CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75830

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA # 75-830

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

FIRM: Faulding Pharmaceutical Co.

DOSAGE FORM: Injection

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

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form :

The drug product will be manufactured, processed, packaged and labelled at:

Faulding Puerto Rico, Inc.
P.O. Box 250471
1071 Parallel Road
Aguadilla, PR 00604-0471
(OK on May 15, 2000).

Manufacturer-Active Ingredients:

The manufacturer of the drug substance, Milrinone, is:

[redacted]

DMF

Contract Laboratories:

The contract analytical testing Laboratories are listed as follows:

BIO STUDY:

Satisfactory,

The waiver of in vivo bioavailability was granted and satisfactory per Makary reviewed on 6-27-2000.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Acceptable.

Non-Compendial.

The drug substance and drug product are non-USP item.

Methods validation for the drug substance and drug product was sent to the Philadelphia District Laboratory on 9-30-2000 and found acceptable with comments on 2-28-2001 and found acceptable per L. Tang reviewed on 10-12-2001.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability protocol: Satisfactory

Expiration date:

2 years expiration date with 1, 2 and 3 month accelerated stability data (40°C± 2°C) and 3 month room temperature stability data (25°C±2°C) on both inverted and upright mode.

The container/closure system and lots used for the 10 mL, 20 mL and 50 mL stated as follows:

1 mg/mL, 10 mL/vial:

Executed batch #99S007A for 10 mL vial vial, 20 mm 20 mm 4432/50 V35, non-coated gray rubber stopper, flip-off, green cap.

1 mg/mL, 20 mL/vial:

Executed batch #99S007B for 20 mL vial, 20 mm 4432/50 V35, non-coated gray rubber stopper, flip-off, green cap.

1 mg/mL, 50 mL/vial (12-1-2000 amendment):

Executed batch #00S003 for 50 mL vial, 4432/50 S-127 20 mm Gray rubber stopper, and aluminum seal flip off cap 20 mm finish with controlled score and green color plastic button.

LABELING:

Satisfactory per A. Vezza reviewed on 10-12-2001.

STERILIZATION VALIDATION (IF APPLICABLE):

Satisfactory

Microbiological review was satisfactory per M. Stevens-Riley on 7/17/2001.

sterilize the product at 121.1°C (121.0°C-122.5°C) for 15 minutes.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

1 mg/mL, 10 mL/vial:

vials (executed batch #99S007A)

1 mg/mL, 20 mL/vial:

vials (executed batch #99S007B)

1 mg/mL, 50 mL/vial (12-1-2000 amendment):

vials (executed batch #00S003)

The revised DMF as reviewed by L. Tang and found satisfactory on 5-11-2001.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The stability batch size:

1 mg/mL, 10 mL/vial:

vials (executed batch #99S007A)

1 mg/mL, 20 mL/vial:

vials (executed batch #99S007B)

1 mg/mL, 50 mL/vial (12-1-2000 amendment):

vials (executed batch #00S003)

Stability batches were the same as the bio batches as above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

The proposed production batch (blank batch):

1 mg/mL, 10 mL/vial:
( ) vials (intended blank batch record)

1 mg/mL, 20 mL/vial:
a. ( ) vials (intended blank batch record)
b. ( ) vials (intended blank batch record)

1 mg/mL, 50 mL/vial (12-1-2000 amendment):
a. ( ) vials (intended blank batch record)
b. ( ) vials (intended blank batch record)

The proposed production batches have the same manufacturing process as the test batches or Bio-batches (see above). Scale-up meets OGD PPG 22-90.

CHEMIST: Lucia C. Tang DATE: 10-15-2001 10-29-01

SUPERVISOR: Ubrani Venkataram DATE: 10-16-2001

MAY 21 2001

cry Comments to be Provided to the Applicant

75-830 APPLICANT: Faulding Pharmaceutical Co.

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

deficiencies presented below represent Minor deficiencies.

Chemistry deficiencies:

The Philadelphia District Laboratory has provided the following comments:

a. In the Milrinone Assay Determination on the dried basis, page 839, Section 7.2, the condensed equation is off by a factor of ten. Please revise.

b. In the and Drug Product Impurities testing, the Milrinone peak in the samples may obscure the Impurity The Milrinone peak spans about 6-minutes. Please comment.

Sincerely yours,

/S/

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

1. CHEMIST'S REVIEW NO. 1

2. ANDA # 75-830

3. NAME AND ADDRESS OF APPLICANT

Faulding Pharmaceutical Co.
11 Commerce Drive
Cranford, NJ 07016

4. LEGAL BASIS for ANDA 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

7. NONPROPRIETARY NAME

Milrinone Lactate Injection

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

9. AMENDMENTS AND OTHER DATES:

Firm:

1-31-2000: Original Submission.

FDA:

4-19-2000: Acknowledgment.

10. PHARMACOLOGICAL CATEGORY

Inotropic Vasodilator

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF Drug Substance, Milrinone,

See item 37

13. DOSAGE FORM

Injection, 1 mg/mL, 10 mL and 20 mL vials

14. POTENCY

1 mg/mL, 10 mL and 20 mL vials

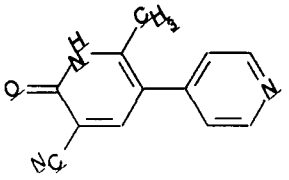
15. CHEMICAL NAME AND STRUCTURE

Chemical name: Milrinone

[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

Status:

a. EER status: Pending

EER was requested for Faulding Puerto Rico Inc. and by Tim Ames on April 3, 2000 and found pending.

b. Method Validation status: Pending
Non-Compendial.

Required since both drug substance and finished product are not official USP items.

c. Bio-review status: Satisfactory

The waiver of in vivo bioavailability was granted and satisfactory per Makary reviewed on 6-27-2000.

d. Micro-review status: pending

e. Labeling review status: Not Satisfactory

Not Satisfactory per A. Vezza reviewed on 4-26-2000.

f. DMF Not satisfactory

DMF# was reviewed per L. Tang and found not satisfactory on August 16, 2000.

18. CONCLUSIONS AND RECOMMENDATIONS

The application should be considered not approvable - Major.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 8-16-2000

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Chem Review #1

SEP 11 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-830 APPLICANT: Faulding Pharmaceutical Co.

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

The deficiencies presented below represent Major deficiencies.

A. Chemistry Deficiencies

1. Regarding composition:

Please explain and provide the calculation for the actual amounts of Milrinone and Lactic Acid that has been used in the components and composition statements, adjusted based on the assay values of the lot used.

2. Regarding the drug substance:

a. We note that the total impurities specification for Milrinone at test specification (page 127) is NMT(%. However, this specification in the Certificate of Analysis for Milrinone from Faulding (page 129) is NMT %. Please be consistent, revise and resubmit.

b. Please include bacterial endotoxins and bioburden tests and specifications in the drug substance test specification.

3. Please provide the Certificate of Analysis for the Water for Injection, USP.

4. The submission fails to provide a complete formula card and satisfactory batch records. In this regard:

a. Submit a table comparing equipment and procedure used in the manufacture of the present demonstration batch with the intended post-approval production batch.

b. You indicate a 10 mL fill in 10 mL vials and 20 mL fill in 20 mL vials in your test batch

records and packaging components. We also note that the target fill volumes are mL for the 10 mL vials and mL for 20 mL vials. Please clarify that the sizes of vials are sufficient to hold the excess fill volumes.

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

d. Please include a density test and specifications in the in-process test specifications (page 710).

5. Regarding the container/closure systems

a. Please submit information specific to this application. Irrelevant material such as must be deleted.

b. Please submit certification of compliance from the glass vial manufacturer to meet the USP 24 requirements.

c. Please provide results of USP <381> using the drug product vehicle and as extraction solvents.

6. Regarding the finished dosage form:

a. Please include additional identification tests for the presence of milrinone and lactate.

b. Please include tests, methods and limits for color of solution and dextrose content in the finished dosage form at release.

c. Please provide data comparing your drug product impurity profile with the innovator's impurity profile.

d. Please reduce the limits for known impurities, unknown and total impurities

based on the finished product results and stability data reports.

e. The stability-indicating assay method is incomplete. Please present in percentages the assay results of the active ingredient and degradation products from the dosage form under various stress conditions in tabular form.

7. Regarding stability:

a. Please submit revised stability protocols based above comments 6d & 6e.

b. We note that the batch sizes were listed as L for Lot 99S007-A (10 mL fill in 10 mL vials) and L for Lot 99S007-B (20 mL fill in 20 mL vials) in the stability protocol (Page 1064). However, the batch sizes were indicated as L for 10 mL vials and L for 20 mL vials in the stability data report. Please clarify and revise and resubmit.

c. Please submit the stability data for Milrinone Lactate Injection, 10 mL and 20 mL, manufactured using vials.

d. We note that mm aluminum seal with flip-off, gray caps (page 724) were used for both the 10 mL and 20 mL vials in the packaging materials controls. However, mm Flip-off, green caps were listed for both 10 mL and 20 mL vials in the stability data report. Please clarify and revise and resubmit.

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

1. DMF has been reviewed and found deficient. A fax letter outlining the deficiencies will be sent to This ANDA cannot be

approved until these deficiencies have been resolved.

2. Methods validation will be performed on the drug substance and drug product by an FDA laboratory.

3. A satisfactory compliance evaluation for the firms referenced in the ANDA is required for approval. The Establishment Evaluation Request (EER) is pending.

Sincerely yours,

/S/

for

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

1. CHEMIST'S REVIEW NO. 2

2. ANDA # 75-830

3. NAME AND ADDRESS OF APPLICANT

Faulding Pharmaceutical Co.
11 Commerce Drive
Cranford, NJ 07016

4. LEGAL BASIS for ANDA 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

7. NONPROPRIETARY NAME

Milrinone Lactate Injection

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

9. AMENDMENTS AND OTHER DATES:

Firm:

3-31-2000:	Original Submission
11-22-2000:	Amendment
11-28-2000:	MV amendment
11-30-2000:	MV amendment
01-05-2001:	Withdrawal of 76-040
12-01-2000:	Addition new strength (1 mg/mL, 50 mL vials)

FDA:

4-19-2000:	Acknowledgment.
9-11-2000:	1st NA letter

10. PHARMACOLOGICAL CATEGORY

Inotropic Vasodilator

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF ( ) Drug Substance, Milrinone, ( )

See item 37

13. DOSAGE FORM

Injection, 1 mg/mL, 10 mL and 20 mL vials

14. POTENCY

1 mg/mL, 10 mL, 20 mL and 50 mL vials

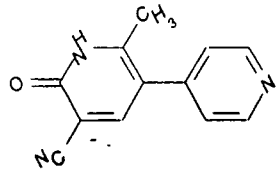
15. CHEMICAL NAME AND STRUCTURE

Chemical name: Milrinone

[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

A. Chemistry Deficiencies

Q: 1. Regarding composition:
Please explain and provide the calculation for the actual amounts of Milrinone and Lactic Acid that has been used in the components and composition statements, adjusted based on the assay values of the lot used.

A: OK (See response 1 and Attachment 1 of 11-22-2000 amendment)

2. Regarding the drug substance:

Q: a. We note that the total impurities specification for Milrinone at test specification (page 127) is NMT( )%. However, this specification in the Certificate of Analysis for Milrinone from Faulding (page 129) is NMT %. Please be consistent, revise and resubmit.

A: OK (See response 2a and Attachment 2 of 11-22-2000 amendment).

Q: b. Please include bacterial endotoxins and bioburden tests and specifications in the drug substance test specification.

A: OK (See response 2b and Attachments 2 & 3 of 11-22-2000 amendment).

Q: 3. Please provide the Certificate of Analysis for the Water for Injection, USP.

A: OK (See response 3 and Attachment 4 of 11-22-2000 amendment).

4. The submission fails to provide a complete formula card and satisfactory batch records. In this regard:

Q: a. Submit a table comparing equipment and procedure used in the manufacture of the present demonstration batch with the intended post-approval production batch.

A: OK (See response 4a [pages 11-12] of 11-22-2000 amendment).

Q: b. You indicate a 10 mL fill in 10 mL vials and 20 mL fill in 20 mL vials in your test batch records and packaging components. We also

note that the target fill volumes are (mL for the 10 mL vials and( ) mL for 20 mL vials. Please clarify that the sizes of vials are sufficient to hold the excess fill volumes.

A: OK (See response 4b [pages 13] of 11-22-2000 amendment).

Q: c. Please specify in the batch record the maximum bulk solution holding times both pre and post filtration.

A: OK (See response 4c and Attachment 5 of 11-22-2000 amendment).

Q: d. Please include a density test and specifications in the in-process test specifications (page 710).

A: OK (See response 4d and Attachment 5 of 11-22-2000 amendment).

5. Regarding the container/closure systems

Q: a. Please submit information specific to this application. Irrelevant material such as (must be deleted.

A: OK (See response 5a [pages 16] of 11-22-2000 amendment).

Q: b. Please submit certification of compliance from the glass vial manufacturer to meet the USP 24 requirements.

A: OK (See response 4b [pages 17] and Attachment 7 of 11-22-2000 amendment).

Q: c. Please provide results of USP <381> using the drug product vehicle and(as extraction solvents.

A: OK (See response 4c [pages 18] and Attachments 8&9 of 11-22-2000 amendment).

6. Regarding the finished dosage form:

Q: a. Please include additional identification tests for the presence of milrinone and lactate.

A: OK (See response 6a [pages 19] and Attachments 10&11 of 11-22-2000 amendment).

Q: b. Please include tests, methods and limits for color of solution and dextrose content in the finished dosage form at release.

A: OK (See response 6b [pages 19] and Attachments 11&12 of 11-22-2000 amendment).

Q: c. Please provide data comparing your drug product impurity profile with the innovator's impurity profile.

A: OK (See response 6c [pages 21] of 11-22-2000 amendment).

Q d. Please reduce the limits for known impurities, unknown and total impurities based on the finished product results and stability data reports.

A: OK (See response 6d [pages 22] and Attachments 11&13 of 11-22-2000 amendment).

Q: e. The stability-indicating assay method is incomplete. Please present in percentages the assay results of the active ingredient and degradation products from the dosage form under various stress conditions in tabular form.

A: OK (See response 6e [pages 24-25] of 11-22-2000 amendment).

7. Regarding stability:

Q: a. Please submit revised stability protocols based above comments 6d & 6e.

A: OK (See response 7a [pages 26] and Attachment 14 of 11-22-2000 amendment).

Q: b. We note that the batch sizes were listed as L for Lot 99S007-A (10 mL fill in 10 mL vials) and L for Lot 99S007-B (20 mL fill

in 20 mL vials) in the stability protocol (Page 1064). However, the batch sizes were indicated as L for 10 mL vials and L for 20 mL vials in the stability data report. Please clarify and revise and resubmit.

A: OK (See response 7b [pages 27] and Attachment 15 of 11-22-2000 amendment).

Q: c. Please submit the stability data for 10 mL and 20 mL vials manufactured from

A: OK (See response 7c [pages 29] of 11-22-2000 amendment).

Q: d. We note that mm aluminum seal with flip-off, gray caps (page 724) were used for both the 10 mL and 20 mL vials in the packaging materials controls. However, mm Flip-off, green caps were listed for both 10 mL and 20 mL vials in the stability data report. Please clarify and revise and resubmit.

A: OK (See response 7d [pages 30] of 11-22-2000 amendment).

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

Q: 1. DMF has been reviewed and found deficient. A fax letter outlining the deficiencies will be sent to This ANDA cannot be approved until these deficiencies have been resolved.

A: Pending for review.

Q: 2. Methods validation will be performed on the drug substance and drug product by an FDA laboratory.

A: The Philadelphia District Laboratory has provided the following comments:

In the Milrinone Assay Determination on the dried basis, page 839, Section 7.2, the condensed equation is off by a factor of ten.

In the and Drug Product Impurities testing, the Milrinone peak in the samples may obscure the Impurity The Milrinone peak spans about 6-minutes, past the Impurity retention time-see worksheets Attachment B for Milrinone sample and Impurity identification chromatograms.

Q: 3. A satisfactory compliance evaluation for the firms referenced in the ANDA is required for app roval. The Establishment Evaluation Request (EER) is pending.

A: OK (see EES on 5-15-2000).

Status:

a. EER status: Acceptable

EER was requested for Faulding Puerto Rico Inc. and by Tim Ames on April 3, 2000 and found acceptable on May 15, 2000.

b. Method Validation status: Acceptable with comments.

Non-Compendial.

Methods validation for the drug substance and drug product was sent to the Philadelphia District Laboratory on 9-30-2000 and found acceptable with comments on 2-28-2001.

c. Bio-review status: Satisfactory

The waiver of in vivo bioavailability was granted and satisfactory per Makary reviewed on 6-27-2000.

d. Micro-review status: Pending for the 50 mL

Acceptable for the 10 mL vial and the 20 mL vial. Pending for the 50 mL vial (12-1-2000 amendment).

e. Labeling review status: Not Satisfactory

Not Satisfactory per A. Vezza reviewed on 5-8-2001.

f. DMF( ) Satisfactroy

The revised DMF# dated November 3, 2000 is reviewed per L. Tang and found satisfactory on 5-11-2001.

18. CONCLUSIONS AND RECOMMENDATIONS

The application should be considered not approvable - Minor.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 5-8-2001, 5-17-2001

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Chem Review #2

MAY 21 2001

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-830 APPLICANT: Faulding Pharmaceutical Co.

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

The deficiencies presented below represent Minor deficiencies.

Chemistry deficiencies:

The Philadelphia District Laboratory has provided the following comments:

a. In the Milrinone Assay Determination on the dried basis, page 839, Section 7.2, the condensed equation is off by a factor of ten. Please revise.

b. In the and Drug Product Impurities testing, the Milrinone peak in the samples may obscure the Impurity. The Milrinone peak spans about 6-minutes. Please comment.

Sincerely yours,

/S/

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

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 75-830

3. NAME AND ADDRESS OF APPLICANT

Faulding Pharmaceutical Co.
11 Commerce Drive
Cranford, NJ 07016

4. LEGAL BASIS for ANDA 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

7. NONPROPRIETARY NAME

Milrinone Lactate Injection

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

9. AMENDMENTS AND OTHER DATES:

Firm:

3-31-2000:	Original Submission
11-22-2000:	Amendment
11-28-2000:	MV amendment
11-30-2000:	MV amendment
01-05-2001:	Withdrawal of 76-040
12-01-2000:	Addition new strength (1 mg/mL, 50 mL vials)
09-26-2001:	Amendment

FDA:

4-19-2000:	Acknowledgment.
9-11-2000:	1st NA letter
5-21-2001:	2nd NA letter

10. PHARMACOLOGICAL CATEGORY

Inotropic Vasodilator

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF( ); Drug Substance, Milrinone,(

See item 37

13. DOSAGE FORM

Injection, 1 mg/mL, 10 mL and 20 mL vials

14. POTENCY

1 mg/mL, 10 mL, 20 mL and 50 mL vials

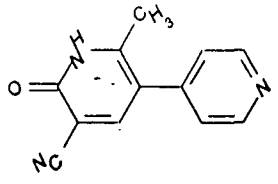
15. CHEMICAL NAME AND STRUCTURE

Chemical name: Milrinone

[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

The Philadelphia District Laboratory has provided the following comments:

Q: a. In the Milrinone Assay Determination on the dried basis, page 839, Section 7.2, the condensed equation is off by a factor of ten. Please revise.

A: OK (See Response a and Attachment 1 of September 26, 2001 amendment).

Q: b. In the and Drug Product Impurities testing, the Milrinone peak in the samples may obscure the Impurity The Milrinone peak spans about 6-minutes. Please comment.

A: OK (See Response b and Attachments 2, 3, & 4 of September 26, 2001 amendment regarding impurities testing)

Status:

a. EER status: Acceptable

EER was requested for Faulding Puerto Rico Inc. and Firms were found acceptable on May 15, 2000.

b. Method Validation status: Acceptable with comments.

Non-Compendial.

Methods validation for the drug substance and drug product was sent to the Philadelphia District Laboratory on 9-30-2000 and found acceptable with comments on 2-28-2001. Comments were adequately addressed in the firms September 26, 2001 submission (subject of this review).

c. Bio-review status: Satisfactory

The waiver of in vivo bioavailability was granted and satisfactory per Makary reviewed on 6-27-2000.

d. Micro-review status: Satisfactory

Acceptable for the 10 mL vial, the 20 mL vial.

and the 50 mL vial per M Stevens-Riley reviewed on 7-17-01.

e. Labeling review status: Satisfactory

Satisfactory per A. Vezza reviewed on 10-12-2001.

f. DMF( ) Satisfactroy

The revised DMF#( ) dated November 3, 2000 is reviewed per L. Tang and found satisfactory on 5-11-2001.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is eligible for approval (tentative).

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 10-15-2001

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Chem-Review #3

1. CHEMIST'S REVIEW NO. 4

2. ANDA # 75-830

3. NAME AND ADDRESS OF APPLICANT
Faulding Pharmaceutical Co.
650 From Road, Second Floor
Mack Cali Center II
Paramus, NJ 07652

4. LEGAL BASIS for ANDA SUBMISSION

Innovator Product: Primacor®
Innovator Company: Sanofi-Synthelobo, Inc.
Patent Expiration Date: 5/26/02

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

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME

Milrinone Lactate Injection

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

9. AMENDMENTS AND OTHER DATES:

Firm:

3-31-2000:	Original Submission
11-22-2000:	Amendment
11-28-2000:	MV amendment
11-30-2000:	MV amendment
01-05-2001:	Withdrawal of 76-040
12-01-2000:	Addition new strength (1 mg/mL, 50 mL vials)
09-26-2001:	Amendment

03-06-2002: **Amendment**
10-26-2001: Amendment
FDA:

4-19-2000: Acknowledgment.
9-11-2000: 1st NA letter
5-21-2001: 2nd NA letter
11-9-2001: TA letter

10. PHARMACOLOGICAL CATEGORY

Inotropic Vasodilator

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF ( ) - Drug Substance, Milrinone, ( )

See item 37

13. DOSAGE FORM

Injection, 1 mg/mL, 10 mL, 20 mL and 50 mL vials

14. POTENCY

1 mg/mL, 10 mL, 20 mL and 50 mL vials

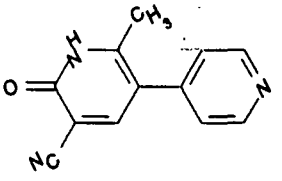
15. CHEMICAL NAME AND STRUCTURE

Chemical name: Milrinone

[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

Status:

a. EER status: Pending

EER was requested for Faulding Puerto Rico Inc. and Firms were found acceptable on May 15, 2000 and re-requested per S. Shepperson on 5-9-2002 and found pending.

b. Method Validation status: Acceptable with comments.

Non-Compendial.

Methods validation for the drug substance and drug product was sent to the Philadelphia District Laboratory on 9-30-2000 and found acceptable with comments on 2-28-2001. Comments were adequately addressed in the firms September 26, 2001 submission.

c. Bio-review status: Satisfactory

The waiver of in vivo bioavailability was granted and satisfactory per Makary reviewed on 6-27-2000.

d. Micro-review status: Satisfactory

Acceptable for the 10 mL vial, the 20 mL vial.and the 50 mL vial per M Stevens-Riley reviewed on 7-17-01.

e. Labeling review status: Satisfactory

Satisfactory per A. Vezza reviewed on 10-12-2001.

f. DMF ( ) Satisfactroy

The updated DMF#( ) is reviewed per L. Tang and found satisfactory on 5-9-2002.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is eligible for full Approval.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 5-9-2002

SEP 1 1 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-830 APPLICANT: Faulding Pharmaceutical Co.

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

The deficiencies presented below represent Major deficiencies.

A. Chemistry Deficiencies

1. Regarding composition:

   Please explain and provide the calculation for the actual amounts of Milrinone and Lactic Acid that has been used in the components and composition statements, adjusted based on the assay values of the lot used.

2. Regarding the drug substance:

   a. We note that the total impurities specification for Milrinone at test specification (page 127) is NMT(%. However, this specification in the Certificate of Analysis for Milrinone from Faulding (page 129) is NMT %. Please be consistent, revise and resubmit.

   b. Please include bacterial endotoxins and bioburden tests and specifications in the drug substance test specification.

3. Please provide the Certificate of Analysis for the Water for Injection, USP.

4. The submission fails to provide a complete formula card and satisfactory batch records. In this regard:

   a. Submit a table comparing equipment and procedure used in the manufacture of the present demonstration batch with the intended post-approval production batch.

   b. You indicate a 10 mL fill in 10 mL vials and 20 mL fill in 20 mL vials in your test batch

records and packaging components. We also note that the target fill volumes are (10.50) mL for the 10 mL vials and (20.60) mL for 20 mL vials. Please clarify that the sizes of vials are sufficient to hold the excess fill volumes.

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

d. Please include a density test and specifications in the in-process test specifications (page 710).

5. Regarding the container/closure systems

a. Please submit information specific to this application. Irrelevant material such as (must be deleted.

b. Please submit certification of compliance from the ~~glass~~ vial manufacturer to meet the USP 24 requirements.

c. Please provide results of USP <381> using the drug product vehicle and(as extraction solvents.

6. Regarding the finished dosage form:

a. Please include additional identification tests for the presence of milrinone and lactate.

b. Please include tests, methods and limits for color of solution and dextrose content in the finished dosage form at release.

c. Please provide data comparing your drug product impurity profile with the innovator's impurity profile.

d. Please reduce the limits for known impurities, unknown and total impurities

based on the finished product results and stability data reports.

e. The stability-indicating assay method is incomplete. Please present in percentages the assay results of the active ingredient and degradation products from the dosage form under various stress conditions in tabular form.

7. Regarding stability:

a. Please submit revised stability protocols based above comments 6d & 6e.

b. We note that the batch sizes were listed as L for Lot 99S007-A (10 mL fill in 10 mL vials) and L for Lot 99S007-B (20 mL fill in 20 mL vials) in the stability protocol (Page 1064). However, the batch sizes were indicated as L for 10 mL vials and L for 20 mL vials in the stability data report. Please clarify and revise and resubmit.

c. Please submit the stability data for Milrinone Lactate Injection, 10 mL and 20 mL, manufactured using vials.

d. We note that 20 mm aluminum seal with flip-off, gray caps (page 724) were used for both the 10 mL and 20 mL vials in the packaging materials controls. However, 20 mm Flip-off, green caps were listed for both 10 mL and 20 mL vials in the stability data report. Please clarify and revise and resubmit.

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

1. DMF has been reviewed and found deficient. A fax letter outlining the deficiencies will be sent to This ANDA cannot be

approved until these deficiencies have been resolved.

2. Methods validation will be performed on the drug substance and drug product by an FDA laboratory.

3. A satisfactory compliance evaluation for the firms referenced in the ANDA is required for approval. The Establishment Evaluation Request (EER) is pending.

Sincerely yours,

/S/

for

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