CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75660

CORRESPONDENCE

ANDA 75-660

APR 30 2002

Bedford Laboratories
Attention: Molly L. Rapp
270 Northfield Road
Bedford, OH 44146

Dear Madam:

This is in reference to your abbreviated new drug application dated June 29, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Milrinone Lactate Injection, 1 mg(base)/mL, packaged in 10 mL, 20 mL, and 50 mL single-dose vials).

Reference is also made to your amendments dated January 25, February 13, and April 30, 2002.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Primacor Injection of Sanofi Synthelabo, Inc., is subject to a period of patent protection. U.S. Patent No. 4,313,951 (the '951 patent) is due to expire on May 26, 2002. Your application contains a Paragraph III Certification under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market this drug product prior to the expiration of this patent. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the '951 patent has expired, i.e., currently May 26, 2002.

In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. An amendment should be submitted even if none of these changes were made. This submission should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to May 26, 2002, you should amend your application accordingly.

At the time you submit any amendments, you should contact Stanley Shepperson, Pharm.D., Project Manager, at 301-827-5798, for further instructions.

Sincerely yours,

/S/

Gary Buehler 4/30/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-660

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
270 Northfield Road
Bedford, OH 44146

AUG 2 1999

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

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

DATE OF APPLICATION: June 29, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 1, 1999

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BEDFORD
LABORATORIES™

Acdc for filing
S. Middleton
7/19/99
505(j)(2)(A)

June 29, 1999

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

RE: Abbreviated New Drug Application
Product: Milrinone Injection; 1 mg/mL; 10 mL and 20 mL vials

Dear Sir/Madam:

In accordance with Section 505 (j)(1) of the Federal Food, Drug and Cosmetic Act, Bedford Laboratories™ is submitting in triplicate (an archival copy, a review copy and a field copy) an Abbreviated New Drug Application for Milrinone Injection, 1 mg/mL, 10 mL and 20 mL vials. Please note that the field copy is being sent directly to FDA District Office in Cincinnati, Ohio.

The drug product subject to this application will be manufactured by Ben Venue Laboratories, Inc., located at 270 Northfield Road, Bedford, Ohio 44146.

This abbreviated new drug application contains the information required by Section 505 (j)(2)(A)(i), (ii)(I), (iv), (v) and (vi). The application is provided in the format suggested by your office (Guidance for Industry, "Organization of an ANDA," OGD #1, revised February, 1999) and contains a copy of the package insert of the "listed drug" (Sanofi Winthrop's Primacor®). This application consists of three volumes.

In accordance with Title 21 CER 320.22 Bedford Laboratories™ requests a waiver of the requirements for submission of evidence demonstrating the *in vivo* bioavailability/ bioequivalence for the drug product that is the subject of our application (Milrinone Injection, 1 mg/mL, 10 mL and 20 mL vials). The drug product is intended for intravenous administration and it contains the active ingredient in the same concentration as in the listed drug product.

Bedford Laboratories™ certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug product are in conformity with the cGMP in accordance with Title 21 CFR 210 and 211. Ben Venue's signed statement is provided in Section IX (MANUFACTURING FACILITY) Subsection C (cGMP Certification).

Two copies of the analytical methods which were used to test this product and the analytical method validations are enclosed separately along with this application.

CENTER FOR DRUG
REC'D
JUL 0 1 1999
OGD
EVALUATION AND RESEARCH

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

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Office of Generic Drugs
June 29, 1999

Milrinone Injection
ANDA

Section XXII of this application, located in Volume III, contains the Sterilization Assurance Data and Information as well as the following: a copy of the label and labeling, description of the manufacturing process including the components and composition statement, and copies of the executed batch record containing holding times, filtration integrity testing and sterilization records. These products are(

If the Agency needs any assistance in the review of this application, the phone numbers for contact are (440)-232-3320, ext.333 (direct) and (440)-232-2772 (fax).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

forward to reviewer 12/7/01 DWS

November 30, 2001

BEDFORD LABORATORIES™

Minor Amendment/Response to Chemistry Deficiencies

ORIG AMENDMENT N/AM.

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

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 03 2001
OGD

Re: ANDA 75-660/Minor Amendment
Product: Milrinone Lactate Injection; 1 mg/mL, 10 mL, 20 mL and 50 mL vials

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-660, for Milrinone Lactate Injection, 1 mg/mL, 10 mL, 20 mL and 50 mL vials, to remove the deficiencies cited in the Minor Deficiency of June 8, 2001.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Form 356h is provided in Attachment I.

A. Chemistry Deficiencies

1. The Test Specifications for the Active Ingredient, located in Attachment II, have been revised to include the identity of Known Impurity (NMT %) as

2.&3. Please refer to Attachment II for the revised Test Specifications for the Active Ingredient which corrects the specifications for and adds a specification for

Bedford Laboratories wishes to withdraw Ben Venue Laboratories' Quality Control Analytical Test Method "Quantitation of in the Milrinone Drug Substance," in support of this application. Bedford Laboratories' will use the results from the manufacturers' Certificate of Analysis for Residual Solvents testing.

Also located in Attachment II are the revised Certificates of Analysis from which includes specifications and results for Residual Solvents testing for the two lots of Milrinone used in the exhibit batches (82683 and 82751).

4. The quantitation of in the drug substance has been included in the Residual Solvents testing, as discussed in A. 2. and A. 3.

5. Please refer to Attachment III for the revised OVI Certification from

12/5/01

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300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

6. Bedford Laboratories™ proposes to delete the Loss on Drying test from the Test Specifications for Active Ingredient (Attachment II). With the inclusion of Residual Solvents testing (- - , and Water testing (Karl Fischer), the LOD monitoring does not provide any additional value, as testing for Residual Solvents and Water lends a higher degree of accuracy and specificity than that attained with LOD testing. The test was initially included in Bedford Laboratories' specifications, as it was a part of the manufacturer's specification.

7. Bedford Laboratories acknowledges that if an Individual Unknown Impurity with a value above % is obtained, the Agency may request that said impurity be identified.

8. Lactic Acid testing was added as a specification in the Minor Amendment of May 8, 2001, with only a limited amount of data available. Testing for Lactic Acid Content was performed on 25-month samples of Milrinone Lactate Injection, Lot 2002-57-156969 and 29-month samples of Lot 2002-49-127009; the results were mg/mL, respectively, with no evidence of precipitation. These results are higher than those previously reported in the Minor Amendment of May 8, 2001. The available data are as follows:

Test Point	2002-49-127009		Test Point	2002-57-156969	
	Upright	Inverted		Upright	Inverted
15 month	mg/mL	mg/mL	10 month	ng/mL	mg/mL
24 month	mg/mL	mg/mL	20 month	ng/mL	mg/mL
29 month	mg/mL	mg/mL	25 month	ng/mL	mg/mL

The Lactic Acid data does not appear to support a definitive trend, and the initial drop may be a result of analytical variation. Due to the data variation, Bedford Laboratories™ wishes to retain the proposed Lactic Acid Content stability specifications of mg/mL to mg/mL; Bedford Laboratories™ commits to reviewing the data from the first three marketable production lots and revising the specifications accordingly.

B. Acknowledgments

Bedford Laboratories has received notification that has responded to the deficiencies regarding DMF for the Milrinone drug substance. This response was received by the Agency on June 25, 2001 and a copy of the letter is provided in Attachment IV.

Please note, Bedford Laboratories' wishes to amend Section III of the original application, Patent Certification, to reflect the current information provided in the Approved Drug Products with Therapeutic Equivalence (Electronic Orange Book) regarding US Patent No. 4,313,951. The revised Patent Certification is located in Attachment V.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440) 201- 3576 or facsimile at (440) 232-2772, for any additional information.

BEDFORD LABORATORIES™

Sincerely,
for Bedford Laboratories™

Molly L. Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

May 8, 2001

BEDFORD LABORATORIES™

Minor Amendment/Response to Chemistry Deficiencies

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

N/Am

ORIG AMENDMENT

Re: **ANDA 75-660/Minor Amendment**
Product: **Milrinone Lactate Injection; 1 mg/mL, 10 mL, 20 mL and 50 mL vials**

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-660, for Milrinone Lactate Injection, 1 mg/mL, 10 mL, 20 mL and 50 mL vials, to remove the deficiencies cited in the Minor Deficiency of February 15, 2001. Please note, the Microbiological deficiencies cited in the Agency's letter of August 23, 2000, were responded to in the Major Amendment of September 12, 2000.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Form 356h is provided in Attachment I.

1. Chemistry Deficiencies

1. Please refer to Attachment II for a complete listing of test specifications and methods for Water for Injection, USP.

2. In accordance with USP/NF <381>, Elastomeric Closures for Injections, an extraction study was performed using as the extraction solvent. The report is located in Attachment III.

3. The Raw Material Specifications, located in Attachment IV, have been revised to include a specification for Impurity

4. The Raw Material Specifications have also been revised to include Residual Solvents testing. The specifications are located in Attachment IV.

5.a. Please refer to the Post-Approval Stability Protocol, #SP-99034.02, located in Attachment V, which has been revised to reduce the specification for Individual Unknown Impurities.

5.b. The aforementioned Post-Approval Stability Protocol has also been revised to add testing for Lactic Acid Content. The available data for Lactic Acid testing is as follows: RECD

CENTER FOR DRUG EVALUATION AND RESEARCH
MAY 0 9 2001
OGD

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Test Point	2002-49-127009		2002-51-127010	
	Upright	Inverted	Upright	Inverted
15 Month	mg/mL	mg/mL	mg/mL	mg/mL
24 Month	mg/mL	mg/mL	mg/mL	mg/mL

Test Point	2002-57-156969	
	Upright	Inverted
10 Month	mg/mL	mg/mL
20 Month	mg/mL	mg/mL

Lactic Acid Content

In consideration of this data, the stability specification for Lactic Acid Content has been set at mg/mL.

5.c. Bedford Laboratories™ has included in the Post-Approval Stability Protocol, located in Attachment V; **24- month** data for is as follows:

Minimum Amide

Position	2002-49-127009	2002-51-127010	2002-57-156969
Upright	<LOQ	<LOQ	ND
Inverted	<LOQ	<LOQ	ND

5.d. Please refer to Attachment V for the Post-Approval Stability Protocol #SP-99034.02, which includes a specification for

2. Acknowledgements

1. Please refer to Attachment VI for the available room temperature stability data for exhibit lots 2002-49-127009, 2002-51-127010 and 2002-57-156969.

2. As indicated in Attachment VII, has amended DMF as of April 23, 2001.

Please note, the Test Specifications for the Active Ingredient, located in Attachment IV, have been revised to reflect the current Agency request regarding the specifications.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440) 201-3333 or facsimile at (440) 232-2772, for any additional information.

BEDFORD LABORATORIES™

Sincerely,
for Bedford Laboratories

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

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September 12, 2000

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

Major Amendment/Response to Chemistry, Labeling and Microbiological Deficiencies

tpl
NDA ORIG AMENDMENT
Ac

Re: **ANDA 75-660/Major Amendment**
Product: **Milrinone Lactate Injection, 1 mg/mL, 10 mL, 20 mL and 50 mL vials**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-660, for Milrinone Lactate Injection, 1 mg/mL, 10 mL, 20 mL and 50 mL vials, to remove the deficiencies cited in the Major Deficiency dated of December 29, 1999 and the Microbiological Deficiency of August 23, 2000.

Please note, in addition to answering the deficiencies cited in the Agency's letter, Bedford Laboratories™ is also submitting for review an additional dosage size, a single-dose 50 mL vial. This dosage form has the exact formulation as that previously submitted in the original application and the same manufacturing process.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Form 356h is provided in Attachment I.

A. Chemistry Deficiencies

1. a.

1. b. Please refer to Attachment II for the revised Pages 057 and 059 of ~~the original application~~, which include as a component.

major amendment

Attachment II did have the revised page 5

1. c. Please refer to Page 374 of the original application, under "Solution Transfer" which gives the option the solution. Below that is the box for the Lot Number.

2. Please refer to Attachment III for the Organic Volatile Impurities Certification from for Milrinone.

3. Please refer to Attachment III for the revised specifications which delineate the

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SEP 14 2000
OGD

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300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

identity of Known Impurity as with a specification of NMT %.

4. The revised specification, located in Attachment III, contains the re-worded specification for ID test (IR), General Chapters <197>, as requested.

5. has been added as a retest for the as indicated in the revised specifications, located in Attachment III.

6. Attachment III also contains the re-submitted Page 069, as requested.

7. Please refer to Attachment IV for a complete listing of test specifications and methods for Lactic Acid USP, Dextrose Anhydrous USP and Sodium Hydroxide NF.

8. Ben Venue Laboratories, Inc., Standard Operating Procedure SOP D-44/D-510, Release of Bulk Solutions (Assay and Time Limitations) addresses the issue of pre-filtration holding times. References to this SOP can be found in the Master Production Record, Compounding Instructions and Sections. Please note, bulk solutions are never held post-filtration, as filtration and filling are a continuous operation.

9. In accordance with USP/NF <381>, Elastomeric Closures for Injections, an extraction study was performed using the Milrinone Lactate drug product. The report is located in Attachment V.

10. Finished Dosage Form

a. An additional identification test (Identification Test B for Milrinone Drug Product) has been added to the Finished Product Specification, as indicated in Attachment VI. The method for this test, 2002-00-020, is also located in Attachment VI.

b. Please refer to Attachment VII for Study Report TTP-BIA-M0170 from which provides the identity of Please note, the Finished Product Specification, located in Attachment VI, reflects the identity of this compound.

c. Please refer to Attachment VIII for test method 2002-00-018, "Assay of the Lactic Acid Content of the Milrinone Injection Drug Product," and the accompanying validation report. As indicated on the Finished Product Specification, Lactic Acid Content will be tested at the release of product.

d. Samples of the reference listed drug (Sanofi's Primacor®, Lot 451753A, expiration of 10/1/00, ~ 21 month sample) were tested along with Bedford's Lot 2002-51-127010, manufactured 3/3/99 (~ 16 month sample). The impurities are as follows:

	Individual	Total
Primacor®	%, %, %	%
Milrinone Lactate	%	%

Please refer to Attachment IX for the associated chromatograms.

√e. Please refer to Attachment VI for the revised Finished Product Specification for Milrinone Lactate Injection which includes a specification for (Impurity and the revised Post-Approval Stability Protocol #SP-99034, located in Attachment XI, which also includes a specification for

√11. The method, "Quantitation of Milrinone in the Milrinone Injection In-Process Solution, Identification and Quantitation of the Drug in the Drug Product and Stability Samples, and Chromatographic Purity of Milrinone in the Milrinone Injection Drug Product and Stability Samples," Method Number 2002-00-024, has been revised to add the information necessary to quantify A validation of this method revision has been completed. The revised method and validation report can be found in Attachment X.

12. Stability

√a. Please refer to Attachment XI for the revised Post-Approval Stability Protocol, #SP-99034, which reflects lowered stability specifications for (Milrinone) and for Individual Unknown Impurities.

√b. Bacterial Endotoxins testing has been added to the 12-month test point, as requested. Please refer to Attachment XI for the revised Post-Approval Stability Protocol, #SP-99034.

√c. These intervals have been amended in the revised Post-Approval Stability Protocol, #SP-99034.

√d. The specifications presented on Page 732 of the Post-Approval Stability Protocol are not the specifications for the IV solution study. The IV solution study is performed only once, and is to meet the specifications typically outlined in the package insert labeling. Because the package insert labeling for Milrinone Lactate Injection lacks this information, the "Handbook on Injectable Drugs," by Lawrence Trissel was consulted for IV solution compatibility and a copy of this reference material is provided in Attachment XII. When compared to the reference material, the data presented on Pages 746 and 747 of the original application are acceptable.

B. Acknowledgements

√1. The pharmaceutical function of each ingredient in the formulation of Milrinone Lactate

Injection is as follows: Milrinone: active pharmaceutical ingredient; Lactic Acid, USP: acidifying agent; Dextrose Anhydrous, USP: tonicity agent; Sodium Hydroxide, NF: pH modifier; Water for Injection, USP: vehicle.

2. Please refer to Attachment XIII for the available room temperature stability data.

3. Bedford Laboratories™ acknowledges that satisfactory compliance evaluations of referenced firms are required for approval of this application.

4. Bedford Laboratories™ acknowledges that Analytical Methods Validation will not be initiated until all comments regarding product test specifications and methods have been satisfactorily addressed.

5. As indicated in Attachment XIV, the holder of DMF # has amended the DMF as of May 22, 2000.

6. June, 1996 is the Retest Date of Lactic Acid, USP, Lot 94-0394, incorrectly stated as the Expiration Date on Page 078 of the original application. Bedford Laboratories™ apologizes for any inconvenience this may have caused the Agency.

C. Labeling

All deficiencies cited have been corrected. Please refer to Attachment XV for 12 final printed vial labels, unit carton labeling and package insert labeling. Please note, all computer generated labels and labeling are of actual size, color and clarity.

Also, in accordance with 21 CFR 314.94(a)(8)(iv), Attachment XV provides a side-by-side comparison of the currently proposed labeling versus that which was previously submitted.

D. Microbiology

A. 1. In accordance with Corporate Operations Policy OP-01 (current revision), "Bulk Solutions Holding Times," unfiltered solutions may be held at room temperature (+15°C to +30°C) for a maximum of thirty hours. This time limit starts at the addition of the first component to the compounding vessel and ends with the stoppering of the last vial. Please note, this product is through a redundant m filter system and then

As previously stated, Bedford Laboratories™ is submitting for review an additional dosage size, a single-dose 50 mL vial. Information specific to this dosage size in provided to review in Attachment XVI. Please note, the manufacturing process is identical to that of the 10 mL and 20 mL dosage forms, including the sterilization process validation information.

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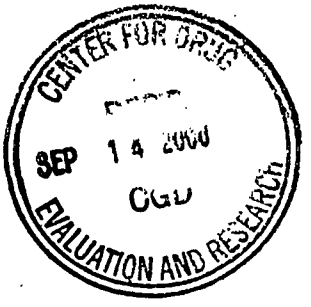
ANDA 75-660
Office of Generic Drugs

Milrinone LactateInjection
September 12, 2000

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440) 232-3320, ext. 3333, or facsimile at (440) 232-2772, for any additional information.

Sincerely,
for Bedford Laboratories

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.



A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD
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April 30, 2002

FACSIMILE AMENDMENT

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

NEW CORRESP

RECEIVED
MAY 0 1 2002
OGD / CDER

RE: ANDA 75-660/Facsimile Amendment
Product: Milrinone Lactate Injection, 1 mg/mL; 10 mL, 20 mL and 50 mL vials

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-660, for Milrinone Lactate Injection, 1 mg/mL, 10 mL, 20 mL and 50 mL vials, to remove the deficiency discussed between Mr. Vilayat Sayeed of the Agency and Ms. Margaret VanDine of Ben Venue Laboratories, Inc., in their telecon of April 22, 2002. Attached is FDA Form 356h.

The Final Product specification was revised in August, 2000, to include Lactic Acid Content testing with a concentration of mg/mL to mg/mL. Bedford Laboratories has performed additional testing to determine whether our product can support the proposed Lactic Acid specification throughout the proposed shelf-life of the product. Samples of the expired exhibit lots were pulled and subjected to 3 different cycles (22 minutes, 44 minutes and 66 minutes) and then tested. This testing was performed on product which was highly stressed (in excess of normal product conditions) to ensure that the product will meet the proposed specifications. All results are mg/mL.

Test Point	2002-49-127009			Test Point	2002-51-127010		
	Cycle 1	Cycle 2	Cycle 3		Cycle 1	Cycle 2	Cycle 3
34 month	*			34 month			

Test Point	2002-57-156969		
	Cycle 1	Cycle 2	Cycle 3
29 month			

* Test sample spilled; not enough sample to repeat.

In response to the above results, the Post-Approval Stability Protocol #SP-99034 has been revised to reflect this same specification for the Lactic Acid Content. Both of these items are

BEDFORD LABORATORIES™

attached for review.

As requested, Mr. Stan Shepperson of the Agency has been notified of this revision.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440) 201-3576 or facsimile (440) 232-2772, for any additional information.

Sincerely,
for Bedford Laboratories™

Molly L. Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

A3.1 555 2-15-02

Fax copy previously forwarded to chemist. NA1
D. Shepperson 2-14-02

BEDFORD LABORATORIES™

February 13, 2002

FACSIMILE AMENDMENT

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

ORIG AMENDMENT
N/FA

RE: ANDA 75-660/Facsimile Amendment
Product: Milrinone Lactate Injection, 1 mg/mL; 10 mL, 20 mL and 50 mL vials

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-660, for Milrinone Lactate Injection, 1 mg/mL, 10 mL, 20 mL and 50 mL vials, to remove the deficiency discussed between Mr. Stan Shepperson and Ubrani Venkataram of the Agency and Ms. Margaret VanDine of Ben Venue Laboratories, Inc., in their telecon of February 13, 2002. Attached is FDA Form 356h.

As presented in the Facsimile Amendment of January 25, 2002 to this ANDA, Bedford Laboratories™ commited to reducing the specification for Individual Unknown Impurities for post-approval stability batches to NMT [redacted] %. Attached to this letter is a revised Post Approval Stability Protocol listing the specification for Individual Unknown Impurities to NMT [redacted] %.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440) 201-3321 or facsimile (440)232-2772, for any additional information.

Sincerely,
for Bedford Laboratories™

Margaret A. VanDine
Senior Regulatory Affairs Associate
Ben Venue Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 14 2002
DGD

BEDFORD
LABORATORIES™

January 25, 2002

FACSIMILE AMENDMENT

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

NC to Fax

NEW CORRESP

RE: ANDA 75-660/Facsimile Amendment
Product: Milrinone Lactate Injection, 1 mg/mL; 10 mL, 20 mL and 50 mL vials

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-660, for Milrinone Lactate Injection, 1 mg/mL, 10 mL, 20 mL and 50 mL vials, to remove the deficiencies cited in the Facsimile Deficiency of December 26, 2001. Attached is FDA Form 356h.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication.

They do have 24 months data on file.

Chemistry Deficiencies:

1.a.,b. Bedford Laboratories™ commits to reducing the specification for Individual Unknown Impurities for stability to match that of final product (%). Due to the limited amount of data available from the three exhibit lots of Milrinone Lactate Injection, a further reduction in the specifications for final product and stability may be premature. In addition, we believe that the change in the impurity levels observed between final product and stability are within normal analytical variation. Upon the manufacture of post-approval production batches, Bedford Laboratories commits to reviewing the applicable data and revising the limits for Individual Unknown Impurities as necessary.

Also, upon review of the Agency's Draft Guidance for Industry, "ANDAs: Impurities in Drug Products," (December, 1998) the proposed limit of % for Individual Unknown Impurities is reasonable, based upon the maximum daily dose of mg/kg/day. This dosage results in a daily maximum dose of mg/day for a average 70 kg adult. The mg/day dose falls within the % degradant threshold proposed in the referenced draft guidance (Page 12 of 20).

2. A solution of 1 mg/mL of Milrinone and mg/mL of Lactic Acid was formulated and examined for precipitation; after one week at room temperature, no precipitation was witnessed.

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 28 2002

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD LABORATORIES™

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440) 201-3576 or facsimile (440)232-2772, for any additional information.

Sincerely,
for Bedford Laboratories™

Molly L. Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

BEDFORD
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December 19, 2001

NEW CORRESP

NC

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

RE: **ANDA 75-660/Methods Validation Package**
Product: **Milrinone Lactate Injection, 1 mg/mL; 10 mL, 20 mL and 50 mL vials**

Dear Sir/Madam:

We wish to provide the Agency with copies from our unapproved Abbreviated New Drug Application, 75-660 for Milrinone Lactate Injection, 1 mg/mL, 10 mL, 20 mL and 50 mL vials, as requested in the telephone communication of December 14, 2001, between Mr. Stan Shepardson of the Agency and Ms. Molly Rapp of Ben Venue Laboratories.

Provided are two copies of the following methods and method validation reports:

BNCH3731-024

PPD Report 99-0049.2

2002-00-018.1

PPD Report 00-0053

2002-00-024.4

PPD Report 99-0050.2

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PPD Report 00-0030.1

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440) 201-3576 or facsimile (440)232-2772, for any additional information.

Sincerely,
for Bedford Laboratories™

Molly L. Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.