CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75660

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA #: 75-660

DRUG PRODUCT: Milrinone Lactate

FIRM: Bedford Laboratories

DOSAGE FORM: Injection

STRENGTHS: 1 mg/mL (10 mL, 20 mL and 50 mL vials)

CGMP STATEMENT/EIR UPDATE STATUS:
An acceptable EER was issued on 12/31/01.

BIO STUDY:
Satisfactory per Zakaria A. Wahba on 08/10/99.

VALIDATION:
Request for Lab assignment for ANDA MV was sent on 02/01/02.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:
Post-approval Protocol and Commitment: Satisfactory
Stability Data: Container closure same as that described in the container closure section; stability data under accelerated and controlled room temperature satisfactory.
Expiration Date: 24 months supported by accelerated and CRT data.

LABELING: Acceptable per A. Vezza on 03/14/01.

STERILIZATION VALIDATION (IF APPLICABLE):
Micro status - Satisfactory per N. Nrapendra, on 06/26/01.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):
1 mg/mL; 10 mL per vial (lot #2002-49-127009) - [L
1 mg/mL; 20 mL per vial (lot #2002-51-127010) - L
1 mg/mL; 50 mL per vial (lot #2002-57-156969) - L

DMF ( ) remains acceptable as of 12/17/01.

SIZE OF STABILITY BATCHES:
Same as bio batch.

PROPOSED PRODUCTION BATCH:

1 mg/mL; 10 mL per vial - L vials)

1 mg/mL; 20 mL per vial - L vials)

ng/mL; 50 mL per vial - vials

Meets OGD 22-90 scale-up criteria; manufacturing process for scale-up batches similar to the exhibit batch using same process conditions and in-process parameters; equipment used are of similar design and/or operating principles.

CHEMIST: Bita Mirzai-Azarm /S/ DATE: 02/15/02 04/15/02.

SUPERVISOR: Ubrani Venkataram, Ph.D. /S/ DATE: 4/16/02.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-660

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories™
A Division of Ben Venue Laboratories, Inc.
Attention Shahid Ahmed
300 Northfield Road
Bedford, Ohio 44146

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Primacor®
Innovator Company: Sanofi Winthrop
Patent Expiration Date: 02/02/01

On page 5 the applicant includes Patent Certification and Exclusivity Statement.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Milrinone Lactate Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Submission date	Submission type
06/29/99	Original
08/02/99 (FDA)	Acceptance for Filing

10. PHARMACOLOGICAL CATEGORY
Inotropic Vasodilator

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
See review element #37

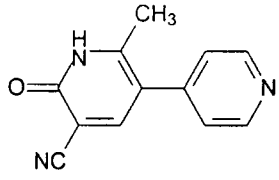
13. DOSAGE FORM
Injection

14. POTENCIES
1 mg/mL

15. CHEMICAL NAME AND STRUCTURE
Chemical name:
[3,4'-Bipyridine]-5-carbonitrile, 1,6-dihydro-2-methyl-6-oxo-

Chemical Formula	Molecular Weight	Cas Number
$C_{12}H_9N_3O$	211.22	78415-72-2

Structure:



16. RECORDS AND REPORTS
N/A

17. COMMENTS
This application has the following CMC deficiencies:
- DMF
- Components & Composition
- Raw Material Controls
- Manufacturing and Processing
- Laboratory Controls
- Stability

Labeling review status: Unsatisfactory, A. Vezza, on 08/18/99

Bioequivalence status: Satisfactory, Zakaria A. Wahba, on 08/10/99

Micro status: Pending

EER: Pending

MV: Need MV since non-USP drug substance and drug product.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable at this time.

19. REVIEWER: Bita Mirzai-Azarm

DATE COMPLETED: 12/08/99

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Chem Review #1

Page 1 of 1	Bita Mirzai-Azarm	/S/	12/28/99
	Reviewer	Signature	Date

DEC 29 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-660 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Milrinone Lactate Injection, 1 mg (base)/mL, 10 mL and 20 mL vials

The deficiencies presented below represent MAJOR deficiencies.

A. Chemistry Deficiencies:

2. Please provide Organic Volatile Impurities Certification from manufacturer of Milrinone.

3. Please include the identity of the Known Impurity in your drug substance specifications on page 63. Please revise and resubmit.

4. Please revise the wording for the ID test (IR) for the drug substance specification. Please refer to <197> in USP 23.

5. We request that you evaluate bioload as part of the drug substance retest.

6. Page 69 is not legible, please resubmit.

7. We acknowledge the submitted certificates of analysis for the inactives, however, we request that you provide a list of current compendial testing specifications and method used in the testing of each inactive.

8. Please specify in the batch record the maximum bulk solution holding times pre and post filtration.

9. Please provide results of USP <381> using Drug Product Vehicle and as extraction solvents.

10. Regarding the finished dosage form:

    a. Please include an additional identification test for the presence of Milrinone.

    b. Please include the identity of the known impurity in your finished product specification on page 724.

    c. Please include a test and provide specifications for assay of Lactic Acid. Please revise and resubmit.

    d. Please provide data comparing your Drug Product impurity profile with the innovator's impurity profile.

    e. Please include a test and provide specifications for impurity both at release and stability.

11. Please include a test and provide specifications for (dextrose degradant). Please either revise the current method or develop an additional method so that the degradant can be monitored.

12. Regarding stability:

a. Based on the stability data submitted, we request that you reduce specifications for related and for individual unknown.

b. You proposed to test for Bacterial Endotoxins at the 24th month. It is recommended that you test at the 12th month in addition to the 24th month.

c. Test intervals for Schedule B and Schedule C are identical on page 733. Please clarify and resubmit.

d. Your stability specifications for the Milrinone IV solution on page 747 are inconsistent with the proposed specifications on page 732. Please explain.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide information on pharmaceutical function of each ingredient in the manufacture of the drug product.

2. Please provide any available room temperature stability data.

3. A satisfactory compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Office of Compliance.

4. Analytical Methods Validation will not be performed by the FDA field laboratory until all of these deficiency comments with respect to product testing specifications and Analytical Methods have been satisfactorily addressed.

5. The referenced DMF ( ) is deficient and the deficiencies have been communicated to the DMF holder.

6. Please verify if June 1996 (page 78) is the expiration date or the retest date. Expiration date is reported as June 22, 1999 on page 76.

Sincerely yours,

/S/

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.** 2

2. **ANDA #** 75-660

3. **NAME AND ADDRESS OF APPLICANT**
Bedford Laboratories™
A Division of Ben Venue Laboratories, Inc.
Attention Shahid Ahmed
300 Northfield Road
Bedford, Ohio 44146

4. **LEGAL BASIS FOR SUBMISSION**
Innovator Product: Primacor®
Innovator Company: Sanofi Winthrop
Patent Expiration Date: 02/02/01

On page 5 the applicant includes Patent Certification and Exclusivity Statement.

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

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Milrinone Lactate Injection

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

9. **AMENDMENTS AND OTHER DATES:**

Submission date	Submission type
06/29/99	Original
08/02/99 (FDA)	Acceptance for Filing
12/29/99	Deficiency Letter
09/12/00	-Major Amendment -Firm also proposed an additional dosage size, a single-dose 50 mL vial

10. **PHARMACOLOGICAL CATEGORY**
short-term intravenous therapy of congestive heart failure

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
See review element #37

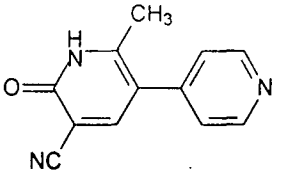
13. **DOSAGE FORM**
Injection

14. **POTENCIES**
1 mg/mL

15. **CHEMICAL NAME AND STRUCTURE**
Chemical name:
[3,4'-Bipyridine]-5-carbonitrile, 1,6-dihydro-2-methyl-6-oxo-

Chemical Formula	Molecular Weight	Cas Number
$C_{12}H_9N_3O$	211.22	78415-72-2

Structure:



16. **RECORDS AND REPORTS**
N/A

17. **COMMENTS**
CMC: Unsatisfactory

Labeling review status: Unsatisfactory, A. Vezza, on 02/05/01

Bioequivalence status: Satisfactory, Zakaria A. Wahba, on 08/10/99

Micro status: Unsatisfactory, N. Nrapendra, on 08/14/00

EER: Acceptable on 01/11/00

MV: Need MV since non-USP drug substance and drug product.

18. **CONCLUSIONS AND RECOMMENDATIONS**

This application is not approvable at this time.

19. **REVIEWER:** Bita Mirzai-Azarm

DATE COMPLETED: 01/24/01

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Chem Review #2

FEB 15 2001

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-660 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Milrinone Lactate Injection, 1 mg (base)/mL, 10 mL, 20 mL and 50 mL vials

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies:

1. Please provide a list of current compendial testing specifications and method for Water for Injection, USP.

2. Please provide results of USP <381> using)as an extraction solvent.

3. Please include a test and provide specifications for impurity B in your drug substance specifications.

4. The DMF holder has revised their specifications to include residual solvents analysis in the drug substance specifications. Please include a test and provide specifications for Residual Solvents in your drug substance specifications.

5. Regarding Stability:

   a. Based on the stability data submitted, we request that you reduce specifications for individual unknown. Please note that impurities with limits above(% need to be identified.

   b. Please include a test and provide specifications for assay of Lactic Acid at stability. Please submit available data.

   c. The stability protocol includes a test and a specification for( )(NMT %). Please include this in your Stability Testing Summary and submit data.

d. Please include a test and provide specifications for (dextrose degradant) at stability.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

1. Please submit available room temperature stability data.

2. The referenced DMF (including 05/22/00 amendment) is deficient and the deficiencies have been communicated to the DMF holder.

Sincerely yours,

/S/

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-660

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories™
A Division of Ben Venue Laboratories, Inc.
Attention Shahid Ahmed
300 Northfield Road
Bedford, Ohio 44146

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Primacor®
Innovator Company: Sanofi Winthrop
Patent Expiration Date: 02/02/01

On page 5 the applicant includes Patent Certification and Exclusivity Statement.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Milrinone Lactate Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. **AMENDMENTS AND OTHER DATES:**

Submission date	Submission type
06/29/99	Original
08/02/99 (FDA)	Acceptance for Filing
12/29/99	Deficiency Letter
09/12/00	-Major Amendment -Firm also proposed an additional dosage size, a single-dose 50 mL vial
02/15/01	Deficiency Letter
05/08/01	Minor Amendment

10. **PHARMACOLOGICAL CATEGORY**
short-term intravenous therapy of congestive heart failure

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
See review element #37

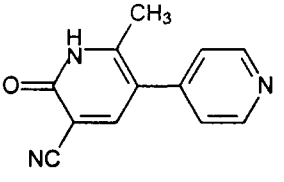
13. **DOSAGE FORM**
Injection

14. **POTENCIES**
1 mg/mL

15. **CHEMICAL NAME AND STRUCTURE**
Chemical name:
[3,4'-Bipyridine]-5-carbonitrile, 1,6-dihydro-2-methyl-6-oxo-

Chemical Formula	Molecular Weight	Cas Number
$C_{12}H_9N_3O$	211.22	78415-72-2

Structure:



16. **RECORDS AND REPORTS**
N/A

17. **COMMENTS**
CMC: Unsatisfactory

Labeling review status: Satisfactory, A. Vezza, 03/14/01

Bioequivalence status: Satisfactory, Zakaria A. Wahba, on 08/10/99

Micro status: Unsatisfactory, N. Nrapendra, on 08/14/00

EER: Acceptable on 01/11/00

MV: Need MV since non-USP drug substance and drug product.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable at this time.

19. REVIEWER: DATE COMPLETED:

Bita Mirzai-Azarm 05/24/01

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Chem Review #3

JUN 8 2001

38. **Chemistry Comments to be Provided to the Applicant**

ANDA: 75-660 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Milrinone Lactate Injection, 1 mg (base)/mL, 10 mL, 20 mL and 50 mL vials

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies:

1. Please include the identity of the Known Impurity in the drug substance specifications.

2. Please reverse the limit of NMT % for and the limit of NMT % for to be consistent with the limits set by the DMF holder. Please provide data for Residual Solvents in the drug substance.

3. Please submit information along with the validation report for the Residual Solvents method

4. The DMF holder acknowledged the use of in the manufacturing process of Milrinone. Please include a test and provide specifications for in the drug substance specifications.

5. Please submit a revised O.V.I Certification from for Milrinone. The original O.V.I Certification suggested the absence of which is incorrect.

6. You have set a limit of NMT % for water and a limit of NMT % for Loss on Drying as part of the drug substance specifications. Please explain if the specification for Loss on Drying takes into account the amount of water driven off during the LOD test. If so, then the proposed limits for Loss on Drying and Water appear inappropriate.

7. You have set a specification for Individual Unknown Impurities of NMT % at release and of NMT % for stability. Please note that impurities with limits above %, may need to be identified.

8. The lower limit of mg/mL for Lactic Acid content at stability differs from the lower limit of mg/mL at release. Please explain the decrease in Lactic Acid Content over time and explain if any precipitation is observed. Please submit available room temperature stability data.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

The referenced DMF (including 04/23/01 amendment) is deficient and the deficiencies have been communicated to the DMF holder.

Sincerely yours,

for /S/

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.** 5

2. **ANDA #** 75-660

3. **NAME AND ADDRESS OF APPLICANT**
Bedford Laboratories™
A Division of Ben Venue Laboratories, Inc.
Attention: Molly L. Rapp
270 Northfield Road
Bedford, Ohio 44146

4. **LEGAL BASIS FOR SUBMISSION**
Innovator Product: Primacor®
Innovator Company: Sanofi Winthrop
Patent Expiration Date: 02/02/01

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

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Milrinone Lactate Injection

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

9. **AMENDMENTS AND OTHER DATES:**

Submission date	Submission type
06/29/99	Original
08/02/99 (FDA)	Acceptance for Filing
12/29/99	Deficiency Letter
09/12/00	-Major Amendment -Firm also proposed an additional dosage size, a single-dose 50 mL vial
02/15/01	Deficiency Letter
05/08/01	Minor Amendment
06/08/01	Deficiency Letter
11/30/01	Minor Amendment
12/19/01	Firm submitted additional copy of the Methods Validation Package
12/26/01	Deficiency Letter
01/25/02	Fax Amendment
02/13/02	Telephone conversation
02/13/02	Telephone amendment

10. **PHARMACOLOGICAL CATEGORY**
short-term intravenous therapy of congestive heart failure

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
See review element #37

13. **DOSAGE FORM**
Injection

14. **POTENCIES**
1 mg/mL
10 mL, 20 mL and 50 mL vials

15. **CHEMICAL NAME AND STRUCTURE**
Chemical name:
[3,4'-Bipyridine]-5-carbonitrile, 1,6-dihydro-2-methyl-6-oxo-

Chemical Formula	Molecular Weight	Cas Number
$C_{12}H_9N_3O$	211.22	78415-72-2

16. **RECORDS AND REPORTS**
N/A

17. **COMMENTS**

CMC: Satisfactory

Labeling review status: Satisfactory, A. Vezza, 03/14/01

Bioequivalence status: Satisfactory, Zakaria A. Wahba, on 08/10/99

Micro status: Satisfactory, N. Nrapendra, on 06/26/01

EER: Acceptable on 12/31/01

MV: Need MV since non-USP drug substance and drug product.

18. **CONCLUSIONS AND RECOMMENDATIONS**

The application may be approved.

19. **REVIEWER:** Bita Mirzai-Azarm

DATE COMPLETED: 02/04/02

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Chem Review #5

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.** 4

2. **ANDA #** 75-660

3. **NAME AND ADDRESS OF APPLICANT**
Bedford Laboratories™
A Division of Ben Venue Laboratories, Inc.
Attention: Molly L. Rapp
300 Northfield Road
Bedford, Ohio 44146

4. **LEGAL BASIS FOR SUBMISSION**
Innovator Product: Primacor®
Innovator Company: Sanofi Winthrop
Patent Expiration Date: 02/02/01

On page 5 the applicant includes Patent Certification and Exclusivity Statement.

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

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Milrinone Lactate Injection

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

9. **AMENDMENTS AND OTHER DATES:**

Submission date	Submission type
06/29/99	Original
08/02/99 (FDA)	Acceptance for Filing
12/29/99	Deficiency Letter
09/12/00	-Major Amendment -Firm also proposed an additional dosage size, a single-dose 50 mL vial
02/15/01	Deficiency Letter
05/08/01	Minor Amendment
06/08/01	Deficiency Letter
11/30/01	Minor Amendment

10. **PHARMACOLOGICAL CATEGORY**
short-term intravenous therapy of congestive heart failure

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
See review element #37

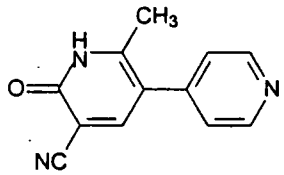
13. **DOSAGE FORM**
Injection

14. **POTENCIES**
1 mg/mL
10 mL, 20 mL and 50 mL vials

15. **CHEMICAL NAME AND STRUCTURE**
Chemical name:
[3,4'-Bipyridine]-5-carbonitrile, 1,6-dihydro-2-methyl-6-oxo-

Chemical Formula	Molecular Weight	Cas Number
$C_{12}H_9N_3O$	211.22	78415-72-2

Structure:



16. **RECORDS AND REPORTS**
N/A

17. **COMMENTS**

CMC: Unsatisfactory

Labeling review status: Satisfactory, A. Vezza, 03/14/01

Bioequivalence status: Satisfactory, Zakaria A. Wahba, on 08/10/99

Micro status: Satisfactory, N. Nrapendra, on 06/26/01

EER: Acceptable on 01/11/00

MV: Need MV since non-USP drug substance and drug product.

18. **CONCLUSIONS AND RECOMMENDATIONS**

This application is not approvable at this time.

19. **REVIEWER:** Bita Mirzai-Azarm

DATE COMPLETED: 12/10/01

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Chem Review #4

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO. 6

2. ANDA # 75-660

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories™
A Division of Ben Venue Laboratories, Inc.
Attention: Molly L. Rapp
300 Northfield Road
Bedford, Ohio 44146

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Primacor®
Innovator Company: Sanofi-Synthelabo, Inc.
Patent Expiration Date: 02/02/01
Expiraton of Exclusivity: 5/26/02

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Milrinone Lactate Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. **AMENDMENTS AND OTHER DATES:**

Submission date	Submission type
06/29/99	Original
08/02/99 (FDA)	Acceptance for Filing
12/29/99	Deficiency Letter
09/12/00	-Major Amendment -Firm also proposed an additional dosage size, a single-dose 50 mL vial
02/15/01	Deficiency Letter
05/08/01	Minor Amendment
06/08/01	Deficiency Letter
11/30/01	Minor Amendment
12/19/01	Firm submitted additional copy of the Methods Validation Package
12/26/01	Deficiency Letter
01/25/02	Fax Amendment
02/13/02	Telephone conversation
02/13/02	Telephone amendment
04/30/02	TA Letter
04/30/02	Fax Amendment
05/07/02	Minor Amendment

10. **PHARMACOLOGICAL CATEGORY**
short-term intravenous therapy of congestive heart failure

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
See review element #37

13. **DOSAGE FORM**
Injection

14. **POTENCIES**
1 mg/mL
10 mL, 20 mL and 50 mL vials

15. **CHEMICAL NAME AND STRUCTURE**
Chemical name:
[3,4'-Bipyridine]-5-carbonitrile, 1,6-dihydro-2-methyl-6-oxo-

Chemical Formula	Molecular Weight	Cas Number
$C_{12}H_9N_3O$	211.22	78415-72-2

16. RECORDS AND REPORTS
N/A

17. COMMENTS
CMC: Satisfactory

Labeling review status: Satisfactory, A. Vezza, 03/14/01 & 5/22/02

Bioequivalence status: Satisfactory, Zakaria A. Wahba, on 08/10/99

Micro status: Satisfactory, N. Nrapendra, on 06/26/01

EER: Acceptable on 12/31/01

MV: Methods found adequate by Denver Laboratories on 05/09/02.

18. CONCLUSIONS AND RECOMMENDATIONS
The application may be approved. Review #6 covers the fax amendment and minor amendment submitted on 04/30/02 and 05/07/02 respectively. On 04/30/02 the applicant revised the lactic acid content for stability per our request. On 05/07/02 the applicant requested Final Approval of the application.

19. REVIEWER: Bita Mirzai-Azarm

DATE COMPLETED: 05/20/02

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Chem Review #6

DEC 26

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-660 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Milrinone Lactate Injection, 1 mg (base)/mL, 10 mL, 20 mL and 50 mL vials

The deficiencies presented below represent FAX deficiencies.

Chemistry Deficiencies:

1. You have set a specification for Individual Unknown Impurities of NMT % at release and of NMT % for stability. With the exception of stability data (T=0, release) which was NMT %, all data for Individual Unknown Impurities were either <LOD or ND. In this regard:

   a. Please explain the decrease in the level of individual unknown impurities over time.
   b. The stability data with the exception of T=0, would suggest a lower specification for Individual Unknown Impurities at both release and for stability. Please tighten the limits.

2. Your response to our comment 8 (06/08/01, deficiency letter) is not satisfactory. In order to assure that milrinone does not precipitate from solutions containing mg/mL of lactic acid, it is recommended that you prepare a solution of 1 mg/mL of Milrinone Lactate with a Lactic Acid Content of mg/mL (lower limit for Lactic Acid Content at stability) and determine its stability. Please submit the necessary data.

Sincerely yours,

for /S/

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 8 2001

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-660 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Milrinone Lactate Injection, 1 mg/mL base/mL
10 mL, 20 mL and 50 mL vials

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies:

1. Please include the identity of the known impurity in the drug substance specifications.

2. Please reverse the limit of NMT % for and the limit of NMT % for to be consistent with the limits set by the DMF holder. Please provide data for Residual Solvents in the drug substance.

3. Please submit information along with the validation report for the Residual Solvents method.

4. The DMF holder acknowledged the use of in the manufacturing process of Milrinone. Please include a test and provide specifications for in the drug substance specifications.

5. Please submit a revised O.V.I Certification from for Milrinone. The original O.V.I Certification suggested the absence of which is incorrect.

6. You have set a limit of NMT % for water and a limit of NMT % for Loss on Drying as part of the drug substance specifications. Please explain if the specification for Loss on Drying takes into account the amount of water driven off during the LOD test. If so, then the proposed limits for Loss on Drying and Water appear inappropriate.

7. You have set a specification for Individual Unknown Impurities of NMT % at release and of NMT % for stability. Please note that impurities with limits above %, may need to be identified.

8. The lower limit of mg/mL for Lactic Acid content at stability differs from the lower limit of mg/mL at release. Please explain the decrease in Lactic Acid Content over time and explain if any precipitation is observed. Please submit available room temperature stability data.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

The referenced DMF (including 04/23/01 amendment) is deficient and the deficiencies have been communicated to the DMF holder.

Sincerely yours,

for /S/

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research