CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-130/S-003
21-131/S-003
21-132/S-003

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Pharmacia & Upjohn Company

NDA # 21-130, Supplement # 003

CERTIFICATION UNDER 21 CFR 314.53(d)(2)(ii)

Pharmacia & Upjohn Co. hereby certifies that the following patent(s) that were previously submitted under this NDA cover the changes that are the subject of the present Supplemental NDA:

Patent No.	Expiration Date
5688792	NOV 18,2014

Pharmacia & Upjohn Company

By: Robert S. Gremban Robert S. Gremban

Title: Regulatory Affairs Manager

Date: June 18, 2002

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-130 NDA 21-131 NDA 21-132	Efficacy Supplement Type SE-5	Supplement Number 003
Drug: Zyvox (linezolid) Tablets, I.V., for Oral Suspension		Applicant: Pharmacia & Upjohn
RPM: Beth Duvall-Miller	HFD-520	Phone # (301) 827-2125
Application Type: (✓) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	( ) Standard (✓) Priority
• Chem class (NDAs only)	n/a
• Other (e.g., orphan, OTC)	n/a
❖ User Fee Goal Dates	December 24, 2002
❖ Special programs (indicate all that apply)	(✓) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(✓) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✓) No
• This application is on the AIP	( ) Yes (✓) No
• Exception for review (Center Director's memo)	n/a
• OC clearance for approval	n/a
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(✓) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(✓) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	Enclosed
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	none
General Information	
❖ Actions	
• Proposed action	(✓) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	none
• Status of advertising (approvals only)	(✓) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(✓) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release (✓) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	enclosed
• Most recent applicant-proposed labeling	enclosed
• Original applicant-proposed labeling	enclosed
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	12/10/02; 12/12/02; 12/17/02; 12/18/02 (meetings and telecons)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	n/a – 1st in class
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	n/a
• Applicant proposed	n/a
• Reviews	n/a
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	n/a
• Documentation of discussions and/or agreements relating to post-marketing commitments	n/a
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	enclosed
❖ Memoranda and Telecons	enclosed
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	n/a
• Pre-NDA meeting (indicate date)	February 28, 2002
• Pre-Approval Safety Conference (indicate date; approvals only)	n/a
• Other	labeling (see above for dates)

❖ Advisory Committee Meeting	
• Date of Meeting	n/a
• 48-hour alert	n/a
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	n/a
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	none
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	2/19/03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	12/18/02
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	n/a
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	enclosed
❖ Demographic Worksheet *(NME approvals only)*	n/a
❖ Statistical review(s) *(indicate date for each review)*	10/31/02; 12/19/02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	12/20/02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	n/a
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	12/3/02
• Bioequivalence studies	n/a
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	n/a
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	12/16/02
• Review & FONSI *(indicate date of review)*	n/a
• Review & Environmental Impact Statement *(indicate date of each review)*	n/a
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	n/a
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	12/18/02; 1/14/03
❖ Nonclinical inspection review summary	n/a
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	n/a
❖ CAC/ECAC report	n/a

EXCLUSIVITY SUMMARY for NDA # 21-130 SUPPL # 003

Trade Name Zyvox **Generic Name** linezolid

Applicant Name Pharmacia & Upjohn **HFD-** 520

Approval Date December 19, 2002

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 questions 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.)? SE5

   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?

three

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

YES /___/ NO /✔/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 9.

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 9 (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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

(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:

Investigation #1, Study # M/1260/0082

Investigation #2, Study # M/1260/0065

Investigation #3, Study # M/1260/0045

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✔/

Investigation #2 YES /___/ NO /✔/

Investigation #3 YES /___/ NO /✔/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✔/

Investigation #2 YES /___/ NO /✔/

Investigation #3 YES /___/ NO /✔/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(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"):

Investigation # 1, Study # M/1260/0082

Investigation # 2, Study # M/1260/0065

Investigation # 3, Study # M/1260/0045

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 #49,195;55,618 YES /✔/ NO /___/ Explain:

Investigation #2

IND # 49,195;55,618 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 _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✔/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA 21-130/S-003
Archival NDA 21-131/S-003
Archival NDA 21-132/S-003
HFD-520/Division File
HFD-520/RPM/Duvall-Miller
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Beth Duvall-Miller
2/5/03 01:48:59 PM
Exclusivity summary

Janice Soreth
2/5/03 03:03:49 PM

Pharmacia & Upjohn Company

NDA # 21-130
CLAIM FOR EXCLUSIVITY UNDER 21 CFR 314.108(b)(4) or (b)(5)

Pharmacia & Upjohn Co. is hereby claiming three (3) years of exclusivity under (check one):

[ ] 21 CFR 314.108(b)(4) (NDA) or
[X] 21 CFR 314.108(b)(5) (Supplemental NDA)

New Clinical Investigations
To the best of Pharmacia & Upjohn's knowledge, each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in Sec. 314.108(a).

Essential to Approval (check one)
Pharmacia & Upjohn hereby certifies that it has thoroughly searched the scientific literature for published studies or publicly available reports of clinical investigations that are relevant to the conditions for which Pharmacia & Upjohn is seeking approval.

1) [X] Attached hereto is list of all published studies or publicly available reports of clinical investigations known to Pharmacia & Upjohn through the above literature search. To the best of Pharmacia & Upjohn's knowledge, the list is complete and accurate and, in Pharmacia & Upjohn's opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which Pharmacia & Upjohn is seeking approval without reference to the new clinical investigation(s) in the application. Also attached hereto is an explanation as to why the studies or reports are insufficient.

2) [ ] The literature search did not provide any published studies or publicly available reports of clinical investigations that are relevant to the conditions for which Pharmacia & Upjohn is seeking approval.

Conducted or Sponsored By (check one)
3) [X] Pharmacia & Upjohn was the sponsor named in the Form FDA-1571 for an investigational new drug application (IND) under which the new clinical investigation(s) that is essential to the approval of its application was conducted. IND # 49,195 and 55,618

4) [ ] Pharmacia & Upjohn certifies that it or its predecessor in interest provided substantial support for the clinical investigation(s) that is essential to the approval of its application. A certified statement from a certified public accountant that Pharmacia & Upjohn provided **50** percent or more of the cost of conducting the study is attached.

5) [ ] An explanation of why the FDA should consider Pharmacia & Upjohn to have conducted or sponsored the study if Pharmacia & Upjohn's financial contribution to the study is less than **50** percent or Pharmacia & Upjohn did not sponsor the investigational new drug is attached.

Pharmacia & Upjohn Company

By: Robert S. Gremban Robert S. Gremban

Title: Regulatory Affairs Manager

Date: June 18, 2002

DEBARMENT CERTIFICATION FOR
ZYVOX Tablets, NDA # 21-130, ZYVOX I.V. Injection, NDA # 21-131
and ZYVOX for Oral Suspension, NDA # 21-132

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.

Roberta A. Krieger
Associate Director
Global Regulatory Affairs

6/21/02
Date

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: March 8, 2002

APPLICATION NUMBER: NDAs 21-130, 21-131, 21-132; Zyvox (linezolid)

BETWEEN:

Name:	Dr. Steve Vonderfecht, Director, Preclinical Toxicology
	Dr. Mary Ellen McNerney, Senior Research Scientist, Toxicology
	Dr. Susan Mattano, Director, Regulatory Toxicology
	Dr. Gebre-Mariam Mesfin, Senior Research Scientist, Toxicology
	Dr. Robert Dewitt, Director, Drug Development Toxicology
	Ms. Kathy Bonnema, Senior Biologist, Regulatory Toxicology
	Ms. Roberta Krieger, Associate Director, Regulatory Affairs
	Mr. Robert Gremban, Regulatory Affairs Manager
Phone:	(616) 833-9195
Representing:	Pharmacia & Upjohn

AND

Name:	Ms. Beth Duvall-Miller, Regulatory Health Project Manager
	Dr. Terry Peters, Acting Pharmacology Team Leader
	Dr. Ken Seethaler, Pharmacology Reviewer
	Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Juvenile toxicology study in dogs

Background

Since the approval of Zyvox (linezolid) on April 18, 2000, FDA and Pharmacia & Upjohn have held continued discussions of the pediatric development of linezolid (July 12, 2000 meeting; August 16, 2000 telecon; May 31, 2001 meeting; January 15, 2002; February 28, 2002 meeting). In a facsimile dated February 15, 2002 (FDA comments on pre-sNDA meeting package), FDA recommended that P&U conduct a toxicology study in juvenile beagle dogs to be included in their pediatric sNDA submission. At the February 28, 2002 meeting, FDA reiterated this request despite P&U's contention that the toxicity of linezolid was adequately characterized in pediatrics using rodent models. However, P&U agreed to submit a timeframe for submission of such a study. This summary was forwarded to FDA via email on March 7, 2002 **(attached)**. This telecon was held to provide P&U with FDA's comments on their proposed study and its timeline.

Discussion

- FDA opened the discussion to say that they were in agreement with P&U's proposed study design, but recommended that bone marrow cores be evaluated in addition to bone marrow

smears. FDA clarified that these bone marrow core samples would be taken at necropsy as opposed to taking a biopsy sample. P&U agreed to this request.

- FDA recommended that P&U have the histopathology results from the marrow, testes, and spleen samples peer reviewed and expedited for submission to FDA during the review cycle of the pediatric sNDA. P&U agreed to this request.

- FDA pondered if the proposed dosing regimen (daily doses given orally as two equally divided doses 8 hours apart) was a long enough interval considering the accelerated metabolism in juvenile animals. P&U commented that while it is sufficiently long enough based on existing data, they plan to look at the toxicokinetics to decide on the final dosing regimen. P&U agreed to consider evaluating urine and metabolites collected from puppies but commented that they would need to determine if urine collection was feasible.

- FDA emphasized that the toxicokinetic and expedited tissue sample histopathology results will provide FDA with sufficient information to write the final product label. P&U agreed to provide a full draft report of their proposed study as early in the review cycle as possible.

Ms. Beth Duvall-Miller
Regulatory Health Project Manager

APPEARS THIS WAY
ON ORIGINAL

Pharmacia & Upjohn attachment
from email dated March 7, 2002

Toxicity assessment of Zyvox in juvenile dogs

Introduction: Per FDA's request, we plan to evaluate the toxicity of Zyvox, particularly regarding hematopoietic effects, in juvenile dogs in a 4-week GLP toxicity study. We seek FDA's concurrence for this plan.

Dose levels: Dose levels will be based on preliminary tolerance and TK data. Dose levels in the range finding study will be selected based on data from the 2- and 4-week studies conducted using sexually immature and adult dogs.

Dose Groups for the 4-week GLP study: 3 treated (low-, mid-, and high-dose) and 1 control groups will be used. Reversibility will be examined in the control and high-dose groups.

Number of dogs/group: 6/sex/group in the control and high-dose groups; 4/sex/group in remaining groups. 2/sex/dose in the control and reversibility groups will be killed after a 4-week reversibility period.

Age at dose initiation: 3 weeks postnatal age. This age was chosen as the earliest feasible time for dose initiation for 2 reasons: 1) The maturation profile of hematologic indices in humans and dogs is qualitatively similar from early neonatal life onwards, and 2) Based on functional maturation of the canine kidney during the 3rd week of life, given the renal elimination of Zyvox in dogs and other species.

Dose regimen: The dosing regimen will be the same as that used in the previous toxicity studies in sexually immature and adult dogs (daily doses given orally as 2 equally divided doses 8 hours apart).

Dose duration: 4 weeks of dosing and 4 weeks of reversibility.

Parameters to be evaluated: Toxicokinetics, clinical signs, body weights, ophthalmology, hematology, clinical chemistry, organ weights, and gross and histopathology (including evaluation of bone marrow smears).

Time line:

- **Range finding study:** April
- **Definitive GLP study: to be contracted with** [redacted]
  - Dose initiation: 1 July 2002
  - Preliminary interim clinical/lab data summary of dosing phase: 7 August 2002
  - Preliminary interim clinical/lab reversibility data: 15 September 2002
  - Draft report (unaudited): 30 September 2002
  - Final Report (QA audited): 30 January 2002

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Beth Duvall-Miller
3/13/02 03:17:45 PM
CSO
Minutes of 3/8/02 telecon; tox study in juvenile dogs
sign off

Frances LeSane
3/14/02 04:30:47 PM
CSO

Kenneth Seethaler
3/22/02 02:45:56 PM
PHARMACOLOGIST

Terry Peters
4/1/02 08:05:08 AM
PHARMACOLOGIST

MEMORANDUM OF TELECON

DATE: March 20, 2002

APPLICATION NUMBER: IND 55,618, linezolid

BETWEEN:

Name: Mr. Robert Gremban, Global Regulatory Affairs Manager
Dr. Jon Bruss, Director, Clinical Research
Dr. Charles Hall, Vice President, Product Development
Dr. Gail Jungbluth, Senior Research Scientist, Clinical Pharmacology
Ms. Roberta Krieger, Associate Director, Global Regulatory Affairs
Ms. Susan Speziale, Senior Program Manager, Project Management
Dr. Satish Tripathi, Director, Global Regulatory Affairs

Phone: (616) 833-9195

Representing: Pharmacia & Upjohn

AND

Name: Ms. Beth Duvall-Miller, Regulatory Health Project Manager
Dr. Susan Thompson, Medical Officer
Dr. David Ross, Medical Team Leader
Dr. Jenny Zheng, Biopharmaceutics Reviewer
Dr. Sue Chih Lee, Acting Biopharmaceutics Team Leader
Dr. Janice Soreth, Director
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Linezolid PK in adolescents

BACKGROUND:

Since the approval of Zyvox (linezolid) on April 18, 2000, FDA and Pharmacia & Upjohn have held continued discussions of the pediatric development of linezolid (July 12, 2000 meeting; August 16, 2000 telecon; May 31, 2001 meeting; January 15, 2002; February 28, 2002 meeting). At the February 28, 2002, meeting, FDA stated that the current pharmacokinetic, safety, and efficacy data in adolescents do not provide enough information to decisively support a BID dose. In a March 8, 2002 email (**attached**), FDA requested additional information. P&U responded to this email in a submission dated March 14, 2002. This telecon was held to further discuss the appropriate dosing for adolescents with linezolid.

DISCUSSION:

- FDA opened the discussion by stating that after having reviewed P&U's extrapolated versus observed area under the curve (AUC) results (March 14, 2002 submission), the variability in the PK data does not conclusively support a BID dosing in adolescents. FDA requested that P&U conduct an additional PK study to better define the appropriate dose in adolescents.

FDA commented that ideally, additional samples would be collected after 12 hours in such a study. P&U noted that there are problems obtaining samples from patients beyond 12 hours. FDA commented that they hope that with more samples and longer sampling times, the variability in PK parameters will disappear but acknowledged that there may still be variability in the data from a second study too. FDA proposed that P&U consider conducting the study in ill patients rather than healthy subjects. P&U agreed to discuss this idea with their consultant.

FDA cautioned that the non-linear, concentration-dependent PK of linezolid might result in overestimation of AUC after 12 hours. This would be of particular concern when treating patients with infections caused by organisms with low susceptibility to linezolid. P&U acknowledged FDA's concerns but believes that MIC patterns and current efficacy data suggest that most patients will be adequately treated with 600 mg BID. FDA emphasized that they are not endorsing a TID dose for adolescents, but rather that they are concerned that a BID dose may not adequately treat patients with infections caused by organisms with high MICs and patients with high clearance. P&U remarked that they reviewed the adult PK data out to 48 hours and noted that there was little difference between adults and adolescents with regards to clearance and AUC. FDA wondered how much of the adult AUC data was extrapolated. P&U said that they could provide that information to FDA shortly.

- FDA commented that they also have concern about the study site effect based on the observation that estimated clearance from one site was very different from the other sites. FDA suggested that a new PK study in adolescents might clarify this issue.

- FDA noted that the ultimate goal is to write a label that would provide dosing information for all pediatric age groups. The problem in writing such a label based on the PK data from study 111 would be the variability in the data and resulting uncertainty that BID is the appropriate dose for all adolescent patients. Thus, lack of data from an additional PK study would have a profound effect on the ability to provide dosing information in the label for adolescents.

- P&U acknowledged that they do not have efficacy and safety data from adolescent patients treated with linezolid for hospital-acquired pneumonia or complicated skin and skin structure infections and have limited data from adolescent patients treated under the compassionate use protocol (M/1260/0025). P&U noted that they plan on submitting summarized data from M/1260/0025 in their pediatric sNDA.

- P&U estimated that it would take approximately 12 months to design, conduct, and submit results from a second PK study. FDA proposed that P&U submit their pediatric sNDA without filing adolescent data, knowing that the label would reflect the uncertainty in adolescent dosing. FDA said that submitting the pediatric sNDA without additional PK data in adolescents is not a fileability issue, but rather a labeling issue which will be addressed during negotiations. P&U said that the timeline for conducting the additional study is problematic but that they will propose labeling which reflects just the results from study 111 as well as a timeline for conducting and submitting a second PK study.

ACTION ITEMS:

1. P&U to provide FDA with information as to how much adult AUC data was extrapolated.
2. P&U to propose language for a label that would be based on a sNDA submission without additional PK data in adolescents.
3. P&U to propose a timeline for designing, conducting, and submitting results from a second PK study in adolescents.

Beth Duvall-Miller
Regulatory Health Project Manager

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/s/

Beth Duvall-Miller
4/22/02 02:36:37 PM
CSO
Minutes of 3/20/02 telecon; adolescent dosing ready for sign off

Frances LeSane
4/22/02 05:36:01 PM
CSO

Jenny Zheng
4/26/02 11:18:15 AM
BIOPHARMACEUTICS

Susan Thompson
5/2/02 01:04:56 PM
MEDICAL OFFICER

David Ross
5/2/02 01:14:31 PM
MEDICAL OFFICER

Janice Soreth
5/3/02 01:25:48 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-130; 21-131; 21-132
IND 49,195; 55,618

Pharmacia & Upjohn Company
Attention: Robert S. Gremban
Regulatory Affairs Manager
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Gremban:

Please refer to your correspondence dated August 24, 2001, requesting changes to the December 22, 1999, Written Request for pediatric studies for linezolid. We also refer to the amended Written Request for pediatric studies dated February 28, 2002.

We reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supercedes the Written Request dated December 22, 1999 and the amended Written Request dated February 28, 2002.

- *Type of studies (e.g., double-blind, randomized, parallel group, safety, and/or pk):*

  Study #1: "Assessment of Linezolid Pharmacokinetics in Full Term and Pre-Term Neonates."
  Study #2: "A randomized, blinded comparison of the safety and efficacy of oral linezolid vs. a cephalosporin for treatment of skin and skin structure infections in pediatric patients aged 3 months to 18 years."
  Study #3/4: "A randomized, open-label comparison of IV linezolid/oral linezolid and IV vancomycin (with other IV/oral antibiotic switch, if appropriate) in suspected resistant gram positive infections in pediatric patients." and "A Prospective Study of Vancomycin-Resistant Enterococcal Infections in Pediatric Patients."
  Study #5: "A Randomized, Comparative Trial of Linezolid vs. Vancomycin in Pediatric Patients with CSF Shunt Infections."

- *Indications to be studied (i.e., objective of each study):*

  Study #1: Objective – To assess the pharmacokinetics of linezolid in full-term and pre-term neonates following a single 10 mg/kg intravenous dose of linezolid.
  Study #2: Objectives – To assess the comparative efficacy, safety and tolerance of oral linezolid vs. oral cephalosporin for the treatment of skin and skin structure infections in pediatric patients.
  Study #3/4: Objectives – To evaluate the comparative tolerance of linezolid and vancomycin in the empiric treatment of suspected resistant gram-positive bacterial infections, including methicillin-resistant Staphylococcus aureus (MRSA), other methicillin-resistant Staphylococcus species (MRSS), and penicillin-resistant Streptococcus pneumoniae (PRSP), in pediatric patients. Information on the safety of linezolid and experience with the use of linezolid for VRE infections in pediatric patients will also be gathered in a separate, non-comparative portion of the study. A

secondary objective is to study population pharmacokinetics in pediatric patients receiving linezolid.
Study #5: Objectives – To evaluate the comparative tolerance of linezolid and vancomycin in the treatment of CSF shunt infections due to gram-positive bacteria in the pediatric population. The study may primarily enroll patients with CSF shunt infections due to coagulase-negative staphylococci.

- *Age group in which studies will be performed:*

Study #1: Male and female infants less than 3 months of age, stratified by post-conceptional age (< 34 weeks and ≥ 34 weeks). Further stratification based on other factors (e.g., post-natal age) may also be performed.
Study #2: Pediatric patients (male and female) from 5 through 17 years of age.
Study #3/4: Pediatric patients (male and female) from birth through 11 years of age.
Study #5: Pediatric patients (male and female) from birth through 17 years of age.

- *Study endpoints*

Study #1: Pharmacokinetic parameters will be determined from assessments of linezolid plasma concentrations. Tolerance of a single dose of linezolid in neonates.
Study #2-5: Clinical efficacy, microbiological response, and safety are the endpoints of interest for these studies.

- *Drug information*

dosage form: Intravenous Solution, Oral Tablets, and Oral Suspension

route of administration: Intravenous and/or Oral

- *Statistical information, including power of study and statistical assessments:*

Study #1: A comparison between Term and Pre-term groups will be made for pharmacokinetic parameters. The study should include at least 12 subjects with post-conceptional age < 34 weeks and 12 subjects > 34 weeks gestation.
Study #2: The study should include at least 240 subjects in each treatment arm. Assuming a 90% success rate and 60% clinical evaluability rate and using a 2-sided test with α=5% and power=80%, this target enrollment will provide a sufficient number of clinically evaluable patients to demonstrate equivalence between the two treatment groups to within 10%. All patients may be treated with oral linezolid or comparator.
Study #3/4: The total enrollment should include at least 160 patients. At least 40 subjects should have vancomycin-resistant enterococcal infections treated with linezolid. At least 30 patients should be 3 months of age or less and at least 10 of these young infants should have vancomycin-resistant enterococcal infections treated with linezolid.
Study #5: The study should have a total enrollment of at least 50 patients with CSF shunt infections. This number of patients is selected to provide preliminary information on the tolerance and efficacy of linezolid for CSF shunt infections.

- *Labeling that may result from the studies*: Appropriate sections of the label may be changed to incorporate the findings of the studies.

- *Format of reports to be submitted*: Full study reports addressing the issues outlined in this request with full analysis, assessment, and interpretation should be provided for all requested studies. INCLUDE OTHER INFORMATION AS APPROPRIATE.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before September 30, 2004, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity extends only to existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of studies in response to this Written Request.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

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

Sincerely,

{See appended electronic signature page}

Mark Goldberger, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Mark Goldberger
5/14/02 03:58:37 PM

MEMORANDUM OF TELECON

DATE: Wednesday, June 14, 2002

APPLICATION NUMBER: NDA 21-130, Zyvox (linezolid tablets) Tablets
NDA 21-131, Zyvox (linezolid injection) IV Injection
NDA 21-132, Zyvox (linezolid for oral suspension) Oral Suspension

BETWEEN:

Name: Ms. Kathleen Bonnema, Senior Biologist, Regulatory Toxicology
Dr. Marco Brughera, Senior Director, Global Toxicology
Dr. Jon Bruss, Director, Clinical Research
Dr. Sue Cammarata, Senior Director, Clinical Research
Mr. Scott Denlinger, Director Infectious Disease, Global Prescription Business
Mr. Robert Gremban, Regulatory Affairs Manager, Global Regulatory Affairs
Dr. Charles Hall, Vice President, Product Development
Dr. Marie Borin, Director, Clinical Pharmacology
Ms. Roberta Krieger, Associate Director, Global Regulatory Affairs
Ms. Sharon Olmstead, Executive Director, Washington Liaison Office
Dr. Gebre-Mariam Mesfin, Senior Research Scientist, Toxicology
Dr. Geoffrey Peng, Senior Research Scientist, Drug Metabolism
Ms. Susan Speziale, Senior Program Manager, Project Management
Dr. Steven Vonderfecht, Director, Preclinical Toxicology
Phone: 877-940-6514
Representing: Pharmacia & Upjohn

AND

Name: Ms. Beth Duvall-Miller, Regulatory Health Project Manager
Dr. Terry Peters, Acting Pharmacology Team Leader
Dr. Ken Seethaler, Pharmacology Reviewer
Dr. Susan Thompson, Medical Officer
Dr. David Ross, Medical Team Leader
Dr. Janice Soreth, Director
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Juvenile toxicity studies

Background:

Zyvox (linezolid) Tablets, IV, and for Oral Suspension were approved on April 18, 2000. Pharmacia & Upjohn (P&U) plans to submit supplemental new drug applications for pediatric indications in June 2002. FDA requested this teleconference to discuss preclinical data to support the safety of linezolid in pediatrics. In an email dated May 30, 2002, FDA

requested comparison of pharmacokinetic/toxicokinetic blood level data between animals and humans, for the following two rat studies: Study number 97-151 (Report a0003226) and Study number 2001-0476 (Report a0108336). P&U responded in an email dated June 12, 2002 **(attached)**.

Discussion:

1. Toxicity in juvenile rats:

   P&U summarized the findings in the two recent neonatal rat studies as having shown endocardial thrombosis and lipid degeneration in the liver in most animals. P&U noted that these enhanced toxicities and increased mortalities were not noted previously in juvenile rat studies at the same drug exposure levels and were not seen in different stock of adult rats. P&U explained that blood samples taken from the dead rats indicated that those animals were very sick, but that it is difficult to correlate plasma concentrations to the production of adverse effects. P&U theorized that there appears to be a difference in susceptibility to toxicity of linezolid in the Sprague-Dawley rat stock used between the earlier juvenile rat studies and these studies (IGS). P&U said they have many examples of strain sensitivity (juvenile only) but that there is no way to confirm this theory because they are unable to obtain additional rat stock used in the prior studies.

2. Toxicity in juvenile dogs:

   P&U said that the 3-week range finding study in 3-week old puppies showed high-dose effects (3 deaths) and reduced weight gain in the low-dose arm. The toxicokinetic data from this study showed that drug exposure in pups is not markedly different from adult dogs. P&U noted that there were no cardiac effects seen in the dog study (no evidence in visual inspection of ECGs); ECGs were taken at a time point approximating Cmax (as well as pre-test and end of testing). FDA recommended that P&U vary the time points for ECG measurements as Cmax is not necessarily the time of maximum QT effect. P&U agreed to submit the draft of this report soon.

   P&U confirmed that the definitive GLP 4-week dog study is slated to start on July 1, 2002. P&U said that they should have an interim, clinical pathology report (with gross organ weights) available by August 7, 2002, followed by a peer-reviewed, histopathology report by September 15, 2002. FDA requested that P&U retain liver and heart tissues for histopathological evaluation. P&U agreed to this request. P&U explained that 100 mg/kg/day was chosen as the high dose because of a mortality seen at the 120 mg/kg/day dose. P&U said that it is hard to determine whether the death was drug-related without quantitative data. P&U agreed to submit the definitive GLP 4-week dog study protocol including the rationale for dose selection. P&U said that a full draft report should be available by September 30, 2002 and the final report should be available by January 30, 2003.

   P&U agreed to provide FDA with histopathology results from liver and heart samples in addition to the marrow, testes, and spleen previously requested in the March 8, 2002 telecon expedited for submission after peer review has been completed.

3. Submission timeline:

   P&U said that they plan to submit the pediatric sNDA by June 28, 2002. P&U said that they could include a summary report of preliminary toxicity data in dogs in the sNDA submission. FDA asked P&U to closely adhere to the deadlines stated above from the juvenile toxicity studies. P&U noted that they plan to analyze adverse events (AE), drug-related AEs, and serious adverse events (SAE), particularly cardiovascular events, in their sNDA package.

Action Items:

1. P&U to submit definitive GLP 4-week dog study protocol including the rationale for dose selection. P&U to retain liver and heart tissues for histopathological evaluation.
2. P&U to submit sNDA by June 28, 2002.
3. P&U to provide histopathology results from selected target tissues after peer review has been completed.

Beth Duvall-Miller
Regulatory Health Project Manager

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/s/

Beth Duvall-Miller
7/12/02 03:31:23 PM
CSO
Minutes of June 14, 2002 telecon; juvenile tox requirements sign off

Frances LeSane
7/15/02 05:01:10 PM
CSO

Terry Peters
7/29/02 01:54:53 PM
PHARMACOLOGIST

Susan Thompson
7/29/02 01:57:38 PM
MEDICAL OFFICER

David Ross
7/30/02 04:33:02 PM
MEDICAL OFFICER

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6. **CLINICAL STUDIES:**

P&U said that they preferred including the microbiologically evaluable (ME) results in the tables (18, 19, —— describing the pediatric clinical trials. FDA said that the intent-to-treat (ITT) analyses, particularly the modified ITT (MITT) are the most informative results to include in this section. As a compromise, both parties agreed to retain Tables 18 and — but drop the confidence intervals. In Table 19, both parties agreed to drop the MITT results from the table, but describe them in the text. P&U agreed to revise this section.

7. **ADVERSE REACTIONS:**

On line —, P&U agreed to provide the mortality rates of pediatric patients from study 0082. FDA agreed that P&U's previously proposed sentence stating that ' —— could be reinstated into the label to follow line

Action Items:

1. FDA to provide P&U with revised Table 14 (**DOSAGE AND ADMINISTRATION** section).
2. P&U to revise labeling according to discussions and agreements from this meeting. P&U to send prior to Thursday's (12/12/02) face-to-face meeting.

Beth Duvall-Miller
Regulatory Health Project Manager

DSI CONSULT: Request for Clinical Inspections

Date: August 30, 2002

To: Mathew Thomas, GCPB Reviewer/HFD-47

Through: Janice M. Soreth, M.D., Director, HFD-520

From: Beth Duvall-Miller, Regulatory Health Project Manager, HFD-520

Subject: **Request for Clinical Inspections**
NDA 21-130/S-003; 21-131/S-003; 21-132/S-003
Pharmacia & Upjohn Company
Zyvox (linezolid) Tablets, I.V., and for Oral Suspension

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

These supplements provide for the following expansion of the patient population: the treatment of pediatric patients for skin and skin structure infections, hospital-acquired pneumonia, community-acquired pneumonia, and VRE infections

Indication	Protocol #	Site (Name and Address)	Number of Subjects
Resistant gram-positive infections	0082	Stuart Adler, M.D. (Inv. #48066) Virginia Commonwealth University 1101 East Marshall Steet Sanger Hall Room 12-051, P.O. Box 980163 Richmond, VA 23298	13
Resistant gram-positive infections	0082	Jaime Deville, M.D. (Inv. #48850) UCLA Office of Clinical Trials 10900 Wilshire Boulevard, Suite 170 Los Angeles, CA 90024	13
Uncomplicated skin and skin structure infections	0065	Corazon Oca, M.D. (Inv. #46234) Southland Clinical Research Center 11160 Warner Avenue #219 Fountain Valley, CA 92708	27

Uncomplicated skin and skin structure infections	0065	Paul Qaqundah, M.D. (Inv. #46637) Pediatric Care Medical, Inc. 17822 Beach Boulevard, Suite 278 Huntington Beach, CA 92647	27

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **December 1, 2002**. We intend to issue an action letter on this application by (action goal date) **December 20, 2002**.

Should you require any additional information, please contact Beth Duvall-Miller at (301) 827-2128.

Concurrence: (if necessary)

Susan Thompson, M.D., Medical Officer (Secondary reviewer)
Sumathi Nambiar, M.D., Medical Reviewer

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/s/

Janice Soreth
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