CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-130

21-131

21-132

CORRESPONDENCE

HFD-520/Duvall-Mil

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

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

OCT 14 1999

Dear Mr. DiRoma:

Please refer to your new drug applications (NDAs) for Zyvox™ (linezolid) Tablets, IV Injection, and Oral Suspension.

As per the teleconference on September 8, 1999, between Mr. Peter DiRoma and Ms. Beth Duvall-Miller of this Division, your proposed tradename "Zyvox" is acceptable. Please note, however, that should dispensing errors occur in the future due to similarity of names and doses with other approved drug products, we may ask that you change the proprietary name for linezolid in the U.S.

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

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Pharmacia & Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

Office of:
Peter J. DiRoma
Senior Regulatory Manager
Regulatory Affairs
Telephone No. (616) 833-8070
Facsimile No. (616) 833-8237

November 11, 1999

Dr. Joel Jiang
Division of Anti-Infective Drug Products, HFD-520
Center for Drug Evaluation Research
Food and Drug Administration
9201 Corporate Blvd
Rockville, MD 20850

Re: **NDA 21-130**
ZYVOX (linezolid)
Jaz® disk with additional variables

DESK COPY

Dear Dr. Jiang:

Per your request, enclosed are the additional variables for the new (statplus.xpt) data set. The disk contains four "folders" - one for each of the 4 studies you are working on (31, 33, 48a, and 51). Within each folder are the following files:

statplus.xpt (the transport file of the STATPLUS data set)
fmt3.cpt (the format library)

A complete listing of the variables in the statplus.xpt data set are provided as an attachment. Please note some of the variables listed in the attachment will apply to the data sets that will be sent to Dr. Erica Brittain at a later date.

If you should have any questions on the enclosed information, please contact Peter DiRoma at (616) 833-8070. Please address any correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN CO.

Peter J.DiRoma
Senior Regulatory Manager

PJD:mlw/Attachments
cc: Ms. Beth Duvall-Miller

Office of:
Peter J. DiRoma
Senior Regulatory Manager
Regulatory Affairs
Telephone No. (616) 833-8070
Facsimile No. (616) 833-8237

November 15, 1999

Division of Anti-Infective Drug Products, HFD-520
Center for Drug Evaluation Research
Food and Drug Administration
Document Control Room
9201 Corporate Blvd
Rockville, MD 20850

General Correspondence

Re: NDA 21-130
ZYVOX™ Tablets
(linezolid tablets)

Dear Sir/Madam:

We have received your fax dated 3 November 1999 requesting that a specification is set for linezolid particle size. In regards your request, please find attached our rationale why we believe a specification is not necessary.

We look forward to discussing this issue with you at our 17 November 1999 teleconference.

Attending for P&U:

Dr. Vince McCurdy - Director Pharmaceutical Development
Rick Davison - Pharmaceutical Development
Dr. Gordon Halstead - Pharmaceutical Development
Dr. Gail Jungbluth - Biopharmaceutics
Peter DiRoma – Regulatory Affairs

Should the FDA have any questions regarding this submission, please contact Peter J. DiRoma at (616) 833-8070.

NDA 21-130
ZYVOX™ Tablets

Sincerely,

PHARMACIA & UPJOHN CO.

Peter J.DiRoma
Senior Regulatory Manager
Regulatory Affairs

attachments

Pharmacia & Upjohn

Office of:
Peter J. DiRoma
Senior Regulatory Manager
Regulatory Affairs
Telephone No. (616) 833-8070
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November 17, 1999

Post-it® Fax Note 7671	Date 11/17	# of pages ▶ 8
To BETH DUVALL-MILLER	From PETER DiROMA	
Co./Dept.	Co.	
Phone #	Phone (616) 833-8070	
Fax # (301) 827-2325	Fax #	

Central Document Room
Center for Drug Evaluation Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Re: NDA 21-130
ZYVOX™ (linezolid)

ELECTRONIC ARCHIVAL COPY

AMENDMENT NO. 1

Dear Sir/Madam:

As requested by the Division of Anti-Infective Drug Product, enclosed is a single CD ROM containing new data sets (statplus.xpt) for the following linezolid Phase III studies: M/1260/031, 33, 39a, 48a, 51, 54a and 55). Within each folder are the following files:

statplus.xpt (the transport file of the STATPLUS data set)
fmt3.cpt (the format library)

A complete listing of the variables in the statplus.xpt data set are provided as an attachment.

If you should have any questions on the enclosed information, please contact Peter DiRoma at (616) 833-8070. Please address any correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN CO.

Peter D. DiRoma

Peter J.DiRoma
Senior Regulatory Manager

Attachments
cc: Ms. Beth Duvall-Miller

Hi Beth.
This CD was sent today to 7 Wilkins Ave, Document Control Room. This CD Rom includes the datasets we sent Dr. Jiang last week + the datasets/variables requested by Dr. Brittain. The macros will follow next week. Please call if you have any questions. Peter

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
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Telephone (616) 833-4000

Pharmacia & Upjohn

Office of:
Peter J. DiRoma
Regulatory Manager
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Telephone No. (616) 833-8070
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November 17, 1999

Division of Anti-Infective Drug Products, HFD-520
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 21-130
ZYVOX ™(linezolid tablets)

General Correspondence
Response to Statistical Reviewer Questions

Sir/Madam:

We are responding to the questions received by the FDA on 17 November 1999 (e-mail from Dr. Erica Brittain is attached) regarding patient eveluability for protocol M/1260/0054a.

Patient 5410026 did have a positive culture (of the pleural fluid) within the evaluable window but since the investigator's diagnosis was "bacteremia of unknown source" (and not "other"), the pleural fluid culture was considered an invalid source. The patient did have a positive blood culture but it fell outside of the 96 hour window and so the patient was, in fact, unevaluable (hence inclusion in the MITT but not the ME.).

The remainder of the patients all had cultures which were outside the evaluable window. Many of these seventeen patients had cultures which appear to be within four days of Baseline by dates (e.g., Nov 17 minus Nov 13 = 4 days) but since we do not have the times of culture, we counted each calendar day as a full 24 hours. So, in the above example, Nov 13, 14, 15, 16, and 17 were each counted as a 24 hour period. Thus, 24 + 24 + 24 + 24 + 24 = 120 hours.

If you should have any questions on the enclosed information, please contact Peter DiRoma at (616) 833-8070. Please address any correspondence to Unit 0635-298-113.

Sincerely,

Peter Di Roma

Peter J. DiRoma
Senior Regulatory Manager

Post-it® Fax Note 7671	Date 12/2/99	# of pages ▶ 3
To Beth DuVall-Miller	From Peter J. DiRoma	
Co./Dept. FDA	Co. P&U	
Phone #	Phone # (616) 833-8070	
Fax # (301) 827-2325	Fax #	

Office of:
Peter J. DiRoma
Senior Regulatory Manager
Regulatory Affairs
Telephone No. (616) 833-8070
Facsimile No. (616) 833-8237

December 2, 1999

Central Document Room
Center for Drug Evaluation Research
Food and Drug Administration
9201 Corporate Blvd
Rockville, MD 20850

Re: NDA 21-130
ZYVOX™ Tablets (linezolid tablets)

General Correspondence

Response to Statistical Reviewer Questions

Dear Sir/Madam:

In response to the questions raised by Dr. Erica Brittain of the Division of Anti-Infective Drug Products in a 24 November 1999 e-mail (Attachment 1), please find enclosed P&U's responses:

Response 1:

The variable CULTDONE was added to the STATPLUS data set at the FDA's request. CULTDONE = 1 (Yes) means that a patient had a culture from a valid culture source within the TOC window. This includes cases where a patient did not have a pathogen isolated at baseline, or had culture results assessed by a local laboratory. The first four patients in Study 54A identified by Dr. Brittain did not have a pathogen isolated at baseline; hence they have a missing patient micro outcome (PATOUTC). Eight of the other nine patients had TOC culture results assessed by a local lab. As a general rule, local laboratory micro results were not used in the determination of pathogen or patient micro outcomes. Hence, the patient micro outcomes for these patients are all presumed or indeterminate. (A similar situation may exist for Studies 31 and 48A, where some local lab micro data was collected.) For patient 5410300, there was evidence that a blood culture was obtained and received by the central lab (so CULTDONE = 1), but no other information was available; hence, the patient's micro outcome is presumed.

NDA 21-130
ZYVOX™ Tablets

Response 2:

To determine DEATHEOT (Did Patient Die by EOT), the variable DEATHEND (Day Relative to Date of Last Dose) was compared to the Last day of EOT window as follows:

If DEATHEND <= Last Day of the EOT window, then DEATHEOT=1 (yes)

Patients who did not die had missing values for DEATHEND. In SAS Programming, a value of missing (.) is considered to be less than 0, therefore these patients were assigned DEATHEOT=1.

(The same error occurred in computing DEATHFU and DEATHLTF).

We have now corrected this error, and have rebuilt the STATPLUS data sets for all of the Phase III studies. The corrected version of these data sets was submitted to the FDA on 29 November 1999 (NDA 21-130, Amendment #2). Also, the following code could be used:
if DEATH (from the STATPLUS data set)=0 then do;
DEATHEOT=0; DEATHFU=0; DEATHLTF=0;
end;

Response 3:

For patients with a Primary Diagnosis of "Other", the specific diagnosis can be found using the variable DXINFT (Infectious Diagnosis Specify) from the MRSA_ANL data set.

Response 4:

VREFLAG is defined on the patient level, and =1 if a patient had >=1 qualifying Enterococcus pathogens at baseline with a vancomycin interp='R'; and =0 otherwise (including cases where a patient had no pathogens isolated at baseline). If a patient is in the MITT subpopulation with VREFLAG = 0, that implies that the patient had a pathogen at baseline that was NOT vancomycin resistant.

If you should have any questions on the enclosed information, please contact Peter DiRoma at (616) 833-8070. Please address any correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN CO.

Peter J. DiRoma
Senior Regulatory Manager
Attachments

Post-it® Fax Note 7671	Date 12/6/99 # of pages ▶ 3
To Beth DuVall-Miller	From Peter J. DiRoma
Co./Dept. FDA	Co. P&U
Phone #	Phone # (616) 833-8570
Fax # (301) 827-2325	Fax #

Office of:
Peter J. DiRoma
Senior Regulatory Manager
Regulatory Affairs
Telephone No. (616) 833-8070
Facsimile No. (616) 833-8237

December 6, 1999

Division of Anti-Infective Drug Products, HFD-520
Center for Drug Evaluation Research
Food and Drug Administration
Document Control Room
9201 Corporate Blvd
Rockville, MD 20850

General Correspondence

Re: NDA 21-130
ZYVOX™ Tablets
(linezolid tablets)

Dear Sir/Madam:

P&U is responding to the questions in the 6 December 1999 e-mail from Ms. Beth Duvall-Miller and Dr. Erica Brittain to P&U (attachment 1) regarding the algorithms in the study report for VRE protocol M/1260/0054. Please find our response in attachment 2.

Should the FDA have any questions regarding this submission, please contact Peter J. DiRoma at (616) 833-8070.

Sincerely,

PHARMACIA & UPJOHN CO.

Peter J. DiRoma
Senior Regulatory Manager
Regulatory Affairs

NDA 21-130
ZYVOX™ Tablets

Attachment 2

Table 7 in the Algorithms document deals with the situation where a pathogen (from a valid culture source) is present at baseline. In this case, sponfu=missing (actually .) and no micro data from a valid culture source results in patoutc=9 (formatted to M in displays).

For patients with no pathogen (from a valid culture source) at baseline, one must refer to Table 8 in the Algorithms document, to see that in nearly all cases, the value for patoutc is missing (actually .). This is the case for the 11 patients identified by Dr. Brittain. Note that for analysis purposes, there is effectively no difference between M and . as outcomes for patoutc. The two different designations for missing merely distinguish between the cases of presence and absence of a baseline pathogen.

Finally, all of the above applies to the other Phase III studies as well.

Post-It® Fax Note 7671	Date 12/20/99	# of pages ▸ 3
To Beth DuVall-Miller	From Peter DiRoma	
Co./Dept. FDA	Co.	
Phone #	Phone # (616) 833-8070	
Fax # (301) 827-2525	Fax # (616) 833-8237	

Office of:
Peter J. DiRoma
Regulatory Manager
Regulatory Affairs

Telephone No. (616) 833-8070
Facsimile No. (616) 833-8237

December 20, 1999

Division of Anti-Infective Drug Products, HFD-520
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 21-130
ZYVOX ™(linezolid tablets)

General Correspondence
Response to Statistical Reviewer Questions

Sir/Madam:

We are responding to the e-mail from Dr. Erica Brittain received on 9 December 1999 (attached) regarding discordant culture results for protocol M/1260/0054a.

Question 1: Does the sponsor agree with this breakdown, if so, we would like the sponsor to provide and explanation for the rate of culture, taking into account deaths, primary indication, baseline culture status, and any other relevant information (attachment 1)?

Response: P&U 's breakdown is slightly different than that from the FDA. Our breakdown is as follows:

- Concordant: 24 (clinical cure & DE or clinical failure & DP)
- Discordant: 9 (clinical cure & DP or clinical failure & DE)
- New Pathogen: 6 (1 reinfection, 5 colonizations)
- Only Clinical Missing: 1 (2 additional patients with clinical missing also had a micro outcome of 'M')
- No Culture Result: 101 (This category counted patients with micro outcomes of PE, PP, Indeterminate, or missing. Some of the PP patients included in this count because they used additional antibiotics due to lack of efficacy;)
- (new category) Clinical Indeterminate & DP/DE Micro: 2 (Patients 5410066 and 5410133)

abbreviations: DE-documented eradication, DP-documented persistence, PE-presumed eradication,

PP-presumed persistence, M-missing

Also, although requested by the protocol, whether or not follow-up cultures were obtained was often affected by patient mortality, clinical practice (esp for SST indication - if wound is healed no further culture is collected) and the patient's clinical symptoms.

Question #2: We would like to sponsor to comment on the discordant culture results:

Response: These patients presented with very complex multifactorial disease, multiorganism infections, and the clinical symptoms which were not always predictive of microbiologic status.

If you should have any questions on the enclosed information, please contact Peter DiRoma at (616) 833-8070. Please address any correspondence to Unit 0635-298-113.

Sincerely,

Peter J. DiRoma
Senior Regulatory Manager

Pharmacia & Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

Post-it® Fax Note 7671	Date 1/26/00	# of pages ▶ 2
To BETH DUVALL-MILLER	From P.J.D. ROMA	
Co./Dept. FDA	Co.	
Phone #	Phone # (616) 833-8570	
Fax # (301) 8272325	Fax #	

January 26, 2000

Division of Anti-Infective Drug Products, HFD-520
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 21-130
ZYVOX ™ Tablets
(Linezolid Tablets)

General Correspondence
Response to Dr. John Alexander's Questions

Dear Sir/Madam:

Pharmacia & Upjohn's response to FDA Clinical reviewer questions of 28 December 1999 are enclosed.

Question: In order to expedite my review of the studies for complicated and uncomplicated skin and skin structure, I would like your help in sorting through the patients identified with coagulase negative Staphylococci. Please forward a list of all subjects with skin infection due to coagulase-negative Staphylococci, as opposed to colonization on culture. I expect that most (if not all) of the coagulase-negative Staphylococci in the trials of uncomplicated skin infections are contaminants rather than true pathogens. The same is probably true in the trial of complicated skin infections, but there may be subjects where the coagulase-negative Staphylococci is the actual pathogen. Please provide a list of subjects for whom you believe this is the case.

Response:

The following patients have been identified as having coagulase negative Staphylococci:

Patients with coagulase negative staphylococci		
Protocol	**Investigator #**	**Patient #**
039	18962	3910339
	18980	3910258
055	20192	5563022
	20182	5553033
	20182	5563022
	20182	5525015
031	04597	3132638
	16112	3131977
	17347	3137511
	18541	3139896
	19207	3137024
	19210	3137555
	19810	3134570
	20573	3135035

If you have any questions related to this submission, please contact me at (616) 833-8070 or address correspondence to mailstop 0636-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Peter J. DiRoma
Regulatory Affairs Manager

PJD:kmv
Enclosures

Post-it® Fax Note 7671	Date 12/29/99	# of pages ▶ 15
To BETH DUVALL-MILLER	From PETER DiROMA	
Co./Dept. FDA	Co.	
Phone #	Phone # (616) 833-8070	
Fax # (301) 827-2225	Fax # (616) 833-8237	

Office of:
Peter J. DiRoma
Regulatory Manager
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e-mail: peter.j.diroma@am.pnu.com

December 29, 1999

Division of Anti-Infective Drug Products, HFD-520
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 21-130
ZYVOX ™ Tablets
(Linezolid Tablets)

GENERAL CORRESPONDENCE

Response to Statistical Reviewer Questions of 23 December 1999.

Dear Sir/Madam:

Please find enclosed our response to the 23 December 1999 e-mail from Dr. Erica Brittain regarding sponsor follow-up clinical assessments for study M/1260/0055 (attachment 1).

Response: Sponsor's Clinical Outcome at the follow-up depends not only on the investigator's assessment (at both EOT and follow-up) but also depends on the level of compliance (days or doses) and whether or not an antibiotic was taken for lack of efficacy. Please refer to Tables 5 and 6 in Section 9.5.2.2 of the protocol M/1260/055 study report for appropriate algorithms (attachment 2).

Please note that these tables were subsequently amended by IND [redacted] to reflect the QID rather than BID dosing regimen employed in this double-blind, double-dummy designed trial (attachment 3).

If you should have any questions regarding this information, please contact me at (616) 833-8070. Please address correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Peter J. DiRoma
Regulatory Affairs Manager

Attachments

Attachment 1: 12/23/99 e-mail from Dr. Erica Brittain.

Attachment 2: Tables 5 and 6 from protocol 055 study report (original study report submitted to IND [redacted] 22 September 1999).

Attachment 3: Amended tables 5 and 6 for protocol 055 study report (amendment #1 for this study was submitted to [redacted] 8 October 1999).

Office of:
Peter J. DiRoma
Senior Regulatory Manager
Regulatory Affairs
Telephone No. (616) 833-8070
Facsimile No. (616) 833-8237

November 15, 1999

Division of Anti-Infective Drug Products, HFD-520
Center for Drug Evaluation Research
Food and Drug Administration
Document Control Room
9201 Corporate Blvd
Rockville, MD 20850

General Correspondence

Re: **NDA 21-130**
ZYVOX™ Tablets
(linezolid tablets)

Dear Sir/Madam:

We have received your fax dated 3 November 1999 requesting that a specification is set for linezolid particle size. In regards your request, please find attached our rationale why we believe a specification is not necessary.

We look forward to discussing this issue with you at our 17 November 1999 teleconference.

Attending for P&U:

Dr. Vince McCurdy - Director Pharmaceutical Development
Rick Davison - Pharmaceutical Development
Dr. Gordon Halstead - Pharmaceutical Development
Dr. Gail Jungbluth - Biopharmaceutics
Peter DiRoma – Regulatory Affairs

Should the FDA have any questions regarding this submission, please contact Peter J. DiRoma at (616) 833-8070.

NDA 21-130
ZYVOX™ Tablets

Sincerely,

PHARMACIA & UPJOHN CO.

Peter J.DiRoma
Senior Regulatory Manager
Regulatory Affairs

attachments