CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 17-422/S-045

Name: BiCNU® (Carmustine), powder for injection 100 mg/vial

Sponsor: Emcure Pharmaceuticals Limited, India

Approval Date: September 18, 2013

This "Changes Being Effected" supplemental new drug application provides for the addition of Emcure Pharmaceuticals Limited in Pune, India, as an additional manufacturer of the diluent for the drug product.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-045

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Approvable Letter	
Labeling	
Division Director's Memo	
Labeling Reviews	
Medical Reviews	
Chemistry Reviews	**X**
Environmental Assessment	
Pharmacology / Toxicology Reviews	
Statistical Reviews	
Microbiology Reviews	**X**
Clinical Pharmacology & Biopharmaceutics Review	
Other Reviews	
Administrative and Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-045

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 17422/S-045

APPROVAL LETTER

Emcure Pharmaceuticals Limited, India
Attention: Pankaj Dave, PhD
Emcure Pharmaceuticals Limited, USA
Vice President, Regulatory Affairs
21B Cotters Lane
East Brunswick, New Jersey 08816

Dear Dr. Dave:

Please refer to your Supplemental New Drug Application (sNDA) dated March 16, 2013, received March 18, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BiCNU® (Carmustine, powder for injection 100 mg/vial).

This "Changes Being Effected" supplemental new drug application provides for the addition of Emcure Pharmaceuticals Limited in Pune, INDIA as an additional manufacturer of the diluent for drug product.

We have completed our review of this supplemental new drug application. This supplement is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Hasmukh Patel, Ph.D.
Branch Chief, Branch III
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

HASMUKH B PATEL
09/18/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-045

CHEMISTRY REVIEWS

QUALITY (CMC) REVIEW #1	1. ORGANIZATION	2. NDA NUMBER
	ONDQA Div 1, Branch 3 HFD-150	017422

3. NAME AND ADDRESS OF APPLICANT	4. COMMUNICATION, DATE
Emcure Pharmaceuticals Limited (Emcure) Plot No, P-2, I.T.B.T. Park, Phase-II, MIDC, Hinjwadi Pune (city), Maharashtra 411057 INDIA	S045 (SDN 164) CBE-0 PDUFA Date: Sep. 18, 2013

5. PROPRIETARY	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
BiCNU®	carmustine	N/A

8. COMMUNICATION PROVIDES FOR:

Addition of Emcure Pharmaceuticals Limited in Pune, INDIA as a manufacturer of the diluent (Dehydrated Alcohol Injection, USP) for BiCNU®

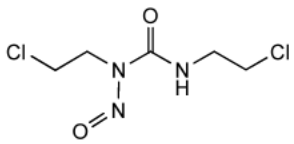
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Multiple Myeloma/Plasma Cell Disorders (8053006)	Rx only	N/A
12. DOSAGE FORM	**13. POTENCY**	
Lyophilized, for Injection	100 mg/vial	

14. CHEMICAL NAME AND STRUCTURE

1,3-Bis(2-chloroethyl)-1-nitrosourea, or *N*,*N*'-Bis(2-chloroethyl)-*N*-nitroso-urea

CODE NAME:	BCNU, L01AD01, BMY-22588
EMPIRICAL FORMULA:	$C_5H_9Cl_2N_3O_2$
MOLECULAR WEIGHT:	214.06
CASRN:	154-93-8

CHEMICAL STRUCTURE:



INDICATION:	Brain tumors, multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphomas.

15. COMMENTS

The applicant proposed to add Emcure Pharmaceuticals Limited in Pune, INDIA as an additional manufacturer of the diluent for drug product BiCNU® for Injection. Emcure has performed process validation at the proposed site including [redacted] (b) (4), sterility test, extractable study, process simulation, reconstitution and admixture study. The process validation data, comparative data (3 batches) and stability data submitted are deemed ADEQUATE to support the proposed change. The proposed site has received an overall recommendation of ACCEPTABLE from the OC. The proposed site has been recommended for APPROVAL from the Microbiology Quality perspective (B. S. Riley, Sep. 17, 2013). There are no other changes for the NDA. The proposed change will not impact adversely the identity, strength, purity and quality of the drug product.

16. CONCLUSION AND RECOMMENDATION

From the CMC perspective this supplemental application is recommended for APPROVAL.

17. REVIEWER NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Huai T. (Ted) Chang	See appended electronic signature sheet	Sep. 18, 2013

DISTRIBUTION: ORIGINAL JACKET, CSO, REVIEWER, DIVISION FILE

REVIEW NOTES — CHEMISTRY, MANUFACTURING AND CONTROLS

BACKGROUND—DRUG SUBSTANCE AND DRUG PRODUCT

BiCNU® (carmustine for injection) is available in 100 mg single dose vials of sterile lyophilized material—pale yellow flakes or congealed mass in appearance. Carmustine is highly soluble in alcohol and lipids, and poorly soluble in water. Sterile diluent for constitution of BiCNU is co-packaged with the active drug product. The diluent is supplied in an ampule containing 3 mL of Dehydrated Alcohol Injection, USP. BiCNU is administered by intravenous infusion after reconstitution as recommended. BiCNU should be stored in a refrigerator at 2–8°C (36–46°F). Diluent can be stored at controlled room temperature at 15°–30°C (59°–86°F) or in a refrigerator at 2°–8°C (36°–46°F).

The drug substance—carmustine or BCNU (bis-chloroethylnitrosourea)—is a mustard gas-related β-chloro-nitrosourea compound used as an alkylating agent in the chemotherapy of certain neoplastic diseases. As a dialkylating agent, carmustine is able to form interstrand crosslinks in DNA, which prevents DNA replication and DNA transcription.

NDA 017422 for BiCNU®—a 505(b)(1) NME application—was approved initially in 1977. Both Carmustine and Carmustine for Injection are in the current USP/NF Monograph. On Feb. 7, 2013 Emcure notified FDA that the ownership of NDA 017422 has been transferred from Bristol-Myers Squibb (BMS) to Emcure Pharmaceuticals Limited in INDIA.

PROPOSED CHANGE

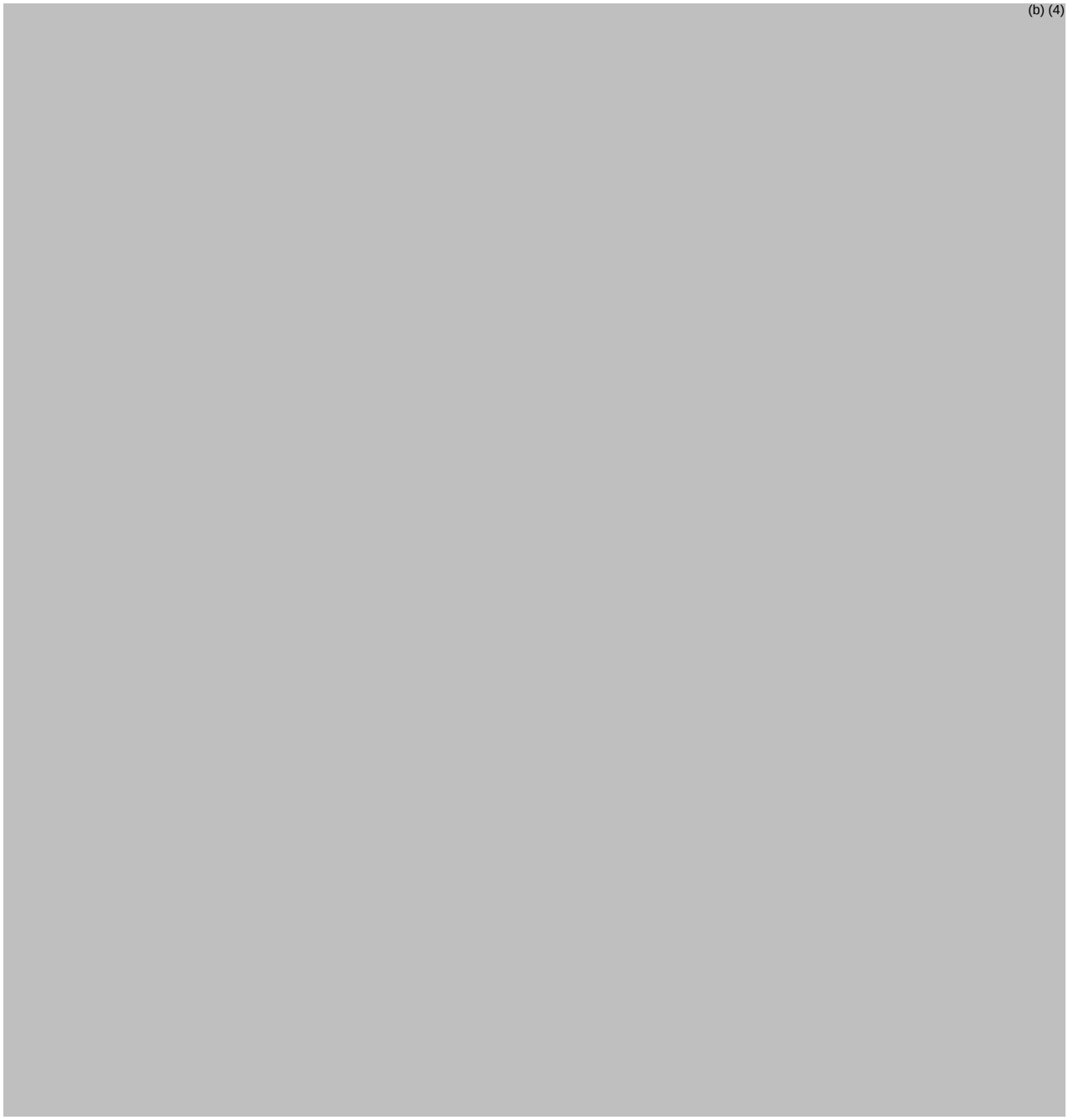
This supplement is submitted for inclusion of Emcure Pharmaceuticals Limited in Pune, INDIA as an additional manufacturer of the diluent (i.e. Dehydrated Alcohol Injection, USP) of the drug product BiCNU® 100 mg/vial. Emcure Pharmaceuticals Limited performs manufacturing, testing, stability studies and packaging of the drug product.

Diluent Manufacturing Site
Emcure Pharmaceuticals Limited (b) (4) Plot No, P-2, I.T.B.T. Park Phase-II, MIDC Hinjwadi, Pune 411057 INDIA FEI: 3005151215
Applicant U.S. Agent:
Emcure Pharmaceuticals USA Inc. 21-B Cotters Lane East Brunswick, NJ 08816

The currently approved manufacturer for diluent is Luitpold Pharmaceuticals, Inc. in Shirley, New York—added/approved in S037 in May 2007.

DETAIL OF PROPOSED CHANGE AND REVIEW

CMC Review Notes: Although there are no changes in the manufacturing process the applicant provided, as a reference, a brief description and flow diagram for the diluent manufacturing.



Emcure has performed process validation for the manufacturing of diluent at the proposed site including (b) (4) studies, sterility test, extractable study, process validation on 3 batches, process simulation study (media fill study), and reconstitution and admixture study of

Dehydrated Alcohol Injection, USP with BiCNU. The batch size for the process validation is [redacted] (b) (4)). Details are provided in the Process Validation report.

Comparative Batch Analysis

CMC Review Notes: The specification for Diluent—Dehydrated Alcohol Injection, USP—updated and approved in S037 in May 2007 has not changed. The specification is reproduced here as a background reference and for the ease of review.

Specification—Diluent (Dehydrated Alcohol Injection, USP) for BiCNU®

Test	Acceptance Criteria	Method
[redacted] (b) (4)		

Following this page, 2 pages withheld in full - (b)(4)

The applicant stated that "based on the results of (b) (4) studies, sterility test, extractable study, process validation study on 3 batches, process simulation study, reconstitution and admixture study, stability studies in accelerated and long-term condition and comparative batch analysis, it can be concluded that Dehydrated Alcohol Injection, USP, manufactured by Emcure Pharmaceuticals Limited, INDIA has no impact on the product quality. Dehydrated Alcohol Injection, USP manufactured by Emcure Pharmaceuticals Limited, INDIA can be used in addition to the diluent manufactured by Luitpold Pharmaceuticals, Inc."

CONSULT REVIEW —MICROBIOLOGY QUALITY

The changes proposed in this supplement have been reviewed and recommended for "APPROVAL" from the Microbiology Quality perspective (B. S. Riley, Sep. 17, 2013).

ESTABLISHMENT EVALUATION

The proposed diluent manufacturing site—Emcure Pharmaceuticals Limited in INDIA—has received an overall recommendation of ACCEPTABLE from the Office of Compliance (OC).

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 17422/045	**Sponsor:**	EMCURE PHARMS LTD
Org. Code:	161		21B COTTERS LANE
Priority:	1S		EAST BRUNSWICK, NJ 08816
Stamp Date:	18-MAR-2013	**Brand Name:**	BICNU
PDUFA Date:	18-SEP-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	CARMUSTINE
District Goal:	14-AUG-2013	**Product Number; Dosage Form; Ingredient; Strengths**	001; POWDER, FOR INJECTION SOLUTION; CARMUSTINE; 100MG/VIAL

FDA Contacts:	N. CHIDAMBARAM	Prod Qual Reviewer		3017961339
	J. MARTIN	Product Quality PM	(HFV-530)	3017962072
	T. CARIOTI	Regulatory Project Mgr		3017962848
	N. CHIDAMBARAM	Team Leader		3017961339

Overall Recommendation:	ACCEPTABLE	on 01-MAY-2013	by T. SHARP	()	3017963208
	PENDING	on 05-APR-2013	by EES_PROD		
	PENDING	on 26-MAR-2013	by EES_PROD		

Establishment:	**CFN:**	**FEI:**	3005151215
	EMCURE PHARMACEUTICALS LIMITED PL P1/P2,ITBT PARK, PHASE II		
	HINJWADI, PUNE, MAHARASHTRA, INDIA		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE OTHER TESTER		
	FINISHED DOSAGE PACKAGER		
Profile:	STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	01-MAY-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

CMC ASSESSMENT, CONCLUSION AND RECOMMENDATION

In this supplement the applicant proposed to add Emcure Pharmaceuticals Limited in Pune, INDIA as an additional manufacturer of the diluent (i.e. Dehydrated Alcohol Injection, USP) for drug product BiCNU® 100 mg/vial. The currently approved manufacturer for diluent is Luitpold Pharmaceuticals, Inc. in Shirley, New York. Emcure Pharmaceuticals Limited will perform manufacturing, testing, stability studies and packaging of the drug product. Emcure has performed process validation at the proposed site including (b) (4) studies, sterility test, extractable study, process validation (3 batches), process simulation study, reconstitution and admixture study. The process validation data, comparative release batch data and stability data submitted are deemed adequate to support the proposed change.

The proposed diluent manufacturing site—Emcure Pharmaceuticals Limited in INDIA—has received an overall recommendation of ACCEPTABLE from the Office of Compliance.

The changes proposed in this supplement have been recommended for APPROVAL from the Microbiology Quality perspective (B. S. Riley, Sep. 17, 2013).

There are no other changes—including manufacturing process/train, in-process controls, and specification for the drug product.

The proposed change will not impact adversely the identity, strength, purity and quality of the drug product. From the CMC perspective this supplemental application is recommended for APPROVAL.

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/s/

HUAI T CHANG
09/18/2013

HASMUKH B PATEL
09/18/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-045

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

17 SEPTEMBER 2013

NDA: 17422/S045

Drug Product Name
Proprietary: BiCNU
Non-proprietary: Carmustine for Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
16 March 2013	18 March 2013	21 March 2013	22 March 2013

Submission History (for 2nd Reviews or higher) – N/A

Applicant/Sponsor
Name: Emcure Pharmaceuticals Limited, India
Address: Plot No. P-2, (b) (4) I.T.B.T. Park, Phase-II, MIDC, Hinjwadi, Pune, Maharashtra, India
Representative: Pankaj Dave, Ph.D.
Telephone: 732-238-7880

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: CBE-0

2. SUBMISSION PROVIDES FOR: An alternate manufacturing site for the Sterile Diluent

3. MANUFACTURING SITE: Proposed for Sterile Diluent:

Emcure Pharmaceuticals Limited
Plot No. P-2, (b) (4)
I.T.B.T. Park, Phase-II,
MIDC, Hinjwadi, Pune,
Maharashtra, India

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Lyophilized powder for injection in a glass vial, 100 mg/vial packaged with dehydrated alcohol injection diluent in a glass vial, 3 mL/5 mL vial.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Anti-neoplastic agent

B. SUPPORTING/RELATED DOCUMENTS: Product quality microbiology reviews of NDA 17422/S-043 DARRTS dated 4 May 2011 and 17 May 2011.

C. REMARKS: This was an electronic submission. The proposed manufacturing site and filling equipment for the (b) (4) diluent are the same as the approved manufacturing site and filling equipment for the (b) (4) lyophilized drug product.

filename: N017422S045R1

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The diluent is (b) (4) (b) (4).

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____
Bryan S. Riley, Ph.D.
Team Leader (Acting) OPS/NDMS

B. Endorsement Block _____
Stephen E. Langille, Ph.D.
Senior Review Microbiologist OPS/NDMS

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE – N/A

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – No Change.
- Drug product composition – No Change to the diluent composition.
- Description of container closure system – The container closure system for the diluent will be a 5 mL glass vial with a 13 mm rubber stopper

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity – N/A
- Preservative Effectiveness – N/A
- Justification for not having a microbial limit specification for a non-sterile drug product – N/A

ADEQUATE

P.3 Manufacture

P.3.1 Manufacturers

Proposed alternate diluent manufacturing site

Emcure Pharmaceuticals Limited Plot No. P-2, (b) (4)
I.T.B.T. Park, Phase-II, MIDC,
Hinjwadi, Pune,
Maharashtra, India

P.3.3 Description of the Manufacturing Process and Process Controls

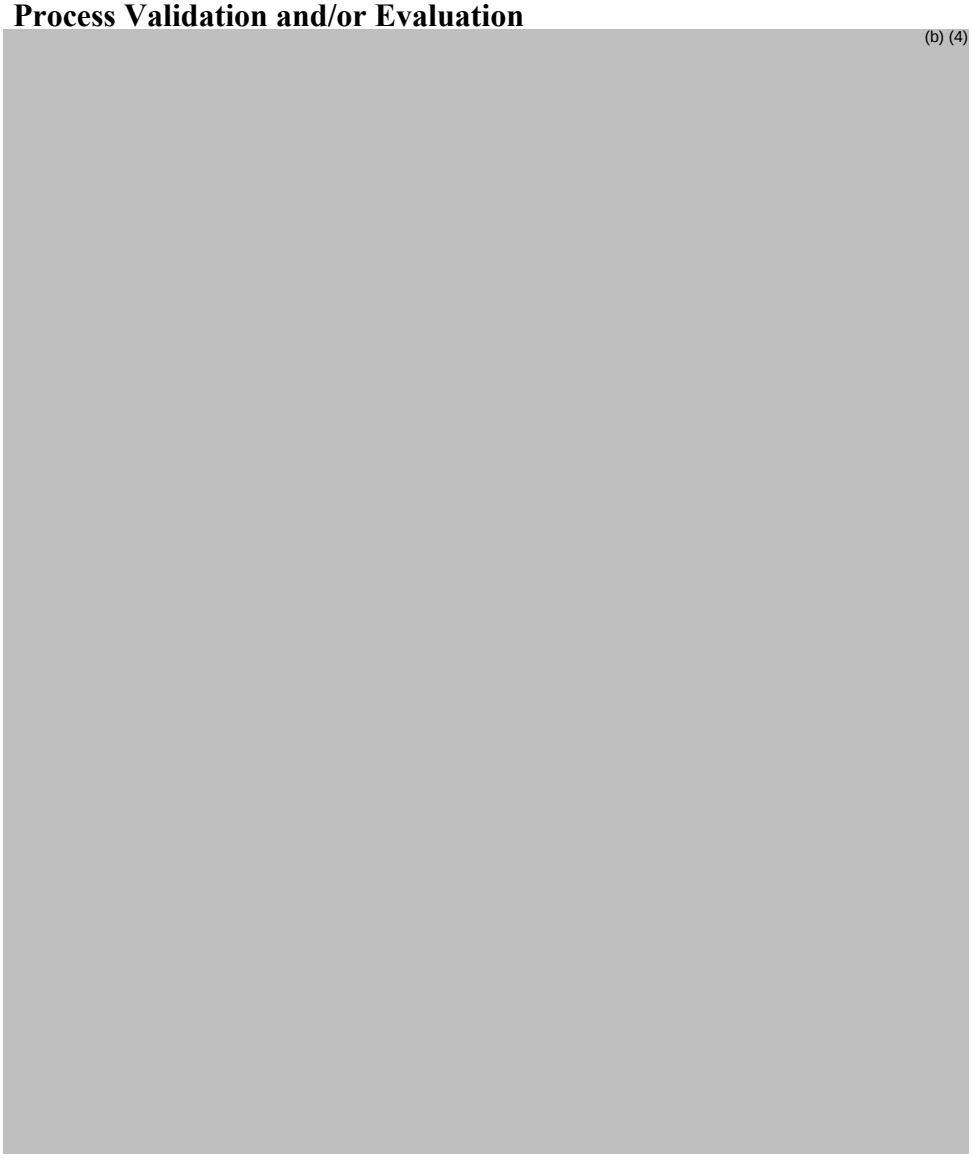
(b) (4) are the same as that approved to manufacture the drug product.

ADEQUATE

REVIEWER COMMENT – The manufacturing facility and equipment are the same as that approved for the drug product.

P.3.5 Process Validation and/or Evaluation

(b) (4)



ADEQUATE

REVIEWER COMMENT – The diluent filling manufacture is performed using the same filling equipment as the approved drug product filling process. Therefore, detailed review of the diluent process was not performed. The (b) (4) was validated for use with the diluent following standard industry practice. The results of the (b) (4) media fill were acceptable and a (b) (4) media fill was adequate for this process.

P.5 Control of Drug Product
P.5.1 Specifications
P.5.2 Analytical Procedures

- (b) (4)
-
-

ADEQUATE

REVIEWER COMMENT – The sterility test method suitability was verified for the diluent following the compendial procedure.

P.7 Container Closure System – See section P.1 of this review.

P.8 Stability
P.8.1 Stability Summary and Conclusion

P.8.2 Post-Approval Stability Protocol and Stability Commitment
Specifications and testing schedule for post-approval stability program.

- (b) (4) – No Change
- (b) (4) – No Change
- (b) (4) – N/A

P.8.3 Stability Data – N/A

A APPENDICES – N/A

R REGIONAL INFORMATION
R.1 Executed Batch Record – N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT – No Change.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: N/A

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/s/

BRYAN S RILEY
09/17/2013

STEPHEN E LANGILLE
09/17/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 17-422/S-045

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 17422/S-045

CBE SUPPLEMENT – ACKNOWLEDGEMENT

Emcure Pharmaceuticals Limited, India
Attention: Pankaj Dave, PhD
Emcure Pharmaceuticals Limited, USA
Vice President, Regulatory Affairs
21B Cotters Lane
East Brunswick, New Jersey 08816

Dear Dr. Dave:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 17422

SUPPLEMENT NUMBER: 045

PRODUCT NAME: BiCNU® (Carmustine, powder for injection 100 mg/vial)

DATE OF SUBMISSION: March 16, 2013

DATE OF RECEIPT: March 18, 2013

This supplemental application, submitted as a "Changes Being Effected" supplement, proposes the following change: inclusion of Emcure Pharmaceuticals Limited, India as an additional manufacturer of diluent for BiCNU.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May17, 2013, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be September 18, 2013.

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Project Manager for Product Quality
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

JEWELL D MARTIN
03/27/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO *(Division/Office)*: **New Drug Microbiology Staff**

E-mail to: **CDER OPS IO MICRO**

Paper mail to: **WO Bldg 51, Room 4193**

FROM: Jewell Martin, ONDQA PM

PROJECT MANAGER *(if other than sender):*

REQUEST DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/21/2013		NDA 17422/S045	CBE-0	3/16/2013

NAMES OF DRUG	PRIORITY CONSIDERATION	PDUFA DATE	DESIRED COMPLETION DATE
BICNU		9/18/2013	7/18/2013

NAME OF APPLICANT OR SPONSOR: EMCURE PHARMACEUTICALS LTD

GENERAL PROVISIONS IN APPLICATION

- ☐ 30-DAY SAFETY REVIEW NEEDED
- ☐ NDA FILING REVIEW NEEDED BY: _____
- ☐ BUNDLED
- ☐ DOCUMENT IN EDR
- ☐ CBE-0 SUPPLEMENT
- ☐ CBE-30 SUPPLEMENT
- ☐ CHANGE IN DOSAGE, STRENGTH / POTENCY

COMMENTS / SPECIAL INSTRUCTIONS:

Sterile injectable product, please review for sterility assurance.

SIGNATURE OF REQUESTER

REVIEW REQUEST DELIVERED BY (Check one):

☐ DARRTS ☐ EDR ☐ E-MAIL ☐ MAIL ☐ HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

☐ EDR ☐ E-MAIL ☐ MAIL ☐ HAND

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/s/

JEWELL D MARTIN
03/21/2013