CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40032

CHEMISTRY REVIEW(S)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?

Unit Dose Blister Label:

Unit Dose Carton Label:

Container Labels:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Cytoxan®

NDA Number: 12-141

NDA Drug Name: Cytoxan® Tablets

NDA Firm: Bristol-Myers Squibb Company

Date of Approval of NDA Insert and supplement #:
December 20, 1995/S-081
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Labels submitted in the jacket for the side-by-side comparison.
Basis of Approval for the Carton Labeling: Labeling submitted in the jacket for the side-by-side comparison.

APPROVAL SUMMARY PACKAGE

ANDA Number 40-032
FIRM: Roxane Labs
DOSAGE FORM Tablets
TRENGTH: 25 & 50 mg
DRUG: Cyclophosphamide Tablets

1. CGMP Statement/EIR Update Status:
   EER update form attached to jacket. ACCEPTABLE as of Dec. 14, 1998.

2. Bio Study:
   Bioeq. study on 50 mg tab, Roxane lot 969064 was found acceptable 9-9-1998. Waiver granted for 25 mg tablet.

3. Methods Validation (Description of Dosage Form the same as the firm's?):
   USP drug product.

4. Stability - Are Containers used in the Study Identical to those in the Container Section (#26)?:
   Two sizes: Bottles of 100 and unit dose blisters: 100/carton

5. Labeling:
   Review summary prepared 4-02-99 is sat.

6. Sterilization Validation (if applicable):
   n/a

7. Size of Bio Batch (Firm's source of NDS OK?):
   New Bio batch #969064 of tablets.
   DMF for the BDS is acceptable 07/07/99.

8. Size of Stability Batches (If different from bio batch were they mfg. *via* the same process?):
   tablets. same

9. Proposed Production Batch (Manufacturing process the same as Bio/Stability?):
   Lot size (theor. no. of tablets): (50 mg)& (25 mg).
   Same process - blank batches submitted.

/s/ 7/6/99

Chemist: B. Cai, Ph.D./07/08/99
Supervisor: M.Smela/07/08/99
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/s/ 7/12/99

Addendum to ANDA 40-032/CR#8

July 26, 1999

FIRM: Roxane Laboratories
P.O. Box 16532
Columbus, Ohio 43216-6532

DOSAGE FORM: Tablets

STRENGTH: 50 mg & 25 mg

DRUG: Cyclophosphamide Tablets USP

Following information has been provided since last chemistry review (CR#8, 07/08/99).

1. On 07/13/98, Roxane provided a Fax Amendment for a "Letter of Commitment to FDA Request" as requested by the Labeling Division.

2. On 07/23/99, Roxane provided another Telephone Amendment to clarify an issue regarding our concerns about their stability data for the 50 mg tablets and their post-approval expiration dating extension (see tele-con record on 07/15/99). Roxane offered the following commitments to the Center:

- If their application is approved before 09/29/99, the request for extending the expiration dating periods for 25 mg and 50 mg tablets beyond 24 months will be submitted as a Prior Approval Supplement, rather than in the annual report.

- As agreed in the 07/15/99 phone call, the extension of the expiration dating period for the 25 mg tablet from 18 months to 24 months may be filed in the annual report.

- In addition, if the application is still pending approval on 09/29/99 (the 24 month checkpoint for the 25 mg tablets):

  a) Roxane will provide a fax amendment to request the agency to grant initial expiration dated of 24 months for both the 25 mg and 50 mg tablets, if the data (25 mg stability) remain within specification.

  b) Roxane will also provide the agency a commitment in above fax amendment the either 1)their request to extend the expiration dating period 24 months will be submitted as a prior approval supplement, rather than the annual report, or

2) a request to extend the expiration dating periods to 36 months will be filed in the annual report, however, they will not request extensions beyond 36 months. Roxane will only propose the later commitment if the additional stability data would support such a position. **Roxane also requested OGD to withhold issuing a decision as to which commitment would be acceptable until the fax amendment is submitted with additional data.**

Roxane committed that they would like to work with the agency to resolve this issue.

Based on above facts, this reviewer decides not to ask any question regarding their stability expiry protocol. The application is approvable.

Bing Cai/Review Chemist/07/19/99
Mike Smela, Team Leader
Division of Chemistry I
OGD/CDER

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Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST's REVIEW #8**

2. **ANDA 40-032**

3. **APPLICANT, Name/Address/Telephone:**
Roxane Laboratories
Attention: Sean Alan Reade
P.O. Box 16532
Columbus, Ohio 43216-6532
Tel. 614/276-4000

4. **LEGAL BASIS FOR ANDA SUBMISSION:** 505 j

5. **SUPPLEMENT(S)** N/A

6. **PROPRIETARY NAME:** none
Innovator drug: Cytoxan® Tablets (Bristol Myers).

7. **NON-PROPRIETARY NAME:** Cyclophosphamide Tablets USP

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS & Other DATES:**

FIRM (Roxane):	
11-26-91 (Filed 12-16-91)	Original Application
08-24-95	Request for a meeting
07-09-97	Bioeq. protocol
04-03-98	Amendment (major)
09-03-98	Bio Amendment
11-25-98	Amendment (minor)
03-31-99	Amendment (minor)
06-22-99	Amendment (minor)
FDA:	
08-12-94	Chem Acceptable, HFD-625
04-27-95	NA lett. need *new in vivo* bio study
06-13-96	Ltr from DOB, protocol accept.
08-14-97	Ltr from JPhillips
04-17-98	Labeling review w deficiencies
11-03-98	NA letter (minor)
12-30-98	NA letter (minor)
06-17-99	NA letter (minor)

10. **PHARMACOLOGICAL CATEGORY:** Cytotoxic Agent

11. **Rx or OTC:** R_x

12. **RELATED ANDA's:** none

13. **DOSAGE FORM:** Tablets

14. **POTENCY:** 50 mg & 25 mg

15. **CHEMICAL NAME:**
2-[*Bis*(2-chloroethyl)amino]tetrahydro-2*H*-
1,3,2- oxazaphosphorine 2-oxide monohydrate.

17. **COMMENTS.**
1. DP and DS are USP.
2. USP updates? None to Supp. #10.
3. There has been no QA review for this drug product.
4. Bioequivalency sat. on new biobatch.
5. EER acceptable Dec. 14th 1998.
6. Labeling sat. on 04/02/99
7. DMF is reviewed and it is adequate per 07/07/99.

A. **Comments for Action Letter:**
Approvable.

B. **Responses to our Last Action Letter:**
The only deficiency, which was cited in last NA letter dated 06/17/99, was that the DMF for the DS was inadequate.

The DMF is reviewed in this review cycle, and it is found adequate to support this ANDA.

18. **CONCLUSIONS and RECOMMENDATIONS:**
Approvable.

19. **Reviewer/Branch Chief:**

Bing Cai, Ph.D.
BRII/DCI/OGD

Michael J. Smela, Jr.
Branch Chief

Date Started: 07-06-99
Date Completed: 07-08-99
revised: -

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Chemistry Review # 8

1. *CHEMIST's REVIEW #4*

2. **ANDA 40-032**

3. APPLICANT, Name/Address/Telephone:
Roxane Laboratories
Attention: Donald H. Chmielewski
P.O. Box 16532
Columbus, Ohio 43216-6532
Tel. 614/276-4000

6. PROPRIETARY NAME: none
7. NON-PROPRIETARY NAME: **Cyclophosphamide Tablets USP**, 50mg
Innovator drug: Cytoxan[R] Tablets (Bristol Myers).

9. AMENDMENTS & Other DATES:
A. **FIRM:**
11-26-91 Application. Filed 12-16-91.
05-17-94 Amendment in response to Bio NA of 3-28-94.
unk -94 Telecon between L.Chuang and Roxane's S.Bastaja.
07-06-94 NC
*12-13-93 Amendment to NA letter re bio info.
*07-12-94 Amendment re bioavailability
B. **FDA:**
93 Labeling NA
03-09-94 Bio Review
03-28-94 NA letter from Bio re Dec.13, 93 amendment.

10. PHARMACOLOGICAL CATEGORY: Cytotoxic Agent
11. Rx or OTC: R_x

12. RELATED ANDA's: none

13. DOSAGE FORM: Tablets
14. POTENCY: 50 mg

15. CHEMICAL NAME: 2-[Bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2- oxazaphosphorine 2-oxide monohydrate.

17. COMMENTS.
A. Comments for Action Letter if any:
Bioequivalency has not been established. Review pending.

B. Responses to our Last Action Letter:
Only bio issues.

18. CONCLUSIONS and RECOMMENDATIONS:
Bio has an outstanding consult to Biometrics still not in as of 8-9-94.
USP status unchanged. DMF sat.
AP Chemistry.

19. Reviewer/Branch Chief:

Robert W. Trimmer
Branch II, Div. of Chem. I, OGD

Michael J. Smela, Jr.
Branch Chief

Date Started: 08-09-94
Date Completed: 08-12-94

CC:
ANDA 40-032
, DUP
, Division File

Endorsements:
HFD-625, R.Trimmer 8/12/94
HFD-625, M.Smela 8/12/94

/S/ 8-12-94

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Chemistry Review # 4