**NDA 21-130**
**NDA 21-131**
**NDA 21-132**

Pharmacia & Upjohn Company
Attention: Peter J. DiRoma
Senior Regulatory Manager, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. DiRoma:

Please refer to your new drug applications (NDA) dated October 15, 1999, received October 18, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyvox™ (linezolid tablets) Tablets, 400 and 600 mg (NDA 21-130); Zyvox™ (linezolid injection) I.V. Injection, 200 mg/100 mL, 400 mg/200 mL, and 600 mg/300 mL bags (NDA 21-131); and Zyvox™ (linezolid for oral suspension) for Oral Suspension, 100 mg/5 mL (NDA 21-132).

We acknowledge receipt of your submissions dated:

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|---|---|---|---|
| May 3, 1999* | December 6, 1999 | February 14, 2000 | March 21, 2000 |
| May 11, 1999* | December 20, 1999 | February 17, 2000 | March 29, 2000 |
| May 18, 1999* | December 22, 1999 | February 21, 2000 | March 30, 2000 |
| June 4, 1999* | December 23, 1999 | February 22, 2000 | April 1, 2000 |
| July 30, 1999* | December 29, 1999 | February 25, 2000 | April 2, 2000 |
| August 11, 1999* | January 13, 2000 | March 3, 2000 | April 7, 2000 |
| October 13, 1999* | January 17, 2000 | March 6, 2000 | April 12, 2000 |
| October 14, 1999* | January 24, 2000 | March 7, 2000 | April 13, 2000 |
| November 5, 1999 | January 25, 2000 | March 8, 2000 | April 14, 2000 |
| November 15, 1999 | January 26, 2000 | March 9, 2000 | April 15, 2000 |
| November 17, 1999 | January 28, 2000 | March 10, 2000 | April 16, 2000 |
| November 29, 1999 | January 31, 2000 | March 14, 2000 | April 17, 2000 |
| November 30, 1999 | February 2, 2000 | March 15, 2000 | April 18, 2000 |
| December 1, 1999 | February 9, 2000 | March 16, 2000 | |
| December 2, 1999 | February 10, 2000 | March 18, 2000 | |

* pre-submissions

These new drug applications provide for the use of Zyvox™ (linezolid) Tablets, I.V. Injection, and Oral Suspension for the treatment of adult patients with vancomycin-resistant *Enterococcus faecium* infections, nosocomial pneumonia, complicated and uncomplicated skin and skin structure infections,

and community-acquired pneumonia.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted draft labeling (immediate container and carton labels submitted August 11, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDAs 21-130, 21-131, and 21-132." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated April 17, 2000. These commitments, along with any completion dates agreed upon, are listed below.

Chemistry

1.

Microbiology

2. A study to characterize further the mechanism of resistance to linezolid
3. Establishment of a surveillance program to monitor development of resistance to linezolid, as well as cross-resistance to other antimicrobials
4. A study report that provides additional microbiologic and clinical summary information on the development of resistance to linezolid observed during any ongoing clinical trials
5. Animal model and appropriate human studies to define further the PK/PD parameters of linezolid

Human Pharmacokinetics and Bioavailability

6. A drug-drug interaction study with antioxidants
7. A study to investigate further any pharmacokinetic differences due to race

Clinical

8. Submission, as soon as possible, of remaining efficacy and safety data from study 54 (as electronic datasets and case report forms), and an integrated summary of safety from studies 54A and 54

9. Submission, as soon as possible, of pharmacokinetic data from studies 54A and 54
10. Additional clinical efficacy data for *Staphylococcus aureus* infections, including methicillin-resistant *S. aureus*, associated with bacteremia
11. Additional clinical efficacy data for the treatment of infections due to penicillin-resistant *Streptococcus pneumoniae*
12. Additional pharmacokinetic data, clinical data, and information on the safety of linezolid and its two metabolites in patients with renal insufficiency
13. Additional pharmacokinetic data, clinical data, and information on the safety of linezolid in patients with hepatic insufficiency
14. Provide additional information of the hematologic effects of linezolid, including definition of risk factors for thrombocytopenia
15. In vitro studies to characterize further the effect of linezolid on platelets (e.g., platelet function)
16. A post-marketing surveillance program to monitor potential medication errors. The protocol should be submitted to the Agency within 2-4 weeks after approval and the program should be implemented within 2-3 months after approval

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until November 1, 2001. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of

receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

We wish to remind you that the Agency issued a written request for linezolid on December 22, 1999, for pediatric studies to be conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act. Please note that FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as are required to fulfill the requirements of the pediatric rule. Therefore, it is important that you submit a pediatric plan describing your proposal for meeting your obligations associated with this approval under 21 CFR 314.55.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Anti-Infective Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug products when they are available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely yours,

Dianne Murphy, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure