

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
40032

CORRESPONDENCE

Cyclophosphamide
Tablet, 50 mg
ANDA # 40-032

MAR 9 1992

Mr. Donald H. Chmielewski
Director, Regulatory Affairs
Roxane Laboratories, Inc.
P. O. Box 16532
Columbus, OH 43216-6532

Dear Mr. Chmielewski:

Reference is made to the protocol for a bioequivalence study and associated dissolution data submitted November 26, 1991 in support of your cyclophosphamide tablets.

The protocol has been reviewed by the Division of Bioequivalence and we have the following comments:

COMMENTS:

1. As the bioequivalence study has already been started, the review of protocol #12427 will not be done at this time, we await submission of the final study report.
2. The in vitro dissolution data does not meet with agency specifications and is, therefore, not acceptable.

RECOMMENDATIONS:

The in vitro dissolution testing conducted by Roxane Laboratories, Inc. on its cyclophosphamide tablets, 50 mg, lot # 919027, is not acceptable. Both the volume of the dissolution medium and the methodology are not according to the FDA requirements. The dissolution testing should be conducted on 12 individual dosage units each of both the test and the reference products' in 900 mL of water (deaerated) using USP XXII Apparatus 1, (basket) at 100 rpm. The test drug should meet the following specifications:

Not less than % of the labelled amount of the drug
in the dosage form is dissolved in 45 minutes.

You should redo dissolution testing according to the above specifications giving individual tablet data in a comparative dissolution profile measured at 15, 30, 45 and 60 minutes, and submit such data in full with the final report of the in vivo bioequivalence study.

All responses and correspondence with regard to this letter should be sent to the Office of Generic Drugs, HFD-630.

Sincerely yours,

|S|

Shrikant V. Dighe, Ph. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

cc: 3/6/92
HFD-632 Pollock/
HFD-650 (Dighe, CST)
lsg 02-28-92 (N40032.PRO)
bio letter

Cyclophosphamide Tablets USP, 50 mg
ANDA 40-032

APR 27 1995

*Chmielewski
LNC_{max}*

Roxane Laboratories
Attention: Donald H. Chmielewski
P.O. BOX 16532
Columbus, OH 43216

Dear Mr. Chmielewski:

This is in reference to your abbreviated new drug application dated November 26, 1991, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cyclophosphamide Tablets USP, 50 mg.

Reference is also made to your amendments dated May 17, 1994, July 12, 1994 and January 5, 1995, January 13, 1995; and to our previous deficiency letter of March 28, 1994.

The Office of Generic Drugs in consultation with the Division of Biometrics, has concluded that the application is not approvable under section 505 of the Act, since the bioequivalence study has failed to demonstrate that the test product is bioequivalent to the reference listed drug for the following reasons [21 CFR §314.127(a)(6)(i)]:

1. The overall 90% confidence interval (CI) for log-transformed C_{max} (LNC_{max}) of _____ %, is not within the acceptable range of 80 - 125%.
2. There were four dosing regimens (50 mg, 100 mg, 150 mg and 200 mg) used in the bioequivalence study, which when statistically analyzed demonstrated a significant dose-by-treatment interaction for LNC_{max} . The LNC_{max} data fails to establish the equivalence of test and reference products at the 50 mg, 100 mg, or 150 mg doses and also fails to consistently demonstrate equivalence at the 200 mg dose, the cause of which can not be elucidated from the data. Even after excluding subject #8, who was in the 100 mg dose regimen during the study, the p-value for dose-by-treatment interaction for $Ln C_{max}$ was sufficiently small ($P < .10$) thus, it cannot be assumed that the relative performance of the products is the same for all doses. The LNC_{max} data from the study cannot consistently establish the equivalence of the test and reference product at the four dosing regimens.

3. The exclusion of subject #8 is not acceptable since there are no documented test results on the subject that demonstrates that her gastrointestinal function was affected.
4. In the future, please consider that dissolution testing utilizing the same lots of both the test and reference products that were used in the bioequivalence study is required, and was not included in this submission. Dissolution testing should be conducted in 900 mL of deaerated water, at 37°C using USP 23 apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

Not less than % of the labeled amount of cyclophosphamide in the dosage form are dissolved in 45 minutes.
5. No explanation was provided for the "no samples received for assay" status of subject #13.

Based upon the deficiencies outlined above, it is the opinion of the Division of Bioequivalence, that a new *in vivo* bioequivalence study will be needed to support the approval of this abbreviated new drug application.

The Office of Generic Drugs will suspend any further review of this application until an amendment containing complete information and data necessary to support your chosen plan of action is submitted to the Agency.

The file is now closed. It is required that an action described under 21 CFR §314.120 and 21 CFR §314.96 be taken, which will either amend or withdraw the application. **Should it be decided to amend the application, the amendment should respond to all cited chemistry, labeling and bioequivalence deficiencies stated above and/or to those presented in previous letters.** In the event that reformulation of the test product is needed to meet the agency's bioequivalence requirements, revised chemistry, manufacturing, controls and labeling information should also be included in the amendment. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. **The response to this letter will be considered as a Major Amendment and should be so designated in your cover letter. The cover letter should clearly state what information is being provided in the submission (i.e., Chemistry, Bioequivalence, Labeling).** If there is substantial disagreement with our reasons for not approving this application, a hearing request can be submitted.

If you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

^
/S/ ^

4/27/95

Douglas L. Sporn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation
and Research

The guidance offered in this correspondence represents the best judgement the Office can offer based on submitted information, current scientific knowledge, and the proposed issue(s) at hand. Revisions of our statements may be necessary as scientific knowledge progresses and information changes. Should you have any questions, please call Jason Gross, Pharm.D., Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

~~Keith K. Chan, Ph.D.~~
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

September 3, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ANDA 40-032 AMENDMENT

N/AB

Re: ANDA 40-032
Cyclophosphamide Tablets, USP, 25 mg & 50 mg

Telephone Bioequivalence Amendment

Dear Sir or Madame:

Reference is made to the above mentioned abbreviated new drug application, and to a telephone conversation between Robert W. Pfeifer of Roxane Laboratories and Lizzie Sanchez, Pharm.D. of the Division of Bioequivalence on August 24, 1998.

Requests in the telephone conversation were the following:

In the Analytical Report, (1) what was the actual number of serum samples received from the clinical sites, and (2) what was the reason for each of the missing data points (address each data point individually).

In the Clinical Report, (1) what was the number of blood samples actually collected at the clinical sites, and (2) what were the specific reasons for failure to transport any serum samples to the analytical site.

Information on all missing analytical data points is provided in the attached **Table A**. There were a total of 38 missing data points following receipt of samples for analysis. Please note that although these samples were received at _____, results were not reported due to reasons presented in the table.

A summary of the samples collected per site and per patient is provided in the attached **Table B**. Actual number of samples received for analysis was 824. Please note that those samples that were missed (i.e., not drawn) and/or lost at the site are included in the table.

In preparing this amendment, minor discrepancies concerning sample draw data and samples received were discovered on the data listings included in Appendices 16.2.5.4.1 and 16.2.5.5.2 of the final clinical study report. Please note that file notes have been added to the Case Report Forms in question to explain these discrepancies. Tables A & B include information correcting these discrepancies.

SEP 04 1998

Patient safety or conclusions presented in the final report were not affected by these discrepancies.
We apologize for any confusion.

If you have any comments or questions, please contact me at the telephone number listed below.
Thank you.

Respectfully,

A handwritten signature in cursive script that reads "Johnnie for Sean Alan Reade".

Sean Alan F. X. Reade, M.A.
Director
Regulatory Affairs - New Drugs and Services
Roxane Laboratories, Inc.
614/276-4000, ext. 2345
FAX: 614/276-0321

Enclosure

August 10, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

~~BY AVAILABILITY~~

ORIG AMENDMENT

N/A

Attention: Ms. Lizzie Sanchez

**Re: Cyclophosphamide Tablets, USP, 25 mg & 50 mg
Amendment to ANDA 40-032**

Dear Ms. Sanchez:

Per your request, enclosed please find the study and pharmacokinetic data files for the bioequivalence study which supports our amendment. Do not hesitate to contact me if you have any difficulties in opening these diskettes. We are sending two complete sets (review and archive).

The first diskette contains the study CRF datasets and clinical laboratory datasets in Transport Format. This transport file was created with SAS Version 6.12 and using the Proc Cport command. NOTE: The MEMTYPE engine V608 was used to ensure compatibility with older versions of SAS (see SAS log file).

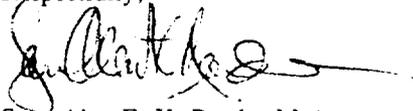
Also included are the PROC CONTENTS, annotated CRFs, data restoration instructions, the SAS Transport program's log output and the SAS Formats program for this first diskette.

The second diskette contains comma delimited files of the concentration data and the pharmacokinetic parameters calculated from the concentration data. Note that these files are divided into the 150 and 200 mg dose groups. PLA1PARM.FDA contains the pharmacokinetic parameters calculated for the 150 mg dose group and PLA2PARM.FDA contains the pharmacokinetic parameters calculated for the 200 mg dose group.

Also included for your convenience, are hard copies of the annotated CRF and contents procedure for SAS data sets.

If you have any comments or questions, please contact me at the telephone number listed below. Thank you.

Respectfully,



Sean Alan F. X. Reade, M.A.
Director
DRA - New Drugs & Services
Roxane Laboratories, Inc.
614/276-4000, ext. 2345
FAX: 614/276-0321

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AUG 11 1998

GEN. DRUGS



Boehringer Ingelheim
Roxane Laboratories

FPL Roxane Laboratories, Inc.

Mr. Douglas Sporn
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

AM

March 31, 1999

Attention: Lt. Denise Huie, Project Manager (301-827-5848)

**Subject: ANDA 40-032
Cyclophosphamide Tablets USP, 25 mg and 50 mg**

**MINOR AMENDMENT
Chemistry/Labeling Deficiencies**

Jonathan Dohnalek
Telephone (614)241-4132
Telefax (614)276-0321
E-Mail jdohnalek@col.boehringer-
ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Mr. Sporn:

We wish to amend ANDA 40-032. Enclosed please find a point-by-point response to the questions in the deficiency letter dated December 30, 1998.

We have also submitted a copy of this amendment to Ms. Deborah Grelle (Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097).

I can be reached by telephone at 614/241-4131 and by telefax at 614/276-0321. In my absence do not hesitate to contact my colleague, Jonathan Dohnalek, at 614/241-4132.

Respectfully,

Sean Alan F.X. Reade, M.A.
Director, DRA – New Drugs & Services
Roxane Laboratories, Inc.

APR 31 1999

RECEIVED

Adeline
11-5-99

November 25, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA ORIG AMENDMENT
N/A

Attention: Lt. Denise Huie

Subject: ANDA 40-032
Cyclophosphamide Tablets USP, 25 mg and 50 mg

MINOR AMENDMENT

Dear Lt. Huie:

We wish to amend ANDA 40-032. Enclosed please find a point-by-point response to the questions in the deficiency letter dated November 3, 1998.

We have also submitted a copy of this amendment to Ms. Deborah Grelle (Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097).

If you have any comments or questions, please contact me at the telephone number listed below. Thank you.

Respectfully,



Sean Alan F. X. Reade, M.A.
Director, DRA - New Drugs & Services
Roxane Laboratories, Inc.
614/276-4000 ext. 2345
FAX: 614/276-0321

Enclosure

85-1-21
10/27/98



Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Mr. Douglas Sporn
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA 40-032 AMENDMENT

June 22, 1999

Attention: Lt. Denise Huie, Project Manager (301-827-5848)

Subject: ANDA 40-032
Cyclophosphamide Tablets USP, 25 mg and 50 mg

**MINOR AMENDMENT
Chemistry Deficiency**

Jonathan Dohnalek
Telephone (614)241-4132
Telefax (614)276-0321
E-Mail jdohnalek@col.boehringer-
ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Mr. Sporn:

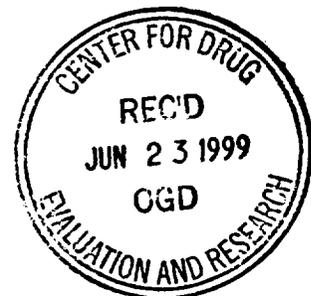
We wish to amend ANDA 40-032. Enclosed please find a response to the question in the deficiency letter dated June 17, 1999.

We have also submitted a copy of this amendment to Ms. Deborah Grelle (Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097).

I can be reached by telephone at 614/241-4131 and by telefax at 614/276-0321. In my absence do not hesitate to contact my colleague, Jonathan Dohnalek, at 614/241-4132.

Respectfully,

Sean Alan F.X. Reade, M.A.
Director, DRA – New Drugs & Services
Roxane Laboratories, Inc.



Handwritten signature

April 3, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Labeling is now complete of C. Hologram 4/17/98

*** RETURN RECEIPT REQUESTED ***

**Re: Cyclophosphamide Tablets, USP, 25 mg & 50 mg
Major Amendment to ANDA 40-032**

Dear Sir or Madame:

Under the provisions of 21 CFR 314.96, Roxane Laboratories, Inc. herewith submits an amendment to our unapproved ANDA 40-032, Cyclophosphamide Tablets, USP. This ANDA amendment is formatted in accordance with the Guidance for Industry, Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application, issued April 1997.

The reference listed product is Bristol-Myers Squibb Oncology's CYTOXAN® Tablets (cyclophosphamide tablets, USP). The active ingredient is Cyclophosphamide USP.

The product will be manufactured, packaged, labeled and tested by Roxane Laboratories, Inc. No contract manufacturers or packagers are used. The product will be tested according to the enclosed specifications and will be labeled and marketed as Cyclophosphamide Tablets, USP, 25 mg & 50 mg.

Revised and new draft labeling are contained in Section V, and the *in vivo* bioequivalence protocol and final clinical study report are provided in Section VI of this amendment.

Samples and/or a methods validation package will be submitted upon the Office's request and direction.

An Executive Summary of this amendment and all previous submissions to this application is provided on the following pages.

If you have any comments or questions, please contact me at the telephone number listed below. Thank you.

Respectfully,



Sean Alan F. X. Reade, M.A.
Director of Regulatory Affairs
Roxane Laboratories, Inc.
614/276-4000, ext. 2345
FAX: 614/276-0321

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APR 06 1998

Enclosure

1. Summary of Previously Submitted Information

- November 26, 1991 - Roxane submitted original application for the 50 mg tablet.
- January 10, 1992 - FDA letter designated application as ANDA 40-032.

- March 9, 1992 - FDA issued letter with comments on the bioequivalence study and dissolution data.

- May 4, 1992 - FDA issued a deficiency letter (CMC, Labeling, Bioequivalency).
- June 18, 1992 - Roxane submitted major amendment in response to deficiency letter.

- November 20, 1992 - FDA issued a deficiency letter (CMC, Labeling, Bioequivalency).
- March 2, 1993 - Roxane submitted major amendment in response to deficiency letter.

- At this point, all chemistry, manufacturing and control and labeling deficiencies on the 50 mg tablet were resolved.*

- August 27, 1993 - FDA issued a deficiency letter (Bioequivalency).
- December 13, 1993 - Roxane submitted amendment in response to deficiency letter.

- March 28, 1994 - FDA issued a deficiency letter (Bioequivalency).
- May 17, 1994 - Roxane submitted amendment in response to deficiency letter.

- July 6, 1994 - Dr. Lin Whei Chuang (FDA) called Roxane Laboratories requesting bioequivalency information.
- July 6, 1994 - Roxane telefaxed amendment in response to FDA request.

- July 6, 1994 - Dr. Chuang called requesting additional bioequivalency information.
- July 12, 1994 - Roxane submitted amendment in response to FDA request.

- January 5, 1995 - Roxane submitted unsolicited amendment (Bioequivalency).

- January 13, 1995 - Roxane submitted unsolicited amendment (Bioequivalency).

- April 27, 1995 - FDA issued a deficiency letter (Bioequivalency).

- January 8, 1996 - Roxane submitted amendment with proposed bioequivalence protocol (No. 17680/CCP0196).

- June 13, 1996 - FDA issued letter with comments on the bioequivalence protocol.
- July 9, 1997 - Roxane submitted amendment to revise bioequivalence protocol.

- August 14, 1997 - FDA issued letter regarding status of application.
- August 21, 1997 - Roxane submitted letter stating results of second biostudy would be submitted to application in early 1998.

2. Summary of this Major Amendment

2.1 Chemistry, Manufacturing and Controls

Introduced the manufacture, packaging, specifications, analytical methods, stability and test results of the Cyclophosphamide Tablet, USP, 25 mg strength.

Provided documentation and test results on a new biostudy/stability lot of Cyclophosphamide Tablet, USP, 50 mg strength (**the components and composition of the 50 mg tablet were not revised**).

Updated all relevant tests and methods to USP 23/NF 18.

Updated master batch record to reflect consolidation of operations at Roxane Laboratories' Oak Street facility. Previously, some steps were performed at Roxane's Wilson Road facility.

Tightened in-process specifications.

Added additional related compound specifications for the drug product.

Updated analytical validation reports.

2.2 Bioavailability and Bioequivalence

Submitted results of a second bioequivalence study of CYTOXAN Tablets and Roxane Laboratories' Cyclophosphamide Tablets, USP. The study, conducted by [redacted] determined that the two products are bioequivalent in that the 90% confidence intervals for the log-transformed Cmax and AUC for Roxane's product were both within the range of [redacted] % of the values for the reference listed drug.

2.3 Labeling

Updated previously submitted final printed labeling for the 50 mg tablet to currently approved reference listed drug labeling (version July 1996).

Introduced draft labeling for the 25 mg strength tablet.

July 9, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855

**Re: ANDA 40-032
Cyclophosphamide Tablets USP, 50 mg**

**AMENDMENT TO PENDING APPLICATION
Bioequivalence Protocol**

Dear Sir or Madam,

Reference is made to the above mentioned abbreviated new drug application and to the January 8, 1996 submission of the protocol for the proposed bioequivalence study.

The enclosed protocol and revisions thereto, "An Open, Two-Way Crossover Bioequivalence Study of Two Formulations of Cyclophosphamide Tablets in Patients with Breast Cancer", summarizes the study. This study is a repeat of the previous study in breast cancer patients which took two years to complete and was rejected in April, 1995. The repeat bioequivalence study is ongoing, and we anticipate completion in September, 1997.

Enclosed are the Protocol Amendment I dated March 13, 1997 which has the changes marked, a list of the administrative changes made to the protocol and a final copy of the protocol with all of the changes incorporated.

Please forward these protocols to the above referenced abbreviated new drug application.

Sincerely,

A handwritten signature in black ink, appearing to read 'Sean Reade', with a long horizontal flourish extending to the right.

Sean Alan F. X. Reade, M.A.
Director, Regulatory Affairs

Enclosures

RECEIVED

JUL 10 1997

GENERIC DRUGS

January 8, 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855

NEW COMES **BIOAVAILABILITY**
NC/810

*Noted
N/A
8/11/96
H/C*

Re: **NDA 40-032**
Cyclophosphamide Tablets USP, 50 mg

AMENDMENT TO PENDING APPLICATION
Bioequivalence Protocol

Gentlemen:

Reference is made to the above mentioned new drug application.

The enclosed protocol, "An Open, Two-Way Crossover Bioequivalence Study of Two Formulations of Cyclophosphamide Tablets in Patients with Breast Cancer", summarizes our proposed future study. This study is a repeat of the previous study in breast cancer patients that was recently rejected. The only major difference is that the dose of the drug is now limited to 150 mg or 200 mg of cyclophosphamide.

Please forward this information to the referenced new drug application.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski
Director
Regulatory Affairs

RECEIVED

JAN 11 1996

GENERIC DRUGS

*Noted
3-26-96*



August 24, 1995

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855

Re: NDA 40-032
Cyclophosphamide Tablets USP, 50 mg

REQUEST FOR A MEETING

Gentlemen:

Reference is made to the above mentioned new drug application, and to the Office of Generic Drugs correspondence dated April 27, 1995 regarding the bioequivalence study submitted by Roxane Laboratories.

Although we do not agree with the final outcome expressed in the correspondence, we must now begin to finalize a new protocol that will be used for ANOTHER bioequivalence study IN CANCER PATIENTS to demonstrate the equivalence of our product to Cytosan. There are currently no generic equivalent drug products for Cytosan, and Roxane is committed to obtain approval for our product.

Pursuant to that goal we have enclosed a protocol for which we ask the Agency's comments. We have addressed the concerns expressed in the April 27 correspondence regarding dose-by-treatment interaction by selecting only the 150 mg and 200 mg dosages of the drug. The drug is dosed to breast cancer patients by surface area (100 mg/m²) in the study. Only those patients with a surface area that requires a 150 mg or 200 mg dose of cyclophosphamide will be eligible for the study. We cannot limit the dose to only one amount since the time to accrue the necessary number of patients to establish bioequivalence would be excessive.

This study, as with the previous study, will be done in breast cancer patients. The time and expense that is necessary to undertake this new study will AGAIN be substantial. We do not wish to proceed until we have met with the Office of Generic Drugs and are assured that there is agreement on our approach to demonstrate the bioequivalence of the Roxane product.

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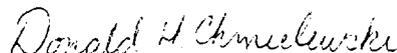
AUG 25 1995

GENERIC DRUGS

Office of Generic Drugs
August 24, 1995
Page Two

We hereby request a meeting with the Office of Generic Drugs' Division of Bioequivalence, as well as Dr. Roger Williams, to discuss this proposed study. Considering the time, effort, and expense expended on the previous study, and the lack of consensus on the acceptability of the data for this crucial drug, we believe that a meeting with Roxane representatives is warranted to discuss the proposed protocol, and obtain any Agency comments on this protocol so we are certain as to how to proceed. Please contact the Regulatory Affairs department so that a date can be arranged for this meeting after you have had time to review the enclosed protocol. We recognize your normal process is to respond in writing, but we sincerely request your assistance and cooperation in meeting with us to resolve this matter.

Sincerely,



Donald H. Chmielewski
Director
Regulatory Affairs

January 13, 1995

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855

Handwritten: IN M 15 058
2/10/95
1-27-95

RECEIVABILITY

NEW CORRESP

Re: NDA 40-032
Cyclophosphamide Tablets USP, 50 mg

**AMENDMENT TO PENDING APPLICATION
Bioequivalence Data**

Gentlemen:

Reference is made to the above mentioned new drug application, and to our correspondence dated January 5, 1995.

In that correspondence, we proposed that the data for the bioequivalence study be reanalyzed excluding Patient #8. We have been provided additional information about Patient #8 from the Investigator, Dr. Vaughn. A letter from Dr. Vaughn is enclosed detailing the malignancy history dating as far back as age twelve. We believe that this is supportive of our conclusion that this patient be excluded from the statistical analysis. We would hope for prompt approval of the bioequivalence study and ANDA.

Please forward this information to the referenced new drug application.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski
Director
Regulatory Affairs

copy: Dr. Roger Williams
Jason Gross, Pharm. D.

RECEIVED

JAN 17 1995

GENERIC DRUGS

Handwritten: 23 Jan 95
Williams

In Mkt for \$100 Divided 1-17-96



Roxane
Laboratories, Inc.

January 5, 1995

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855

RECEIVED

JAN 06 1995

GENERIC DRUGS

Re: NDA 40-032
Cyclophosphamide Tablets USP, 50 mg

**AMENDMENT TO PENDING APPLICATION
Bioequivalence Data**

Gentlemen:

Reference is made to the above mentioned new drug application, and to our pending submissions of bioequivalence data of December 13, 1993 and May 17, 1994.

This unsolicited amendment to the application is submitted pursuant to the approval of the bioequivalence study. A new assessment of the data for this clinical study in breast cancer patients by a bioequivalence/regulatory consultant led to the recommendation that the data be reanalyzed excluding Patient #8. Patient #8 is the only patient in the study who had a concomitant cancer, specifically von Recklinghausen's disease (type I neurofibromatosis), which could have resulted in the unexplainable intraindividual variation in the absorption of cyclophosphamide due to the disease's pathology. Von Recklinghausen's disease is characterized by cutaneous and internal tumors associated with central and peripheral nervous systems. It is estimated that up to 25% of patients with von Recklinghausen's disease have gastrointestinal involvement resulting in disordered gut motility, gastrointestinal stromal tumors, endocrine cell tumors of the duodenum and periampullary region, and other gastrointestinal tumors.

The following references are provided as supportive information for the proposal that the existence of a concomitant cancer with gastrointestinal involvement in a study patient justifies the exclusion from the data analysis:

1. Fuller CE, Williams GT. Gastrointestinal manifestations of type I neurofibromatosis (von Recklinghausen's disease). *Histopathology* 1991, 19:1-11.
2. Barone DA. Neurofibromatosis: a clinical overview. *Postgrad Med* 1979;66:73-80.
3. Hochberg FH, Dasilva AB, Galdabini J, Richardson EP Jr. Gastrointestinal involvement in von Recklinghausen's neurofibromatosis. *Neurology* 1974;24:1144-51.
4. Lukash WM, Johnson RB, Wentz DK. Gastrointestinal aspects of cutaneous and familial diseases. *Am J Gastroenterol* 1970; 54:589-96.
5. Lukash WM, Johnson RB. Gastrointestinal neoplasms in von Recklinghausen's disease. *South Med J* 1969 162:1237-9.

Handwritten signature/initials

Office of Generic Drugs
January 5, 1995
Page Two

Enclosed are copies of the Case Report Forms for Patient #8. All of the patient case report forms were included with the May 17, 1994 submission. Also enclosed are the statistical data for the bioequivalence study including Patient #8 [submitted with the December 13, 1993 and May 17, 1994 amendments], and excluding Patient #8 from the analysis. Reanalysis excluding Patient #8 shows that CMAX, AUC, LogCMAX, LogAUC meet the requirements for the 90% confidence intervals for bioequivalence. We request approval of the bioequivalence study and the new drug application.

Please do not hesitate to contact Roxane if any further information is needed by the Bioequivalence Division to assist in review of the study.

Please forward this information to the referenced new drug application.

Sincerely,



Donald H. Chmielewski
Director
Regulatory Affairs

*Noted - in b1
per M11
Skamjate
7/12/94*



July 12, 1994

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855

MC
BIOAVAILABILITY

Re: NDA 40-032
Cyclophosphamide Tablets USP, 50 mg

**AMENDMENT TO PENDING APPLICATION
Bioequivalence Data**

Gentlemen:

Reference is made to the above mentioned new drug application, and to a telephone conversation between Lin Whei Chuang, OGD, Bioequivalence Division, and Sue Bastaja of Roxane Laboratories on July 6, 1994.

Enclosed is a point by point response to the requests as follows:

- 1. Please provide the subject numbers from each clinical site:

Enclosed is a copy of correspondence from numbers from each clinical study site as requested.

which provides the subject

- 2. Please provide a data diskette with all raw data for the study:

The data diskette with the requested information was forwarded to the Bioequivalence Division under separate cover directly from copy of the cover letter is enclosed. on July 6, 1994. A

Please do not hesitate to contact Roxane if any further information is needed by the Bioequivalence Division to assist in review of the study.

Please forward this information to the referenced new drug application.

Sincerely,

Sue Bastaja

Sue T. Bastaja, R.Ph., J.D.
Manager
Regulatory Affairs

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JUL 13 1994

GENERIC DRUGS

*26 Jul 94
P. Bastaja*

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Roxane
Laboratories, Inc.

May 17, 1994

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855

ORIGINAL COPIES

NC

Re: **NDA 40-032**
Cyclophosphamide Tablets USP, 50 mg

AMENDMENT TO PENDING APPLICATION
Bioequivalence Data

Gentlemen:

Reference is made to the above mentioned new drug application, and to your correspondence dated March 28, 1994.

In response to the requests made in the referenced correspondence, the following information is provided:

General Comments

Roxane Laboratories views this bioequivalence study of cyclophosphamide in breast cancer patients as one of the most significant studies ever undertaken by the company. We approached it by researching the drug and discussing our proposal with the Office of Generic Drugs. Roxane (represented by Dr. Kirk Shepard and Donald Chmielewski) met with Dr. Shrikant Dighe, Director of Bioequivalence Division OGD, on two occasions, i.e., June 24, 1989 and November 21, 1989, to discuss the specifics of the protocol for the clinical study. Prior to this meeting on March 23, 1989, the protocol was submitted for review. In addition, the protocol was submitted with the initial ANDA filing on November 26, 1991. This protocol in all instances clearly stated that only the parent compound would be analyzed, that the study would be done in breast cancer patients, and that the study would be a multiple site study.

Dr. Dighe was very receptive at our meetings to the study design in breast cancer patients who were on recognized chemotherapy protocols. The model was especially interesting since the cyclophosphamide, at the time of the blood concentration samplings, was not administered with any of the other chemotherapy agents. Hence, the clear bioequivalence of the two cyclophosphamide products would be measured. This drug cannot be administered to normals, so this was clearly the only way the bioequivalence could be measured. It was noted that several clinical sites would be necessary to accrue the necessary patients to dose 24 patients. As it was, the study took 14 months to complete, since these patients are very difficult to enroll into such a study.

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GENERIC DRUGS

General Comments (continued)

The blood levels of the parent compound, cyclophosphamide, were measured. Prior to our meeting with FDA, extensive attempts were made to validate an assay for the measurement of the phosphoramidate mustard metabolite, but they were not successful. The compound is very unstable, and difficult if not impossible to detect in body fluids within the context of a bioequivalence study. Refer to Part 4 of this submission for additional discussion on the assay of the parent compound.

Part 1. Reference is made to your statement:

- "1. Cyclophosphamide (CP) has an elimination half-life of 7.5 hours (range 3-12 hours). When it was given once a day, the accumulation factor is 1.2 [Accumulation ratio = $1/(1-e^{-kt})$ [where t is the dosing interval]], which indicates that very little accumulation would occur and blood CP level would not reach steady state. This is evident from the study results that; C_{min} values were near zero (range ug/mL) compared to the mean C_{max} of 4.30 ug/mL. Thus, the study is a multiple single-dose design instead of the multiple-dose design that was proposed."

Response:

As discussed in General Comments, because cyclophosphamide is a cytotoxic agent, cancer patients were used in the study. The protocol regimen for the dosing of oral cyclophosphamide was once daily orally at doses of 1-5 mg/kg (Agency approved dosage and administration). The study was conducted according to the protocol regimens, accepted and established standard protocols for the treatment of breast cancer in the oncologic community. At steady state, the rate of drug absorption is equal to the rate of drug elimination from the body. After seven days of dosing, the blood levels for a compound with a half-life of 3-12 hours will be at steady-state, even though little accumulation occurs.

The bioequivalence study performed is a real life clinical situation with cyclophosphamide administration consistent with clinical practice in breast cancer patients. The debate as to whether the study is a multiple-dose study or a multiple single-dose study has little bearing on the clinical and blood level data obtained to measure the equivalence of the two products.

Part 2. Reference is made to your statement:

- "2. The blood monitoring schedule of the study:

Blood samples were drawn only at predose of day 1 and during day 7. Please explain how the attainment of steady state after the 7-day dosing regimen was ensured."

Response:

Because the bioequivalence study was conducted in breast cancer patients, it was not possible to obtain trough concentrations at times other than zero and 24 hours on day 7 (144 and 168 hours) of each treatment. Although there was a great deal of variability in these patients, the 0 and 24 hours cyclophosphamide concentrations indicate that these patients were at steady-state. This observation is also consistent with the half-life estimates that we obtained from these individuals as well as that quoted in deficiency 1 above.

Part 3. Reference is made to your statement:

- "3. There is evidence that the half-life of CP and its metabolites decrease with multiple doses of CP. The elimination pattern of CP throughout the two consecutive weeks of study should be reported. Please compute the elimination constant of each patient during both phases of the study and obtain the pharmacokinetic parameter, AUC0-inf (the area under the curve from time 0 to infinity). Statistical analysis should be conducted on the resulting AUC0-inf and the 90% confidence interval should be calculated."

Response:

Because the patients in the study were on recognized breast cancer protocols, they were already receiving oral cyclophosphamide as their normal therapy. Therefore, any changes that might occur during continuous treatment with cyclophosphamide should have already occurred before this study was conducted. We have provided the additional parameter (AUC0-inf) requested in our revised Table 1, included in this Part. Data is for non-normalized analysis of results.

Part 4. Reference is made to your statement:

- "4. The parent compound cyclophosphamide (CP) itself is without alkylating or cytotoxic activity. The concentration of the active metabolite, phosphoramidate mustard, should be measured in the study serum samples. The pharmacokinetic parameters, Cmax, AUC0-t, and AUC0-inf of the active metabolite should be calculated and analyzed statistically."

Response:

This request is not consistent with the advise and guidance that was received from the Bioequivalence Division from previous meetings (see General Comments, above). The protocol was submitted and discussed with the clearly stated intention that only the parent compound would be analyzed. We believe that this was consistent with the belief within the Division that parent compound analysis was all that was needed, and this was communicated informally to Roxane and

This conclusion is supported by the fact that the literature clearly documents that the phosphoramidate mustard metabolite is an intracellular alkylating metabolite that is not in the general circulation, and would not be detectable by analysis. Cyclophosphamide is activated by hepatic microsomal (P-450 mixed function oxidase) enzymes. (*Cancer Chemotherapy Handbook*, Dorr R, Fritz W; Elsevier North Holland Inc., NY, 1980; and Colvin M, Padgett CA, Fenselau C, 1973. *Cancer Res*, 33:915-918).

Because the metabolite is an intracellular metabolite and therefore cannot be detected, and because of guidance received prior to study initiation not to analyze the metabolite, the study was performed with the analysis of the parent compound only.

Conclusion:

We conclude that the study as it presently stands demonstrates the bioequivalence of the two products.

Part 5. Reference is made to your statement:

- "5. Adjustment of pharmacokinetic (PK) parameters at the 50-200 mg daily dose to the 150 mg daily dose level:
- a. Since when given at high dose or after multiple doses, CP may not exhibit linear kinetics, please justify the adjustment of the pharmacokinetic parameters.
 - b. To avoid any possible bias introduced from the adjustment of PK parameters, statistical analyses on the log-transformed data of the non-adjusted PK parameters are recommended."

Response:

- a. All dose-related pharmacokinetic parameters were adjusted to a 150 mg dose level in an effort to normalize the data for interpatient comparisons (amendment dated December 13, 1993). There is no evidence of nonlinearity across the 50-200 mg dose range.
- b. The bioavailability parameters have been evaluated both with and without normalization. The results are similar and the conclusions are identical, regardless of which data set is used. (See attached data in this Part for non-normalized data analysis.)

Part 6. Reference is made to your statement:

- "6. During statistical analysis the factors of clinical study site, daily dosage of CP or chemotherapy regimen of each patient were not considered. The appropriate statistical model used to analyze the study data should include terms for site, site-treatment interaction, dose, dose-treatment interaction, regimen and regimen-treatment interaction."

Response:

Under normal circumstance in healthy volunteers, it is agreeable that site and site-treatment interaction, dose and dose-treatment interaction should be included in the analysis. However, in this study it was agreed to from the beginning (refer to General Comments) that multiple sites would be necessary to accrue the breast cancer patients necessary to have sufficient power to measure bioequivalence. The study used 7 sites to accrue the 24 patients for the study, and there was no clear evidence of any difference in the sites. We do not believe that analysis for site and site-treatment interaction, dose and dose-treatment interaction is appropriate for this study design.

Part 7. Reference is made to your statement:

- "7. Please clarify why the analytical results shown in the 'data tracking' section include serum samples with cyclophosphamide concentration of <0.05 ug/mL or <0.1 ug/mL while the limit of quantification of the assay method was stated to be 0.01 ug/mL."

Response:

During the initial method validation process, the limit of quantitation (LOQ) for cyclophosphamide was determined to be ug/mL from a 1 mL sample. However, the precision and reproducibility of the LOQ came into question during the prestudy validation. An evaluation of the prestudy validation LOQ data indicated that the precision and reproducibility of the ug/mL LOQ was not adequate and consequently the LOQ was increased to ug/mL. In this study, the LOQ of ug/mL was generally reported. In certain cases during the study, there was less than 1 mL sample volume which required dilution prior to extraction to insure 1 mL availability for extraction and assay. When these samples were not quantifiable, the dilution factor was taken into account, resulting in alternative LOQ values, as noted. This explains the cyclophosphamide concentrations of <0.05 ug/mL or <0.1 ug/mL.

Part 8. Reference is made to your statement:

- "8. The following should be submitted:
- a. The demography (age, body weight, body height, etc.) of the study patients.
 - b. The study sequence (treatment AB or treatment BA) of each study patient.
 - c. The type of chemotherapy regimen of each patient.
 - d. The patients' clinical records taken during both pre- and post-study and the case report forms reporting adverse experiences.
 - e. Names of clinical study sites and the number of patients at each site.
 - f. The date of clinical study and the names of clinical investigators.
 - g. The lot numbers and the assay potencies of both test and reference products used in the bioequivalence.
 - h. The Institutional Review Board's approval letter of the protocol and a copy of patient's informed consent form.
 - i. An explanation for the 8 patients who did not complete the study and for patient #13 that had no samples received for assay."

Response:

The following sections in Volumes 1 and 2 respond to the point raised as referenced:

- a. Demographics: Refer to Appendix 5.4.1 of the Clinical Conduct of Study Report (Volume 1)
- b. Sequence: Refer to Appendix 5.3 of the Clinical Conduct of Study Report (Volume 1)
- c. Chemotherapy Regimen: All evaluable breast cancer patients were on a CAF, CMF, or CMFVP regimen (See protocol - Appendix 5.1 / Volume 1)
- d. Clinical Records: See Appendix 5.4.0 of the Clinical Conduct of Study Report (Volumes 1 and 2).
- e. Clinical Sites: See Appendix 5.2 of the Clinical Conduct of Study Report (Volume 1).
- f. Investigators and Dates: The dates for the study were 1-21-92 to 2-11-93. See Appendix 5.2 of Clinical Conduct of Study Report for investigators (Volume 1).
- g. Lot Number and Potency: Lot numbers of the bioequivalence products and certificates of analysis were submitted with the December 13, 1993 amendment. Copies of the certificates and protocol are enclosed in this Part.
- h. IRB Approval and ICF: See Appendix 5.1 of Clinical Conduct of Study Report Volume 1).
- i. Noncompleters: See Section 4.1 (Results tab, Clinical Results Section) in text of Clinical Conduct of Study Report (Volume 1).

We hope that the information provided is responsive to the questions of the Agency. Our desire is to provide any information necessary to assist the Bioequivalence Division in approving this study. Please do not hesitate to contact us if additional information is needed.

Office of Generic Drugs
May 17, 1994
Page Seven

Please forward this information to the referenced new drug application.

Sincerely,



Donald H. Chmielewski, R.Ph., RAC
Director
Regulatory Affairs

DHC
Federal Express

December 13, 1993

BIOAVAILABILITY

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855

N/A

Re: NDA 40-032
Cyclophosphamide Tablets USP, 50 mg

AMENDMENT TO PENDING APPLICATION
Bioequivalence Data

Gentlemen:

Reference is made to the above mentioned new drug application.

In fulfillment of the requirement to supply bioequivalence data for the drug product, the following information is provided:

1. Certificate of Analysis for Roxane Cyclophosphamide Tablets USP, 50 mg
Lot 919027
Manufactured May 1991
2. Certificate of Analysis for Cytoxan® (Cyclophosphamide) Tablets
(Mead Johnson)
Lot MMC02
3. Protocol for the bioequivalence study:
"Bioequivalence Study of Dosage Forms of Cyclophosphamide Oral Tablets (Multiple Dose, Two Way Crossover)", Protocol No. 12427 by
4. Expert Medical Opinion

Enclosed is a letter from Doctor Ronald M. Bukowski, an oncologist, regarding the parameter of CMAX being out of acceptable limits by 0.1 (confidence interval).
5. Expert Biopharmaceutical Opinion

Enclosed is a letter from Leslie Z. Benet, Ph.D., regarding the results of the study, especially the parameter of CMAX being out of acceptable limits by 0.1 (confidence interval).
6. Bioequivalence Data (1 volume)
"Bioequivalence Study of Dosage Forms of Cyclophosphamide Oral Tablets (Multiple Dose, 2-Way Crossover)",
Project No. 12427

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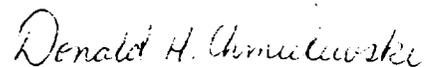
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Office of Generic Drugs
December 13, 1993
Page Two

Please forward this information to the referenced new drug application.

Sincerely,

A handwritten signature in cursive script that reads "Donald H. Chmielewski".

Donald H. Chmielewski, R.Ph., RAC
Director
Regulatory Affairs

DHC
Federal Express

YJW 121

November 26, 1991

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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GENERIC DRUGS

Attention: Office of Generic Drugs
Center for Drug Evaluation and Research
MPN II, HFD-600

Re: Cyclophosphamide Tablets USP, 50 mg

ORIGINAL SUBMISSION

Gentlemen:

Enclosed in duplicate is an abbreviated new drug application submitted for the purpose of allowing Roxane Laboratories, Inc. to manufacture, package, and distribute the drug product.

The product will be tested according to the enclosed specifications and will be labeled and marketed as Cyclophosphamide Tablets USP, 50 mg. Draft labeling is contained in Section V of this application. Samples will be submitted upon assignment of the NDA number and at the Division's request and direction. The "listed" product is Cytosan® Tablets 50 mg (Mead Johnson). A protocol for conducting a bioavailability study is contained in Section VI.

We acknowledge that the manufacturing process for this compression coated tablet is a difficult one to explain. We have made a great effort to diagram and explain it. If it is necessary to have further explanation, please do not hesitate to call us. We will gladly come to Rockville and make a presentation to the Office on the manufacturing process so that everything is understood.

The methods validation package (three copies) is contained in a separate volume under this cover letter.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski, R.Ph.
Director
Regulatory Affairs

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Enclosure

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