.15 \mu\text{g/mL}$  (oral)
- $C_{\min}$  near or above the highest MIC<sub>90</sub> ( $4 \mu\text{g/mL}$ ) for target pathogens

### **Spectrum of Activity**

- Primarily Gram-positive activity, including vancomycin, methicillin, and penicillin-resistant microorganisms
- Bacteriostatic against staphylococci and enterococci
- Bactericidal against most strains of streptococci
- MIC<sub>90</sub> ( $\mu\text{g/mL}$ ) range for target pathogens
  - Staphylococcus* sp. (including methicillin-resistant and VISA strains): 1 – 4
  - Streptococcus pneumoniae* (including penicillin-resistant strains): 1 – 2
  - Streptococcus* sp. (other than *S. pneumoniae*): 1 – 2
  - Enterococcus faecium* and *faecalis* (including vancomycin-resistant strains): 1 – 4
- Minimal activity against Gram-negative organisms
  - MIC<sub>90</sub> ( $\mu\text{g/mL}$ )
  - Haemophilus influenzae* – 16
  - Moraxella catarrhalis* – 8

### **Resistance**

- Has been induced in laboratory
- Point mutation on 23S rRNA creating guanine to uracil transversion
- Frequency < 1 in 10<sup>9</sup>
- Cross-resistance perhaps to lincosamides and chloramphenicol
- Resistant organisms have occurred in patients (only *Enterococcus* sp. involved)
  - Fifteen cases as of 12/31/99
    - 14 *Enterococcus faecium*
    - 1 *Enterococcus faecalis*
  - Resistance development in compassionate use trial (study 25)
    - 705 patients enrolled; 501 with +Cx for enterococcus
    - 9 cases of resistance developed (1.8%)
    - 8 *E. faecium*, 1 *E. faecalis*
    - 6 of 9 patients considered failures
    - 3 of 9 patients considered cured
  - Resistance development in VRE trial (studies 54A/54)
    - 331 patients enrolled; treatment blind not broken for 104 patients
    - 6 cases of resistance developed – all *E. faecium*
    - 2 cases in 600 mg (high dose) arm
      - 1 patient considered cured
    - 4 cases in 200 mg (low dose) arm
      - 1 patient considered cured

### **Other microbiologic characteristics of linezolid**

- Synergism with other antimicrobials not demonstrated
- Antagonism – chloramphenicol and lincosamides and perhaps quinolones
- Post-antibiotic effect has been demonstrated but does not play a role in determining dosing regimen
- Intracellular concentration – penetrates neutrophils, and peripheral monocytes but does not accumulate in them

## II. Clinical Pharmacology

The sponsor has provided information about the pharmacokinetics of linezolid in their package. However, several issues should be considered:

1. The pharmacokinetics of linezolid in humans are highly variable. After administration of multiple oral doses of 400 mg (twice daily), maximum plasma linezolid concentrations ( $C_{max}$ ) ranged from 5.9 to 24  $\mu\text{g/mL}$  and minimum plasma concentrations ( $C_{min}$ ) ranged from 0.5 to 7.1  $\mu\text{g/mL}$ . The area under the curve (AUC) ranged from 34 to 152  $\mu\text{g}\cdot\text{h/mL}$ . After administration of multiple oral doses of 600 mg (twice daily) the maximum plasma linezolid concentration ( $C_{max}$ ) ranged from 10 to 32  $\mu\text{g/mL}$  and minimum plasma concentrations ( $C_{min}$ ) ranged from 2 to 12.3  $\mu\text{g/mL}$ . The area under the curve (AUC) ranged from 68 to 209  $\mu\text{g}\cdot\text{h/mL}$ .

To determine if differences in body weight could explain this variability, the AUC values were normalized by dose/body weight (mg/kg). After normalization, AUC ranged from 6.93 to 33.9  $\mu\text{g}\cdot\text{h/mL}$  per mg/kg dose after 400 mg multiple oral dosing. AUC ranged from 11.2 to 23.8  $\mu\text{g}\cdot\text{h/mL}$  per mg/kg dose after 600 mg multiple oral dosing. Thus, differences in body weight explain some but not all of this variability. The results are listed in Table II.1.

Parameter	After 400 mg multiple doses	After 600 mg multiple doses
$C_{min}$ ( $\mu\text{g/mL}$ ) (range, n=16)	0.5-7.1	10-32
$C_{max}$ ( $\mu\text{g/mL}$ ) (range, n=16)	5.9 -24	2-12.3
AUC ( $\mu\text{g}\cdot\text{h/mL}$ ) (range, n=16)	34-152	68-209
AUC ( $\mu\text{g}\cdot\text{h/mL}$ ) per mg/kg dose (range, n=16)	6.93-33.9	11.2-23.8

2. Linezolid is a reversible MAO-A and B inhibitor. Its inhibitory activity was compared in *in vitro* studies with known MAO inhibitors. The results are shown in Table II.2.

Drug	Inhibitor type	$K_i$		Plasma concentration ( $C_{max}$ )
		MAO-A	MAO-B	
clorgyline	Irreversible MAO-A inhibitor	0.0013 $\mu\text{M}$	0.71 $\mu\text{M}$	N/A
selegiline	Irreversible MAO-B inhibitor	2 $\mu\text{M}$	0.004 $\mu\text{M}$ (0.895 ng/mL)	1 ng/mL (0.0045 $\mu\text{M}$ ) after 10 mg dose
linezolid	Reversible MAO inhibitor	56 $\mu\text{M}$	0.71 $\mu\text{M}$	18 $\mu\text{g/mL}$ (53.4 $\mu\text{M}$ ) after 600 mg dose

Comparison of  $K_i$  values shows linezolid to be a weak MAO inhibitor. However, the average maximal plasma concentration after a single 600 mg dose of linezolid is about 18  $\mu\text{g/mL}$  (53.4  $\mu\text{M}$ ) which is close to its  $K_i$  for MAO-A inhibition and much greater than its  $K_i$  for MAO-B inhibition, indicating that interaction with other sympathomimetic agents is likely. The sponsor conducted four *in vivo* studies to investigate the MAO inhibitory effect

of linezolid; results from these studies may be found in the sponsor's briefing package. The four studies included a tyramine pressor test and drug-drug interaction studies with dextromethorphan, pseudoephedrine and phenylpropanolamine.

In the tyramine pressor study, 100 mg of tyramine was required to raise systolic blood pressure by 30 mm Hg in healthy volunteers when linezolid was given at a dose of 625 mg twice daily.

In the linezolid-dextromethorphan interaction study, patients received linezolid with dextromethorphan or with placebo. Temperature, blood pressure, and pulse were measured, a digit symbol substitution test (DSST) was administered, and the degree of sedation was determined. There were no statistically significant differences at any time point for DSST scores, temperature, systolic blood pressure, diastolic blood pressure, or pulse between dextromethorphan and linezolid plus dextromethorphan treatments. Sedation scores were assessed as "no sedation" for all subjects at all time points. No abnormal neurological findings were reported.

In linezolid drug-drug interaction studies with pseudoephedrine or phenylpropanolamine, the maximum increases from baseline (at time 0) were measured for systolic blood pressure, diastolic blood pressure, and pulse, as well as the maximum systolic blood pressure, diastolic blood pressure and heart rate. Results were compared between patients receiving placebo alone, linezolid alone, pseudoephedrine alone, phenylpropanolamine alone, pseudoephedrine plus linezolid, or phenylpropanolamine plus linezolid. Based on the study results (detailed in the sponsor's package), the sponsor concluded that clinically significant interactions between linezolid and other drugs or tyramine-containing foods are unlikely. Although the results of drug-drug interaction studies were not significant, only one dose was studied for each drug (pseudoephedrine (60 mg), phenylpropanolamine (25 mg), dextromethorphan (20 mg)). Therefore, the relationship between dose and drug-drug interaction potential is not known.

3. The pharmacokinetics of linezolid and its two major metabolites were studied in patients with renal impairment. Linezolid plasma concentrations were similar between healthy volunteers and renally impaired patients except that the AUC was 27% greater in anuric patients than in healthy volunteers. However, exposure to the two linezolid metabolites was significantly higher in renally impaired patients than in healthy volunteers. For metabolite 1 (PNU-142300), compared with the exposure (measured as AUC) in healthy volunteers, the total exposures were 53%, 631%, and 3516% greater in patients with moderate renal impairment, severe renal impairment, and anuria, respectively. Accordingly, the half-lives of metabolite 1 in these patients were increased. For metabolite 2 (PNU-142586), even more exposure was observed. Compared with the exposure (measured as AUC) in healthy volunteers, the total exposures to metabolite 2 were 68%, 566% and 4744% greater in patients with moderate renal impairment, severe renal impairment, and anuria, respectively. The half-lives of this metabolite were also significantly increased. These increased half-lives will result in significant accumulation when repeated doses are given to patients with renal impairment. The clinical significance of such accumulation is unknown because the toxicity of these metabolites has not been studied in animals or humans.

### **III. Clinical/Statistical Analyses of Phase III Trials of Linezolid**

This section summarizes the FDA analyses of pivotal and supportive phase III trials contained in New Drug Applications (NDAs) 21-130, 21-131, and 21-132 for Zyvox® (linezolid) injection, tablets, and suspension. Pharmacia and Upjohn submitted these NDAs on October 15, 1999, to support labeling of linezolid for the following indications in adults:

- Nosocomial pneumonia, including cases with concurrent bacteremia, due to *Staphylococcus aureus* (methicillin-susceptible and resistant strains) or *Streptococcus pneumoniae* (penicillin-susceptible and resistant strains)
- Community-acquired pneumonia, including cases with concurrent bacteremia, due to *Streptococcus pneumoniae* (penicillin-susceptible and resistant strains) or *Staphylococcus aureus* (methicillin-susceptible and resistant strains)
- Uncomplicated skin and soft tissue infections due to *Staphylococcus aureus* (methicillin-susceptible and resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*.
- Complicated skin and soft tissues infections, including cases with concurrent bacteremia, due to *Staphylococcus aureus* (methicillin-susceptible and resistant strains), *Staphylococcus epidermidis* (methicillin-susceptible and resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*.
- Infections due to vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*, including cases with concurrent bacteremia.

The NDAs include data from pivotal controlled clinical trials of linezolid for these indications as well as supportive data from controlled trials of linezolid. The sponsor's development program has also included studies of linezolid in the pediatric population. These studies provide some clinical safety data on a total of 143 patients, but the efficacy information from these open-label, non-comparative studies should be interpreted with caution. Pharmacia & Upjohn has proposed more pediatric studies, and has received a written request for pediatric studies from the FDA. Details of the pediatric studies already completed may be found in the sponsor's briefing package.

This briefing package concentrates on the FDA efficacy analyses of these NDAs. Safety analyses are ongoing; methodology for the FDA safety analysis may be found in the Appendix. Safety analyses to be presented by the FDA at the Advisory Committee meeting will include discussion of gastrointestinal and hematologic toxicities of linezolid, as well as issues related to monoamine oxidase inhibition by linezolid.

### **Summary Of Key Differences In Analytic Methodology Between FDA And Sponsor**

A summary of methods used in the FDA analysis and a fuller description of differences between the FDA's and sponsor's analytic methodology are contained in the Appendix. Key areas of difference between the FDA's analyses and the sponsor's include:

#### Key differences in populations analyzed

- For the pivotal VRE infection trial, which was designed to demonstrate superiority of linezolid 600 mg bid over linezolid 200 mg bid, the FDA focused on a modified intent-to-treat (MITT) analysis that excluded patients without a documented VRE infection at baseline. The sponsor focused on the clinically evaluable (CE) and microbiologically evaluable (ME) populations.
- For the other trials, the FDA examined ITT, MITT, CE, and ME populations. These were similar but not identical to the corresponding populations examined by the sponsor.

#### Key differences in assessment of clinical outcome

- Deaths were generally classified as failures in the FDA ITT and MITT analyses.
- In the sponsor's analyses, a fraction of deaths were considered indeterminate.
- Generally, the sponsor considered patients with no post-baseline assessment as failures, whereas the FDA generally regarded live patients with no post-baseline assessments as missing.

For full details on these differences, please refer to the Appendix.

**Results**

**Community-Acquired Pneumonia**

Pharmacia & Upjohn conducted two studies of community-acquired pneumonia (Studies 33 and 51). Study 33 was a randomized, open-label trial in patients requiring hospital admission for community-acquired pneumonia. It compared IV linezolid 600 mg q12h followed by PO linezolid 600 mg q12h with IV ceftriaxone 1 g q12h followed by PO cefpodoxime 200 mg q12h. Details of the study design can be found in Pharmacia & Upjohn’s briefing package.

Table III.1 shows results of the FDA analysis of clinical outcome in Study 33. The methods used by FDA reviewers to determine clinical success rates are described in the Appendix. A total of 381 linezolid subjects and 366 comparator subjects received at least one dose of study drug. The numbers of subjects listed in Table III.1 exclude patients with missing outcomes, except for analyses where missing outcomes were changed to failures.

<b>Table III.1. FDA Analysis of Clinical Outcome in Study 33 (open-label )</b>					
<b>FDA-Defined Study Population</b>	<b>Linezolid</b>		<b>Ceftriaxone/cefpodoxime</b>		<b>95% Confidence Interval</b>
	<b>N</b>	<b>Success Rates (%)</b>	<b>N</b>	<b>Success Rates (%)</b>	
ITT	330	80.9	313	77.0	(-2.7, 10.5)
ITT (missing as failure)	381	70.1	366	65.9	(-2.7, 11.2)
MITT	109	83.5	117	76.9	(-4.7, 17.8)
MITT (missing as failure)	128	71.1	126	71.4	(-12.3, 11.6)
FDA CE	285	86.3	274	82.1	(-2.2, 10.6)
FDA ME	92	87.0	99	81.8	(-6.2, 16.4)
FDA bacteremic ME	31	90.3	26	61.5	(3.8, 53.7)

Response rates in the FDA analyses were somewhat lower for both treatment arms than in the sponsor’s analyses. The 95% confidence intervals around the difference in response rates between treatment arms were similar in both the FDA analysis and the sponsor’s analysis. The confidence interval for the FDA analysis of bacteremic patients should be interpreted with caution, since this represents a subset analysis that was not prespecified.

Analyses that counted patients with missing outcomes as failures yielded lower response rates, as expected. These analyses should be interpreted with caution, since there were a significant number of patients with missing outcomes, and many of these patients may not have been true therapeutic failures.

Study 51 was a randomized, investigator-blind trial in subjects treated as outpatients for community-acquired pneumonia. It compared PO linezolid 600 mg q12h with PO cefpodoxime 200 mg q12h. Details of the study design can be found in Pharmacia & Upjohn’s briefing package.

Table III.2 shows results of the FDA analysis of clinical outcomes in Study 51. The methods used by FDA reviewers to determine clinical success rates are described in the Appendix. A total of 272 linezolid subjects and 268 comparator subjects received at least one dose of study drug. The numbers of subjects listed in Table III.2 exclude patients with missing outcomes, except for analyses where missing outcomes were changed to failures.

<b>Table III.2. FDA Analysis of Clinical Outcome in Study 51 (investigator-blind)</b>					
<b>FDA-Defined Study Population</b>	<b>Linezolid</b>		<b>Cefpodoxime</b>		<b>95% Confidence Interval</b>
	<b>N</b>	<b>Success Rates (%)</b>	<b>N</b>	<b>Success Rates (%)</b>	
ITT	227	82.8	222	86.5	(-10.8, 3.4)
ITT (missing as failure)	272	69.1	268	71.6	(-10.6, 5.5)
MITT	54	85.2	52	80.8	(-11.8, 20.6)
MITT (missing as failure)	60	76.7	60	70.0	(-10.8, 24.1)
FDA CE	213	84.5	208	89.9	(-12.2, 1.4)
FDA ME	50	88.0	48	81.3	(-9.5, 23.0)
FDA bacteremic ME	3	100	5	60.0	

Response rates in the FDA analysis were lower for both treatment arms than in the sponsor’s analyses. The 95% confidence intervals around the difference in response rates between treatment arms were similar in both the FDA analysis and the sponsor’s analysis of ITT and MITT populations.

Analyses that counted patients with missing outcomes as failures yielded lower response rates, as expected. These analyses should be interpreted with caution, since there were a significant number of patients with missing outcomes, and many of these patients may not have been true therapeutic failures.

### Nosocomial Pneumonia

Pharmacia & Upjohn conducted one study of nosocomial pneumonia (Study 48A). Study 48 was a randomized, double-blind trial in patients with nosocomially-acquired pneumonia. It compared IV linezolid 600 mg q12h with IV vancomycin 1 g q12h. Patients in both arms could receive aztreonam if Gram-negative pathogens were identified. Details of the study design can be found in Pharmacia & Upjohn’s briefing package.

Table III.3 shows results of the FDA analysis of clinical outcome in Study 48A. The methods used by FDA reviewers to determine clinical success rates are described in the Appendix. A total of 203 linezolid subjects and 193 comparator subjects received at least one dose of study drug. The numbers of subjects listed in Table III.3 exclude patients with missing outcomes, except for analyses where missing outcomes were changed to failures.

<b>FDA-Defined Study Population</b>	<b>Linezolid</b>		<b>Vancomycin</b>		<b>95% Confidence Interval</b>
	<b>N</b>	<b>Success Rates (%)</b>	<b>N</b>	<b>Success Rates (%)</b>	
ITT	174	48.9	164	44.5	(-6.9, 15.6)
ITT (missing as failure)	203	41.9	193	37.8	(-6.1, 14.2)
MITT	82	57.3	72	45.8	(-5.5, 28.5)
MITT (missing as failure)	94	50.0	83	39.8	(-5.5, 26.0)
FDA CE	122	57.4	103	60.2	(-16.6, 11.0)
FDA ME	54	66.7	41	63.4	(-18.3, 24.8)
FDA bacteremic ME	4	50.0	6	66.7	
FDA VAP CE	59	40.7	51	37.3	(-16.7, 23.5)

VAP, ventilator-associated pneumonia

Response rates in the FDA analysis were somewhat lower for both treatment arms than in the sponsor’s analyses. The 95% confidence intervals around the difference in response rates between treatment arms were similar in both the FDA analysis and the sponsor’s analysis.

Analyses that counted patients with missing outcomes as failures yielded lower response rates, as expected. These analyses should be interpreted with caution, since there were a significant number of patients with missing outcomes, and many of these patients may not have been true therapeutic failures.

There was a lower all-cause mortality rate in the linezolid arm than in the vancomycin arm (17.7% v. 25.4%, p=0.067, Fisher’s exact test). The rate of mortality due to the initial infection was also lower in the linezolid arm than in the vancomycin arm (5.4% v. 8.8%, p=0.24, Fisher’s exact test).

### Uncomplicated Skin and Skin Structure Infections

Originally, the sponsor proposed one multi-national study of uncomplicated skin and skin structure infections. This was a randomized, double-blind trial comparing linezolid 400 mg PO BID with clarithromycin 250 mg PO BID. When sites in the United States, Canada, and Mexico achieved their target enrollment, the study was split into a North American trial (Study 39A) and a supportive trial of non-North American sites (Study 39). Study 39A was submitted as the pivotal trial for uncomplicated skin and skin structure infections. Details of the study design can be found in Pharmacia & Upjohn’s briefing package.

Table III.4 shows results of the FDA analysis of clinical outcome in studies 39A and 39. The methods used by FDA reviewers to determine clinical success rates are described in the Appendix. A total of 382 linezolid subjects and 371 clarithromycin subjects received at least one dose of study medication in Study 39A. In Study 39, there were 166 subjects who received at least one dose of study medication in both study arms. It should be noted that 10-15% of ITT subjects have missing outcomes, adding uncertainty to the interpretation of study results. The numbers of subjects listed in the FDA analysis table exclude patients with missing outcomes except where missing outcomes were changed to failures.

<b>Table III.4. FDA Analysis of Clinical Outcome in Studies 39A and 39</b>					
<b>FDA-Defined Study Population</b>	<b>Linezolid</b>		<b>Clarithromycin</b>		<b>95% Confidence Interval</b>
	N	Success Rates (%)	N	Success Rates (%)	
<b>Pivotal Study 39A</b>					
ITT	341	85.9	322	83.5	(-3.4, 8.2)
ITT (missing as failure)	382	76.7	371	72.5	(-2.3, 10.7)
FDA CE	320	88.4	307	85.3	(-2.5, 8.7)
FDA ME	108	88.0	121	83.5	(-5.4, 14.4)
<b>Supportive Study 39</b>					
ITT	148	87.8	149	91.3	(-11.1, 4.2)
FDA CE	127	89.0	127	89.8	(-9.2, 7.6)
FDA ME	43	95.3	60	96.7	(-11.1, 8.4)

The FDA analysis focused on the ITT population. Clinical success rates determined using the FDA algorithm are similar in the linezolid and clarithromycin groups. Success rates decreased when subjects with missing outcomes are included as failures, but the results are still similar across the two study arms. The FDA clinically evaluable population differs from the ITT population mainly due to study drug compliance. The FDA microbiologically evaluable population consists of clinically evaluable subjects with one of the following baseline pathogens: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Enterococcus faecium*, or *Enterococcus faecalis*. This microbiologically evaluable population is smaller than that given by the sponsor. Overall, the clinical success rates are comparable in the linezolid and clarithromycin groups. The FDA analyses are consistent with the sponsor’s study results.

Analyses that counted patients with missing outcomes as failures yielded lower response rates, as expected. These analyses should be interpreted with caution, since there were a significant number of patients with missing outcomes, and many of these patients may not have been true therapeutic failures.

### **Complicated Skin and Skin Structure Infections**

Pharmacia & Upjohn conducted one study of complicated skin and skin structure infections (Study 55). This was a randomized, double-blind trial comparing the use of IV/PO linezolid 600 mg q12h with IV oxacillin 2 g QID /PO dicloxacillin 500 mg q6h. Details of the study design can be found in Pharmacia & Upjohn’s briefing package.

Table III.5 shows results of the FDA analysis of clinical outcome in Study 55. The methods used by FDA reviewers to determine clinical success rates are described in the Appendix. A total of 400 linezolid subjects and 419 comparator subjects received at least one dose of study drug. In this trial, 15-20% of ITT subjects had missing outcomes, adding uncertainty to the interpretation of results. The numbers of subjects listed in Table III.5 exclude patients with missing outcomes, except for analyses where missing outcomes were changed to failures.

<b>Table III.5. FDA Analysis of Clinical Outcome in Study 55</b>					
<b>FDA-Defined Study Population</b>	<b>Linezolid</b>		<b>Oxacillin/Dicloxacillin</b>		<b>95% Confidence Interval</b>
	<b>N</b>	<b>Success Rates (%)</b>	<b>N</b>	<b>Success Rates (%)</b>	
ITT	327	85.0	348	78.7	( 0.2, 12.4)
ITT (missing as failure)	400	69.5	419	65.4	(-2.5, 10.8)
ITT-prime	269	86.2	267	82.0	(-2.3, 10.8)
ITT-prime (missing as failure)	316	73.4	313	70.0	(-3.9, 10.8)
FDA CE	245	89.8	242	85.1	(-1.6, 11.0)
FDA ME	101	85.1	108	82.4	(-8.2, 13.7)

The FDA analysis focused on the ITT-prime population. This population represents the subgroup of ITT subjects based on certain baseline criteria of the study. One of the inclusion criteria for this trial specified that subjects should have one of the following: fever, white blood cell count >10,000, or bands >15%. This criterion was used to include subjects with a systemic response to infection as a means of selecting subjects with truly complicated infections. The decrease in the number of subjects in the ITT-prime group (compared to the ITT) is mainly due to application of this baseline criterion. The clinical success rates for the two groups are similar. Similar success rates are also seen when all subjects with missing outcomes are included as failures.

The FDA clinically evaluable population is the subgroup of ITT-prime subjects who met certain post-baseline requirements. The main reason for the decrease in the number of patients included is related to a requirement for study drug compliance. The microbiologically evaluable population is smaller than that given by the sponsor. As with the uncomplicated skin and skin structure infection trial, the FDA microbiologically evaluable population is the subgroup of clinically evaluable subjects who had at least one of the following organisms on baseline culture: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Enterococcus faecium*, or *Enterococcus faecalis*. Overall, the clinical success rates for linezolid are similar to the success rates for the comparator in the populations analyzed.

Analyses that counted patients with missing outcomes as failures yielded lower response rates, as expected. These analyses should be interpreted with caution, since there were a significant number of patients with missing outcomes, and many of these patients may not have been true therapeutic failures.

**Infections due to methicillin-resistant staphylococcal species**

Pharmacia & Upjohn conducted one study of infections due to methicillin-resistant staphylococcal species (Study 31). This was a randomized, open-label trial comparing the use of IV/PO linezolid 600 mg q12h with IV vancomycin 1 g q12h. A third arm enrolled patients who received IV vancomycin q12h followed by PO linezolid q12h; this arm was discontinued after 51 patients had been enrolled. Data on these patients is not included in the analysis. Details of the study design can be found in Pharmacia & Upjohn’s briefing package.

Table III.6 shows results of the FDA analysis of clinical outcomes in Study 31. The methods used by FDA reviewers to determine clinical success rates are described in the Appendix. A total of 240 linezolid subjects and 220 comparator subjects received at least one dose of study drug. The numbers of subjects listed in Table III.6 exclude patients with missing outcomes, except for analyses where missing outcomes were changed to failures.

**Table III.6. FDA Analysis of Clinical Outcome in Study 31**

FDA-Defined Study Population	Linezolid		Vancomycin		95% Confidence Interval
	N	Success Rates (%)	N	Success Rates (%)	
ITT	181	61.3	160	63.1	(-12.7, 9.1)
ITT (missing as failure)	240	46.3	220	45.9	(-9.2, 9.9)
MITT	128	58.6	112	66.1	(-20.5, 5.6)
MITT (missing as failure)	157	47.8	144	51.4	(-15.6, 8.3)
FDA CE	116	80.2	125	72.0	(-3.4, 19.7)
FDA ME	59	76.3	67	71.6	(-12.3, 21.5)
FDA bacteremic ME	17	58.8	14	71.4	

Overall, the clinical success rates for linezolid are comparable to the success rates for the comparator in the populations analyzed. The FDA analysis is, in general, consistent with the sponsor’s analysis, although the FDA analysis of the MITT population showed a different lower bound for the 95% confidence interval (FDA: -20.5; sponsor: -11.4).

Analyses that counted patients with missing outcomes as failures yielded lower response rates, as expected. These analyses should be interpreted with caution, since there were a significant number of patients with missing outcomes, and many of these patients may not have been true therapeutic failures.

Table III.7 shows results of the FDA analysis of clinical outcome in Study 31 by site of infection for the clinically evaluable population with MRSA infection.

**Table III.7. FDA Analysis of Clinical Outcome in Study 31 by site of MRSA infection**

MRSA Infection Site	Linezolid		Vancomycin	
	N	Success Rates (%)	N	Success Rates (%)
All sources	62	79.0	69	72.5
Pneumonia	11	90.9	17	70.6
- with bacteremia	3	100.0	3	66.7
SSTI	38	81.6	41	75.6
- with bacteremia	5	60.0	3	100.0
UTI	2	100.0	1	100.0
Other	9	44.4	6	50.0
- with bacteremia	3	33.3	5	60.0
Bacteremia of unknown origin	2	100.0	3	66.7

**Infections due to vancomycin-resistant enterococci**

Pharmacia & Upjohn conducted one study of infections due to vancomycin-resistant enterococci (Study 54A). This was a randomized, double-blind, dose-response trial designed to demonstrate the superiority of linezolid 600 mg q12h over linezolid 200 mg q12h. The sponsor also submitted supportive data from an ongoing continuation of this study, designated Study 54. Details of the study design can be found in Pharmacia & Upjohn’s briefing package.

Table III.8 shows results of the FDA analysis of clinical outcome in Study 54A. The methods used by FDA reviewers to determine clinical success rates are described in the Appendix. A total of 79 treated subjects were randomized to the 600-mg arm and 66 to the 200-mg arm. The FDA analysis focused on the subset of patients who had VRE isolated from a valid culture source at baseline (MITT-VRE). Results with patients with bacteremia are also provided, as this was a key subgroup of interest, specified in the protocol. The numbers of subjects listed in Table III.7 exclude patients with missing outcomes, except for analyses where missing outcomes were changed to failures.

<b>Table III.8. FDA Analysis of Clinical Outcome in Study 54A</b>					
<b>FDA-Defined Study Population</b>	<b>Linezolid 600 mg</b>		<b>Linezolid 200 mg</b>		<b>p value (Fisher’s exact test)</b>
	<b>N</b>	<b>Success Rates (%)</b>	<b>N</b>	<b>Success Rates (%)</b>	
MITT-VRE	58	67.2	46	52.2	0.158
MITT-VRE (missing as failure)	65	60.0	52	46.2	0.142
Bacteremic MITT-VRE	17	58.8	14	28.6	0.149
Bacteremic MITT-VRE (missing as failure)	18	55.6	16	25.0	0.092

Analyses that counted patients with missing outcomes as failures yielded lower response rates, as expected. All of these analyses should be interpreted with caution, since there were a number of patients with missing outcomes, and many of these patients may not have been true therapeutic failures.

Table III.9 shows the FDA analysis of clinical outcome for the MITT-VRE population, broken down by site of infection. Infections labeled as “Other” consisted primarily of complicated intra-abdominal infections. The numbers of subjects listed in Table III.8 exclude patients with missing outcomes. Sensitivity analyses treating patients with missing outcomes as failures gave lower response rates but were generally comparable. Since no adjustment has been made for multiple comparisons, these results should be viewed cautiously.

FDA-Defined Study Population	Linezolid 600 mg		Linezolid 200 mg		p value (Fisher's exact test)
	N	Success Rates (%)	N	Success Rates (%)	
MITT-VRE (all)	58	67.2	46	52.2	0.158
Bacteremia of unknown origin	10	50.0	7	28.6	0.622
Skin/skin structure	13	69.2	5	100.0	0.278
Urinary tract infection	19	63.2	20	60.0	1.000
Pneumonia	3	66.7	1	0.0	1.000
Other	13	84.6	13	38.5	0.041

Table III.10 shows all-cause mortality rates for the MITT-VRE population, and for MITT-VRE patients with bacteremia at baseline.

FDA-Defined Study Population	Linezolid 600 mg		Linezolid 200 mg		p value (Fisher's exact test)
	N	Mortality Rate (%)	N	Mortality Rate (%)	
MITT-VRE	65	24.6	52	34.6	0.306
Bacteremic MITT-VRE	18	22.2	16	56.3	0.076

In June 1999, the sponsor made a blinded decision to regard patients already randomized to Study 54 as comprising a stand-alone trial for submission, designated Study 54A. Thus, with this decision, the sponsor has opted to “spend all alpha” on Study 54A. However, data from 82 patients from Study 54 have been submitted and reviewed. It is not clear how to utilize information from Study 54 to support Study 54A results without compromising the integrity of the statistical inference. Employing information from Study 54 to augment Study 54A, even informally, might roughly correspond to giving a trial two opportunities to demonstrate a statistically significant result, without an appropriate statistical adjustment. Results from the FDA analysis of the 82 patients from Study 54 are presented in Table III.11.

FDA-Defined Study Population	Linezolid 600 mg		Linezolid 200 mg		p value (Fisher's exact test)
	N	Success Rates (%)	N	Success Rates (%)	
MITT-VRE	28	64.3	35	48.6	0.308
MITT-VRE (missing as failure)	30	60.0	41	41.5	0.153

**IV. Appendix**

**Clinical Trial Review Methods**

Efficacy analysis

Material analyzed

Table A.1 shows the pivotal and supportive phase III trials analyzed in the FDA review.

<b>Table A.1. Phase III trials reviewed</b>				
<b>Study #</b>	<b>Indication (design)</b>	<b>Linezolid Formulation</b>	<b>Comparator</b>	<b>Treated pts</b>
M/1260/0033 <b>(pivotal)</b>	CAP (open-label)	IV, PO	Ceftriaxone IV/Cefpodoxime PO	747
M/1260/0051 <b>(pivotal)</b>	CAP (investigator-blind)	PO	Cefpodoxime PO	540
M/1260/0048A <b>(pivotal)</b>	HAP (double-blind)	IV	Vancomycin IV	396
M/1260/0039A <b>(pivotal)</b>	uSSSI (double-blind)	PO	Clarithromycin	753
M/1260/0039	uSSSI (double-blind)	PO	Clarithromycin	332
M/1260/0055 <b>(pivotal)</b>	cSSSI (double-blind)	IV, PO	Oxacillin IV/Dicloxacillin PO	819
M/1260/0031	MRSS infection	IV, PO	Vancomycin IV	460
M/1260/0054A <b>(pivotal)</b>	VRE infection (double-blind)	IV, PO	Dose comparison; 600 mg v. 200 mg	145
M/1260/0054	VRE infection (double-blind)	IV, PO	Dose comparison; 600 mg v. 200 mg	82

Definition of analytic populations and outcomes

FDA reviewers generally used the same evaluability criteria as the sponsor for constructing ITT, modified ITT (MITT), clinically evaluable (CE), and microbiologically evaluable (ME) populations. However, in the FDA analysis, patients who were discontinued from therapy for lack of efficacy were generally considered clinically evaluable if they received at least four doses of study drug; such patients were not necessarily clinically evaluable in the sponsor’s analysis. In addition, in the FDA analysis, patients who died of their initial infection before follow-up were generally considered clinically evaluable; such patients were generally excluded from the sponsor’s clinically evaluable population. Patients with missing clinical outcomes were excluded from the FDA CE populations.

For individual studies, additional MITT populations were constructed for the FDA review:

- 1) ITT-prime: For the study on complicated skin and soft tissue infections (Study 55), this population included all ITT patients who met baseline inclusion criteria.
- 2) MITT-VRE – This population was constructed for Studies 54A and 54, and included all ITT patients who had vancomycin-resistant enterococci isolated from a valid culture source at baseline.

FDA reviewers used the same definitions of clinical cure and failure as the investigators. However, the algorithm used for determining clinical outcome differed between the FDA and the sponsor.

*Differences between FDA’s and sponsor’s analytic methodology*

Both the FDA’s and sponsor’s analyses started with the test-of cure (TOC) efficacy assessments. However, the FDA’s and sponsor’s decision rules for classifying outcomes differed, primarily in the treatment of patients with missing investigator assessments. This was particularly true for those subjects who had missing assessments because they died prior to the test-of-cure (TOC) visit.

Thus, the two approaches differ mainly in how outcomes of failure and missing were defined. Consequently, there was little difference between the FDA and sponsor for those ITT analyses that counted missing values as failures.

The tables below describe the algorithms and these differences in detail. The outcomes shown apply to the ITT population. The FDA algorithm did not distinguish between indeterminate and missing outcomes, regarding indeterminate outcomes as missing. Patients who had an outcome of missing were not included in the FDA analysis of the CE population.

**Step 1.** Both approaches start with the investigator’s assessment at TOC. However, if the investigator’s TOC assessment was missing or indeterminate, the two approaches differed:

<b>If investigator assessment was missing or indeterminate at TOC:</b>	Sponsor-defined outcome	FDA outcome
Missing or indeterminate at EOT and alive at follow-up	Failure	Missing
Missing or indeterminate at EOT and dead at follow-up	Failure	Failure
Improved or cure at EOT and alive at follow-up	Indeterminate	Missing
Improved or cure at EOT and dead at follow-up	Indeterminate	Failure
Failure at EOT	Failure	Failure

**Step 2.** Revise outcome if there was evidence of lack of efficacy

<b>Evidence of lack of efficacy</b>	Sponsor-defined outcome	FDA outcome
New antibiotic given for lack of efficacy	Failure	Failure
Investigator stated patient discontinued from study due to lack of efficacy	Generally failure	Failure

**Step 3.** Revise outcome if duration of drug exposure was too short

<b>Study drug exposure</b>	Sponsor Outcome	FDA Outcome
Investigator TOC assessment was failure and drug use < 2 days or 4 doses	Missing	Failure
Investigator TOC assessment was cure and drug use < 5 days or 10 doses	Missing	Cure

*Review of evaluability and outcome assessments*

All of the pivotal and supportive phase III trials were reviewed using the algorithms described above. Random sampling of patient data was used for all studies, except for studies

54A and 54 (VRE trials); for these studies, data from all patients was examined. For each of the other trials, the statistical reviewer generated a random sample of enrolled patients. The medical reviewers assessed the evaluability and clinical outcome of patients in these samples. These assessments were performed using scanned images of case report forms (CRFs) and electronic datasets as source data. Reviewers were blinded to treatment group assignment.

For each patient examined, the medical reviewer determined whether they should be included in a particular analytic population (i.e., were evaluable for purposes of ITT, MITT, CE, or ME analysis), and assessed their clinical and microbiologic outcome at TOC. Patients who died before the end of follow-up were considered to have died from the initial infection if either of the following conditions were met:

- the investigator indicated that the initial infection was the cause of death,
- or
- the investigator-supplied cause of death directly indicated an ongoing infectious process (e.g., ‘septic shock’) and clinical observations were consistent with persistence or progression of the original infection. In the case of infections due to VRE, attribution of death to the initial infection also required isolation of the original pathogen from a normally sterile body site or fluid (e.g., blood).

The reviewer’s outcome and evaluability assessments for patients in the random sample were then compared with those generated using the investigators’ assessments, modified by the FDA algorithm as described above. Discrepancies were identified, the reasons for discrepancies were determined, and the assessments were reconciled if possible. Since the number of discrepancies was sufficiently low, the investigator results (modified by the FDA algorithm) were accepted as valid in all trials except for 54A and 54 (the VRE infection studies). The results were then used to generate response rates, confidence intervals around the differences in response rates between treatment arms, and p values where appropriate.

#### Safety analysis

##### Material analyzed

Data from patients in phase II and phase III trials who had received at least one dose of study medication were examined. The primary sources for data analysis were electronic datasets supplied by the sponsor; these contained data on deaths, adverse events, and laboratory results that had been abstracted from CRFs. Random patient samples were examined to assess the accuracy of abstraction of data from CRFs to the electronic datasets.

##### Definitions

FDA reviewers used the same definitions for adverse events, drug-related adverse events, serious adverse events (SAEs), and abnormal laboratory values as the sponsor. Death was attributed to infection using the criteria described above.

##### Mortality analysis

All study reports and CRFs summaries of patient deaths were reviewed. Events were examined for evidence of death due to drug exposure or to lack of drug efficacy. Mortality rates were determined by treatment group for specific subgroups of interest.

Discontinuations

All cases of discontinuations due to adverse events were reviewed. Events were examined for evidence of relation to study drug, or for evidence of lack of drug efficacy. Discontinuation rates were determined by treatment group for specific subgroups of interest.

Serious adverse events

Serious adverse events were reviewed, including examination of SAEs representing lack of drug efficacy. SAE rates were determined by treatment group for specific subgroups of interest.

Laboratory values

Laboratory values were plotted to visualize distributions and compared between treatment groups for specific subgroups of interest. Outliers were identified and reviewed for evidence of a drug-effect relationship.