

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-130

21-131

21-132

ADMINISTRATIVE DOCUMENTS

PATENT SUBMISSION FORM

Patent Information Pursuant to 21 C.F.R. 314.53

For

NDA # 21-130

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Zyvox
- Active Ingredient(s): linezolid
- Strength(s): 400 mg and 600 mg
- Dosage Form: film coated tablets
- Approval Date: (approval pending)

A. This section should be completed for each individual patent.

For more than three patents, copy and paste this section as many times as needed.

U.S. Patent Number: 5,688,792

Expiration Date: November 18, 2014

Type of Patent – Indicate all that apply:

- 1) Drug Substance (Active Ingredient) X Y N
- 2) Drug Product (Composition/Formulation) Y X N
- 3) Method of Use X Y N

- a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: Treatment of microbial infections.

Name of Patent Owner: Pharmacia & Upjohn Company

U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

For more than three patents, please copy and paste this section as needed.

The undersigned declares that the above stated United States Patent Number 5,688,792 covers the composition, formulation and/or method of use of Zyvox (name of drug product). This product is:

- * currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act

OR

- * X the subject of this application for which approval is being sought

EXCLUSIVITY SUMMARY FOR NDA # 21-130 SUPPL # _____

21-131
21-132

Trade Name Zyvox Generic Name linezolid

Applicant Name Pharmacia & Upjohn HFD # 520

Approval Date If Known 4/18/00

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES / / NO / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

no - WR issued 12/22/99

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under

consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / ___ / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO

SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
 IND # _____ YES /___/ ! NO /___/ Explain: _____
 !
 ! _____

Investigation #2 !
 IND # _____ YES /___/ ! NO /___/ Explain: _____
 !
 ! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
 YES /___/ Explain _____ ! NO /___/ Explain _____
 _____ !
 _____ !

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 21-130, 21-131, 21-132 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-520 Trade and generic names/dosage form: Zyvox (linezolid) Tablets, IV, and for Oral Suspension Action: (AP) AE NA

Applicant Pharmacia & Upjohn Therapeutic Class oxazolidinones, IP

Indication(s) previously approved _____
Pediatric information in labeling of approved indication(s) is adequate _____ inadequate

Indication in this application vancomycin-resistant Enterococcus faecium infections, nosocomial (For supplier answer the following questions in relation to the proposed indication.) pneumonia complicated and uncomplicated skin and skin structure infections and community-acquired pneumonia

- 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or in negotiations with FDA.
 - c. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing,
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, attach memo describing status of discussions.
 - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- 5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Signature of Preparer and Title /S/ Project Manager Date 4/18/00

cc: Orig NDA/PLA/PMA # 21-130, 21-131, 21-132
HFD-520 /Div File
NDA/PLA Action Package
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised)

DEBARMENT CERTIFICATION FOR ZYVOX (LINEZOLID)

(NDA #21-130, Tablet, NDA #21-131, Sterile Solution, and NDA #21-132, Oral Suspension)

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.



Ed L. Patt
Associate Director
Global Regulatory Affairs, CMC

8/23/99

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. XXXX-XXXX
Expiration Date: xx/xx/xxxx

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

Re: Linezolid - Various Protocols

TO BE COMPLETED BY APPLICANT

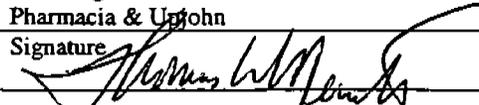
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further clarify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Attached List	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

Name Thomas W. Merritt	Title Vice President, R&D Finance
Firm/Organization Pharmacia & Upjohn	
Signature 	Date October 1, 1999

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer
Paperwork Reduction Project (0910-xxxx)
Humphrey Building, Room 531-H
200 Independence Ave., SW
Washington, DC 20201

An agency may not conduct or sponsor and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this application to this address

DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION
**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
 ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
 Expiration Date: April 30, 2000
 See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
 NDA 21-130

APPLICANT INFORMATION

NAME OF APPLICANT
 Pharmacia & Upjohn Company

DATE OF SUBMISSION
 March 10, 2000

TELEPHONE NO. (Include Area Code)
 (616) 833-8070

FACSIMILE (FAX) Number (Include Area Code)
 (616) 833-8237

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

7000 Portage Road
 Kalamazoo, Michigan 49001

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

ESTABLISHED NAME (a.g., Proper name, USP/USAN name)
 Linezolid Tablets

PROPRIETARY NAME (trade name) IF ANY
 ZYVOX™ Tablets

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) Linezolid (S)-N-[[3-(3-Fluoro-4-(4-morpholinyl) phenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide

CODE NAME (if any)

DOSAGE FORM:

Tablets

STRENGTHS:

400mg, 600 mg

ROUTE OF ADMINISTRATION:

Oral

(PROPOSED) INDICATION(S) FOR USE:
 For Gram Positive Bacterial Infection

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

607

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
 Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION

(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

REASON FOR SUBMISSION

Item 11: CRTs for Renal Impairment

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2) (Electronic Review Aid)
<input type="checkbox"/>	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
<input type="checkbox"/>	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
<input checked="" type="checkbox"/>	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
<input type="checkbox"/>	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (k) (3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 800.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

Peter J. DiRoma

TYPED NAME AND TITLE

Peter J. DiRoma, Regulatory Manager

DATE

March 10, 2000

ADDRESS (Street, City, State, and ZIP Code)

7000 Portage Road, Kalamazoo, Michigan 49001

TELEPHONE NUMBER

(616) 833-8070

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DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Huber H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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MEMORANDUM OF TELECON

DATE: Thursday, November 4, 1999

APPLICATION NUMBER: NDAs 21-130, 21-131, 21-132; Zyvox™ (linezolid) Tablets, I.V., and Suspension

BETWEEN:

Name: Mr. Peter DiRoma, Regulatory Manager
Dr. Sue Mondabaugh, Regulatory Director, Regulatory Affairs
Dr. Barry Hafkin, Linezolid Clinical Program Leader
Dr. Tim Leach, Clinical Monitor
Dr. Tom Oliphant, Biostatistics
Mr. Robert Schaser, Biostatistics
Ms. Lana Turner, Clinical Data Management
Ms. Mary Catherine Krug, Clinical Data Reporting Systems
Mr. Tom Schneider, Clinical Data Reporting Systems
Phone: (616) 833-8194
Representing: Pharmacia & Upjohn

AND

Name: Ms. Beth Duvall-Miller, Project Manager
Dr. David Ross, Medical Officer
Dr. Janice Soreth, Medical Team Leader
Dr. Erica Brittain, Statistical Reviewer
Dr. Daphne Lin, Statistical Team Leader
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Revised outcome variables in datasets

Background:

Pharmacia & Upjohn (P&U) submitted new drug applications (NDAs) 21-130, 21-131, and 21-132, for Zyvox™ (linezolid) Tablets, I.V., and Suspension respectively, on October 15, 1999. Their NDAs seek labeling claims for community-acquired pneumonia, hospital-acquired pneumonia, complicated and uncomplicated skin and skin structure infections, and vancomycin-resistant *Enterococcus* (VRE) *faecalis* and *faecium* infections, including cases with concurrent bacteremia. P&U is also seeking labeling for activity against methicillin-resistant *Staphylococcus aureus* (MRSA).

Since the submission of these NDAs, FDA and P&U have had several communications (October 27, 1999, email **(attached)**; October 28, 1999, telecon; October 28, 1999, email **(attached)**; and November 4, 1999, email **(attached)**) concerning FDA requests for revised datasets. This telecon was held to further clarify the requests.

Discussion:

"Deaths" versus "failures" in analysis: FDA commented that the main difference in analysis approach for study 0054A is that some deaths reported during the follow-up period were labelled "indeterminate" rather than "failure" in P&U's database. P&U acknowledged this to be true but added that in additional analyses, "indeterminates" were considered "failures". P&U commented that not all deaths are failures unless they meet certain criteria. P&U explained that they expected high mortality (~35%) in this trial due to a variety of reasons (e.g., underlying causes) that are not due to drug effect. FDA explained that an intent-to-treat (ITT) or modified intent-to-treat (MITT) analysis requires that every patient have an outcome that is assigned either as a failure or a cure; a per protocol analysis would not consider a patient who died from underlying disease a failure. FDA commented that both an ITT and a per protocol analysis will be done, but that in a trial designed to demonstrate superiority, the ITT (or MITT) analysis is considered the primary analysis. FDA noted that it is important to avoid post-randomization exclusions that may introduce bias into the analysis.

Stratification by MPN2 scores: P&U commented that they do have a program that will look at deaths using a severity of illness indicator. Although they have not yet done this analysis, P&U commented that they can use the MPM2 indicator and narratives from the case report forms to accurately attribute the cause of death in these patients.

True ITT analysis: P&U also commented that in their ITT analysis, deaths were handled both ways (as "cures/failures" and as "indeterminates"). FDA agreed that a sensitivity analysis will be informative but emphasized that it is important to delineate deaths and failures from true unknown outcomes in the overall analysis. FDA commented that 'deaths due to an undetermined cause = failures' is the most conservative approach to this analysis. FDA requested that this same consistent approach be applied to data from all pivotal studies, particularly when these data are presented in March 2000 to the Anti-Infective Advisory Committee. P&U agreed to follow-up on this request.

Patients with short duration of treatment: P&U agreed to assign the FDA's proposed 'sponfid' variable to patients with shortened duration of treatment who were originally classified as "missing".

Patients discontinued due to adverse event: P&U agreed to confirm whether or not patients who were discontinued due to an adverse event were considered "failures".

Deaths through follow-up period: P&U commented that there were several patients in study 0054A who left that study and were later enrolled in study 0025 (compassionate use). P&U agreed to provide the patient numbers for those who were switched and to specify which of those patients died.

Revised variables:

1. *Deatheot:* FDA clarified that this applies to the entire end-of-therapy window.

MEMORANDUM OF TELECON

DATE: Wednesday, November 17, 1999

APPLICATION NUMBER: NDAs 21-130, 21-131, 21-132; Zyvox™ (linezolid) Tablets, I.V., and Oral Suspension

BETWEEN:

- Name: Mr. Peter DiRoma, Regulatory
- Dr. Vince McCurdy, Director, Pharmaceutical Development
- Mr. Rick Davison, Pharmaceutical Development
- Dr. Gordon Halstead, Pharmaceutical Development
- Dr. Gail Jungbluth, Biopharmaceutics
- Mr. Dan Wade, Global Supply Operations
- Phone: (616) 833-0580
- Representing: Pharmacia & Upjohn

AND

- Name: Ms. Beth Duvall-Miller, Project Manager
- Mr. Jim Timper, Chemistry Reviewer
- Dr. David Katague, Chemistry Team Leader
- Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Drug substance particle size specifications and extension of expiry dating

Background:

Pharmacia & Upjohn (P&U) submitted new drug applications (NDAs) for Zyvox™ (linezolid) Tablets, I.V., and Suspension on October 15, 1999. P&U submitted CMC pre-submissions to these NDAs on May 11, 1999, July 30, 1999, and October 15, 1999.

On November 3, 1999, the FDA sent a facsimile (**attached**) that listed two CMC comments and requested a P&U response to these items. This telecon was held to address these two comments as well as to discuss the potential for extension of expiry dating. Prior to this telecon, P&U faxed a response to the FDA's request for a drug substance particle size specification (**see attached facsimile dated November 15, 1999**). In a telephone conversation between Beth Duvall-Miller and Peter DiRoma on November 8, 1999, it was agreed that item #2 of the FDA facsimile would be addressed directly between Pharmacia & Upjohn and the FDA district office that conducted the inspection. Therefore, this issue listed in the FDA facsimile dated November 3, 1999, was not discussed during this telecon.

Discussion:

Discussion of FDA request for a drug substance particle size specification (item #1 of FDA's November 3, 1999, facsimile):

P&U's November 15, 1999, facsimile (also formally submitted to NDA 21-130), P&U provided a rationale as to why they do not think a particle size specification for the drug substance is needed. Specifically, their rationale included information on the effect of drug substance particle size on bioavailability, the bioequivalence of oral tablet and IV administration, and linezolid solubility information. The FDA agreed that while their arguments seem convincing, personnel from the Division of Pharmaceutical Evaluation III were unable to attend this telecon and would have to provide final input on this issue before a definitive decision can be made.

FDA agreed to follow-up with P&U once biopharmaceutics comment is available.

NOTE: In an email communication from Beth Duvall-Miller to Peter DiRoma on November 23, 1999 (attached), FDA agreed that a particle size specification for the drug substance was not necessary.

Discussion of potential for expiry dating extension:

P&U noted that they submitted 12 month stability data for the tablet and IV formulations and 6 month stability data for the suspension formulation in the application. P&U plans to submit updated stability information (18 month and 12 month, IV/tabs and suspension respectively) within a few weeks. P&U further confirmed that they have supportive data out to 24 months from pilot or non-primary batches. P&U requested that FDA consider 24 month expiry dating for the Zyvox products. FDA responded that they will need to conduct a statistical analysis on this data as well as review the supporting data to reach a conclusion as to whether 24 month expiry dating for Zyvox is acceptable. FDA agreed to provide P&U with an answer by January 15, 2000, to provide P&U with enough head time to print IV bags for a pre-launch of this product.

CMC review status:

P&U requested an update of the status of the overall CMC review for these applications. FDA commented that they have already reviewed data on the drug substance and tablet, have started reviewing the suspension data, and will begin reviewing the IV formulation in approximately 2-3 weeks. FDA commented that it would be helpful to have access to the specification tables electronically in a MSWord format.

Action Items:

1. FDA to provide biopharmaceutics comments on P&U's a rationale (November 15, 1999 facsimile/submission) as to why they do not think a particle size specification for the drug substance is needed.

NOTE: In an email communication from Beth Duvall-Miller to Peter DiRoma on November 23, 1999 (attached), FDA agreed that a particle size specification for the drug substance was not necessary.

Action Items (continued):

2. FDA to provide P&U with an answer by January 15, 2000, as to whether 24 month expiry dating is acceptable.
3. P&U to provide Mr. Timper with tables of specifications in a MSWord format.

/s/
Beth Duvall-Miller
Project Manager

cc:

Original NDAs 21-130, 21-131, 21-132
HFD-520/Div. File
HFD-520/PM/B. Duvall-Miller
HFD-520/Chem/J. Timper
HFD-520/TLChem/D. Katague

Concurrence:

HFD-520/CPMS/F. LeSane
HFD-520/Chem/J. Timper
HFD-520/TLChem/D. Katague

drafted: bdm/January 5, 2000/M:\TELECON\N21130.1

r/d initials:

final:

/s/ 1/5/00
TELECON

MEMORANDUM OF TELECON

DATE: Thursday, April 12, 2000

APPLICATION NUMBER: NDA 21-132; Zyvox™ (linezolid) for Oral Suspension

BETWEEN:

Name: Mr. Peter DiRoma, Manager, Regulatory Affairs
Dr. Charles Hall, Therapeutic Area VP
Dr. Vince McCurdy, Director Pharmaceutical Development
Dr. Gail Jungbluth, Clinical Pharmacology
Dr. Joseph Reo, Pharmaceutical Development
Phone: (616) 833-8070
Representing: Pharmacia & Upjohn

AND

Name: Ms. Beth Duvall-Miller, Project Manager
Mr. Jim Timper, Chemistry Reviewer
Dr. Jenny Zheng, Biopharmaceutics Reviewer
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Air entrapment in the oral suspension

Background:

Pharmacia & Upjohn (P&U) submitted new drug applications (NDA) 21-130, 21-131, 21-132, for Zyvox™ (linezolid) Tablets, I.V., and Oral Suspension, respectively, on October 15, 1999. The PDUFA due date for these applications is April 18, 2000.

Study M/1260/0043 was conducted to assess the bioequivalence of linezolid suspension (100 mg/5 mL) to linezolid 600-mg tablets. Based on the results of this study and 90% confidence interval analysis, the formulations were deemed equivalent. This telecon was requested by P&U to communicate recent data that show constitution of the suspension results in air being trapped resulting in delivery to subjects of less than 100% of the desired dose. Therefore, the data from the bioequivalence trial may be difficult to interpret.

Discussion:

P&U explained that they first discovered air entrapment during constitution when testing a new oral suspension formulation (new taste). P&U subsequently retested NDA lots and discovered that the amount of air entrapped during constitution is more than they previously assumed. P&U emphasized that despite this subnominal dose, the results of 0043 still fell within the confidence limits thereby demonstrating bioequivalence. P&U estimates up to 10% of air is entrapped in the oral suspension during constitution. P&U noted that they used specific gravity to calculate the potency of the drug product. While air is removed to determine the specific gravity and hence used in the assay calculation, the patient ultimately receives less suspension than assumed. P&U

asked FDA if they had encountered this same problem with other oral suspensions and hypothesized that the amount of air entrapped may depend on head space or shaking technique. P&U described how the oral suspension was administered to subjects in the bioequivalence study as follows: the powder is reconstituted and shaken, withdrawn by syringe, transferred to a dosing cup, then administered to the subject. P&U confirmed that the method of administration was the same in both the PK studies and clinical studies.

FDA expressed the following concerns:

- ▶ The consistency of these results is unknown, therefore, a statistical analysis of the results is recommended;
- ▶ The data derived from study M/1260/0043 may now be difficult to interpret because the exact amount of suspension administered to study subjects is variable and unknown;
- ▶ Confidence intervals need to be recalculated based on a worst case scenario.

FDA commented that they would need to discuss this issue more internally and asked that P&U provide more data as it becomes available.

Action Items:

<u>Item</u>	<u>Responsible Person</u>	<u>Due Date</u>
1. Update FDA with additional information	P&U	immediately
2. Define worst case scenario and recalculate confidence intervals accordingly	P&U	immediately
2. Discuss issue internally with team leaders and supervisors	FDA	immediately

/S/

Beth Duvall-Miller
Project Manager