CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75834

CORRESPONDENCE

ANDA 75-834

Baxter Healthcare Corporation
Attention: Marcia Marconi
Route 120 and Wilson Road, RLT-10
Round Lake, IL 60073

MAY 30 2000

Dear Madam:

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 in 5% Dextrose Injection in Plastic Container

DATE OF APPLICATION: March 31, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 3, 2000

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/

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

I.V. Systems Division
Regulatory Affairs

Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

Fax: 847.270.4668

labeling review
drafted 6/6/00
A. Vega

Baxter

March 31, 2000

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

Re: Abbreviated New Drug Application

Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container

Submission Includes Sterilization Assurance Information and Data

This application will include a CMC ESD electronic submission. The diskettes (or CD) will be sent as new correspondence within 30 days.

Dear Sir or Madam:

Baxter Healthcare Corporation proposes to market a new product, Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container.

Per the guidance "Organization of an ANDA"[1], Baxter Healthcare Corporation is providing the following information as relevant to the above-referenced submission.

Purpose of the Submission

The purpose of this submission is to seek approval to market Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container. The proposed product is identical in route of administration, dosage form, strength, formulation, volume, and conditions and indications for use to the reference drug, Primacor® (milrinone lactate injection) manufactured by Sanofi Pharmaceuticals, Inc., and described in NDA 20-343 (approved August 9, 1994).

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[1] Guidance for Industry, "Organization of an ANDA", U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), February, 1999.

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Type of Submission

Abbreviated New Drug Application (ANDA)

Proprietary Name

Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container

Established Name

Milrinone Lactate Injection

Number of Volumes Submitted

4 (Review Copy)
4 (Archival Copy)

The table of contents (pages 4 - 9) has been duplicated and placed behind an appropriately labeled tab in each volume.

Number of Copies Submitted

Three full copies of the application are provided: one archival copy (blue), one chemistry, manufacturing and controls review copy (red) and one additional review copy (red) to facilitate the microbiology review of sterility assurance information. The archival copy includes three additional copies of the proposed labeling.

A waiver of the requirements for evidence of *in vivo* bioavailability is being requested in **Section VI** as provided for under 21 CFR §320.22(b)(1).

Additionally, in accordance with the previously referenced guidance, two separately bound copies of **Section XV, Analytical Methods** are included in red review binders. There is no USP monograph for milrinone lactate or milrinone lactate in 5% dextrose injection.

Baxter

A field copy of this submission has been sent to the Chicago District office on the date of this letter in compliance with 21 CFR §314.94(d)(5). A field copy has also been forwarded to the San Juan District Office to facilitate, as necessary, the pre-approval inspection process for Baxter's Jayuya, Puerto Rico manufacturing facility. Baxter certifies that the field copies are true copies of the archival and review copies of the application submitted to FDA headquarters.

A chemistry, manufacturing and controls (CMC) electronic submission document (ESD) produced by the Entry Validation Application (EVA) will be submitted to this file within 30 days of the date of this letter. The ESD will be accompanied by a CMC companion document.

Baxter commits to the resolution of any issues identified in the methods validation process after approval.

Please contact Mr. Stacey Thompson at (847) 270-2577 if you have comments or questions regarding this application. Thank you for your time and consideration in its review.

Sincerely,

Stacey L. Chompt
FOR

Marcia Marconi
Vice President
Regulatory Affairs
(847) 270-4637 (Phone)
(847) 270-4668 (Fax)

Medication Delivery
Regulatory Affairs

Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

Fax: 847.270.4668

Noted
& Shepherd
for reviewed.
5/28/02

Baxter

TRANSMITTED BY FACSIMILE AND
OVERNIGHT DELIVERY

May 22, 2002

Dr. Vilayat Sayeed, Deputy Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
AM

Re: ANDA 75-834: Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container

TELEPHONE AMENDMENT – ADDITION OF LACTIC ACID SPECIFICATION

Dear Dr. Sayeed:

Baxter Healthcare Corporation is submitting this amendment to ANDA 75-834, tentatively approved on October 30, 2001, to add lactic acid (a solubilizer and pH adjuster) as a release test for the finished product and to the stability protocol per the Agency's request of May 20, 2002. This amendment is being made to allow final approval of the application to be made effective after May 26, 2002, the current expiration of marketing exclusivity for the reference listed product (RLD), Primacor® in 5% Dextrose Injection, manufactured by Sanofi Synthelabo, Inc.

Addition of Lactic Acid Specification for the Finished Product

Baxter has updated the Finished Product Testing Methods and Specifications to add the specification for lactic acid. The revised specifications are included in **Attachment 1**, which is an updated **Table XIV-1** (page 68, as submitted July 25, 2001). Baxter commits that the finished product will meet the revised specifications prior to marketing.

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Addition of Lactic Acid to the Stability Protocols

Baxter has revised its stability protocols to include the specification for lactic acid. The revised protocols are included in **Attachment 2** as **Tables 1 - 2.**

A field copy of this submission has been sent to the Chicago District office on the date of this letter in compliance with 21 CFR §314.94(d)(5). A field copy has also been forwarded to the San Juan District Office, the site of Baxter's Jayuya, Puerto Rico manufacturing facility. Baxter certifies that the field copies are true copies of the archival and review copies of the application submitted to FDA headquarters.

Please contact Mr. Stacey Thompson at (847) 270-5829 if you have comments or questions regarding this application. Thank you for your time and consideration in its review.

Sincerely,

Stacey L. Thompson
For

Marcia Marconi
Vice President, Regulatory Affairs
(847) 270-4637 (Phone)
(847) 270-4668 (Fax)

Certified Field Copies: Food and Drug Administration
Chicago District Office
300 S. Riverside Plaza, Suite 550 South
Chicago, IL 60606

Food and Drug Administration
San Juan District Office
466 Fernandez Juncos Avenue
San Juan, PR 00901-3223

cc: Mr. John Quick, Corporate Vice President, Quality Management
Mr. Julio Salwen, Quality Director, Jayuya Manufacturing Facility

Regulatory Affairs
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490
Fax: 847.270.4668

Baxter

February 26, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

Re: ANDA 75-834: Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container

Intent to File Amendment

Dear Sir or Madam:

Per 21 CFR §314.120(a), we are notifying you of our intent to file a minor amendment to the above-referenced ANDA in response to your FAX correspondence dated February 20, 2001 and February 21, 2001. Thank you for incorporating this information into the file. If you have any questions, please contact Mr. Stacey Thompson at (847) 270-2577.

Sincerely,

Stacey L. Thompson
FOR

Marcia Marconi
Vice President, Regulatory Affairs
(847) 270-4637 (Phone)
(847) 270-4668 (Fax)

CENTER FOR RECD FEB 27 2001 OGD EVALUATION AND RESEARCH

Noted. NAI.
B. McNeal
3/6/01

3/1/01

I.V. Systems / Medical Products
Regulatory Affairs

Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

847.270.4637
Fax: 847.270.4668

Baxter

June 7, 2001

Ms. Bonnie McNeal
Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Metro Part North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT

Re: ANDA 75-834: Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container

Information Package for Teleconference on Batch Adjustments

Dear Ms. McNeal:

In a faxed correspondence dated May 29, 2001, Baxter Healthcare Corporation requested a teleconference to discuss one of the chemistry deficiencies identified in the Agency's letters of November 17, 2000 and February 20, 2001 regarding Baxter's practice of
process of Milrinone Lactate in 5% Dextrose Injection. The purpose of this teleconference is to obtain clarification of the Agency's concerns and to facilitate an open discussion of the issue such that the comment can be completely addressed in Baxter's response.

This correspondence is in follow-up to the June 6, 2001 teleconference between you and Dr. Ubrani Venkataram of the Agency and Mr. Stacey Thompson of Baxter. At that time, the Agency stated that Baxter should submit its information package for the teleconference on batch adjustments to the Agency for consideration. The Agency stated that following internal discussions, it would contact Baxter to make arrangements for the teleconference.

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6/12/01

Baxter

The Agency's comment from the November 17, 2000 deficiency letter is restated in bold and is followed by Baxter's response of December 21, 2000 (referenced attachments are not included in this correspondence). The Agency's February 20, 2001 comment is also restated in bold, followed by:

- The specific topic we would like to discuss in the teleconference (highlighted as boxed text).
- Reference to supporting information concerning Baxter's position on the issue of batch adjustments, which is filed behind the tab labeled "**Technical Information.**"

The Agency's November 17, 2000 comment and Baxter's December 20, 2000 response:

6. The description of the manufacturing process

Please revise the manufacturing process

Baxter manufactures products utilizing well-established processing controls. These controls can be found throughout the description of the manufacturing process for milrinone. Although adjustments are infrequent and minor, it is not the intent to allow for repeated adjustments to dextrose and milrinone.

Therefore, the manufacturing process has been revised to

A revised **Section XI.1.c.(1), Solution Mixing Procedure**, is included as **Attachment 5**. **Table XII-1, In-Process Controls and Specifications** (page 142, as submitted 03/31/00) was revised to reflect the changes in the mixing procedure and is included as **Attachment 6**. A revised Material Specification, Document Number D3-15-13-108, a component of the Master Production Record, is included as **Attachment 7**.

Baxter

Premixed intravenous drug solutions, such as milrinone, are ready to use solutions and are thus formulated in 100 mL or higher volumes. Due to these large formulation volumes, the batch size volumes for premixed drug solutions are large, typically ( )liters. Baxter formulates large batch size volumes on a weight/volume basis. During the mixing of the solution, the accuracy of weight and volume measurements and the raw material assay value, which is used to calculate the amount of raw material required, will be within a small range and contribute to minor variability in the resulting drug concentration.

Based on the probability of normal distribution, it should be expected that the individual variabilities discussed above could be occasionally cumulative and result in dextrose and/or milrinone concentrations slightly lower or higher that the established target concentration range. Therefore, an occasional minor adjustment during the solution mixing may be needed.

On February 20, 2001, the Agency responded as follows:

5. **Your response to our comment #6 is not satisfactory. Please revise the manufacturing record and delete these potency adjustments completely.**

We would like to understand why the Agency considers our response not satisfactory and discuss Baxter's position on batch adjustments.

Supporting information concerning Baxter's position on the issue of batch adjustments is filed behind the tab labeled "**Technical Information.**"

Baxter

At this time, the following Baxter representatives plan to participate in the teleconference:

- Rao Chilamkurti, Ph.D., Director, Pharmaceutical Sciences R&D
- Ted Leggett, Quality Director, North Cove, NC and Jayuya, PR manufacturing facilities
- Patricia Barsanti, Director, Regulatory Affairs
- Stacey Thompson, Manager, Regulatory Affairs

Per your request, we are submitting five (5) copies of this correspondence for the teleconference. Baxter would like to schedule the teleconference as soon as possible and will contact the Office of Generic Drugs shortly to follow-up on this request. Please feel free to contact Mr. Stacey Thompson at (847) 270-2577 if you have any comments or questions regarding this request.

Thank you for your time and consideration of this request for a teleconference.

Sincerely,

Stacey L. Thompson
FOR

Marcia Marconi
Vice President
Regulatory Affairs
(847) 270-4637 (phone)
(847) 270-4668 (fax)

I.V. Systems Division
Regulatory Affairs

Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

Fax: 847.270.4668

Baxter

December 21, 2000

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

ORIG AMENDMENT
N/Am

RE: ANDA 75-834: Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container

AMENDMENT in Response to November 17, 2000 Deficiencies

REQUEST TO RECLASSIFY FROM A MAJOR TO A MINOR AMENDMENT

Dear Sir or Madam:

Baxter Healthcare Corporation is submitting this amendment to pending ANDA 75-834 in response to chemistry and labeling deficiencies received on November 17, 2000.

The November 17, 2000 facsimile from the Agency contained 12 chemistry comments/requests and they were classified as major deficiencies. The facsimile stated that Baxter's response should be designated as a MAJOR AMENDMENT.

Upon review of the chemistry comments/requests, we have determined that several of them (Comments 1, 2, 3, 5, 7, 9, and 12) can be addressed with brief clarifications only and reference to previously submitted information in ANDA 75-834, and that three of the comments (Comments 4, 10, and 11) can be addressed by tightening or establishing impurity limits. As a result, this amendment consists of very little new chemistry information and is largely comprised of previously submitted information (attached for ease of review).

Baxter

Baxter respectfully requests that the Agency consider reclassifying the November 17, 2000 deficiencies as MINOR and allowing this response to be a MINOR AMENDMENT.

The specific deficiencies in question and the proposal for reclassification from MAJOR to MINOR were discussed by the Project Manager, Ms. Bonnie McNeal of FDA and Mr. Stacey Thompson of Baxter on December 7, 2000. On December 8, 2000, Ms. McNeal recommended that Baxter submit its amendment in writing with a request to reclassify as a MINOR AMENDMENT. This would permit the Agency to review Baxter's responses in order to determine if a reclassification is appropriate. We appreciate the Agency's consideration of reclassification.

Responses to Chemistry Deficiencies of November 17, 2000:

The Agency's comments are restated in bold and are followed by Baxter's response.

A. Chemistry Deficiencies

1. **The component statement (page 54) provides for the use of whereas the actual material used in the manufacture of the drug product is Dextrose Hydrous. Please revise the component statement and resubmit.**

   The actual component used in the manufacture of the drug product is as specified in **Section VII.1. Components** (page 54, as submitted 03/31/00). The finished product, however, is labeled as Dextrose Hydrous as shown in **Section VII.2. Composition** (page 54, as submitted 03/31/00) for consistency with other Baxter products. This is also consistent with the USP monograph for Dextrose Injection, USP, which describes the concentration of Dextrose based on the labeled amount of dextrose hydrous.

Baxter

2. **The limit for the ID test is not specific. A specific limit should be included. Please revise and resubmit.**

   The limit was provided in **Section XV, Analytical Methods, Addendum 1** of the original application (page 1204, as submitted 03/31/00) as referenced in **SectionVIII.1.c.(1)(b)**, page 57. For further clarification, **SectionVIII.1.c.(1)(b)**, page 57, has been revised to include the additional descriptive information for the limit (Pass indicates that a positive identification of milrinone is confirmed if the retention time of milrinone in the sample injection is within ± 5% of the retention time of milrinone in the standard injection) and the revised page is provided in **Attachment 1** of this correspondence.

3. **Please include tests, methods and limits for Residual Solvents, Color of Solution, Organic volatile impurities and assay in the drug substance release certificate. Data should be submitted for a test batch.**

   Residual Solvents, Color in Solution, Organic Volatile Impurities, and Assay are certified by the approved supplier and are included on the Certificate of Analysis (COA). The COA's for each lot of raw material used in the manufacture of the stability batches were provided in **Section VIII, Addendum 1** (pages 62-64, as submitted 03/31/00) of the original application. The tests performed by Baxter Healthcare Corporation for each lot of raw material were summarized in the original application in **Section XII, Addendum 2A, Table XII-3** (page 1164, as submitted 03/31/00).

   For clarification, **Table XII-3** (page 1164) has been revised to include all test results (those performed by Baxter and those obtained from the COA) for each lot of raw material used in the manufacture of the stability test batches so that all the information is summarized in one location. The revised **Table XII-3** is provided in **Attachment 2** of this correspondence.

Baxter

4. **The limit for total impurities is high and is not supported by your data or that of the DS supplier. Please tighten the limit for total impurities.**

   Based on currently available drug product stability data and the impurity limits in the drug substance, we have determined that it is appropriate to lower the limit for Total Impurities for the proposed drug product from Not More Thar % to Not More Than %. The new limit provides for up to % total impurities in the drug substance and the possible formation of impurities in the drug product over shelf-life, while allowing appropriate latitude to account for normal manufacturing, analytical, and stability profile variation, as provided by FDA's draft *Guidance for Industry: Impurities in Drug Products* (December 1998). **Table XIV-1** (page 1196, as submitted 03/31/00) has been revised to incorporate the new specification of NMT(1.5)% for Total Impurities and is included in **Attachment 3** of this correspondence.

5. **Regarding inactive ingredient testing, we acknowledge the submitted certificates of analysis for the inactives, however, we request that you provide a list of the current compendial tests, methods and limits used in the testing of each inactive. Also, please identify which of these tests are routinely performed for batch release.**

   The compendial tests and specifications for the release of Lactic Acid, USP, and Water for Injection, USP were provided in **Section XII, Addendum 2A, Tables XII-4** through **XII-6** of the original application (pages 1165-1167, as submitted 03/31/00). The tests and specifications listed on these tables are those specified in the current USP[1,2].

---

[1] **Table XII-6** for Water for Injection, USP has been revised to include Bacterial Endotoxin test results which were inadvertently omitted from the original application. The revised **Table XII-6** is provided in **Attachment 4** of this correspondence.

[2] As described in the original application, where the heavy metals test is required, it is performed using sodium sulfide to generate the sulfide ions required for this test.

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As stated in **Section VIII.2.a.** (page 59, as submitted 03/31/00), the methods used in the testing of the compendial inactive ingredients are those specified in the current USP or NF. For clarification, the summary tables provided in **Section XII, Addendum 2A, Tables XII-4** through **XII-6** of the original application (pages 1165-1167) have been updated to include the methods used in the testing. These updated tables are provided in **Attachment 4** of this correspondence. All compendial tests are routinely performed for raw material release.

Sodium Hydroxide, NF was not used for pH adjustment during stability batch production; however, the tests performed for raw material release are those that are specified in the current USP[3]. **Table XII-6A** has been prepared to summarize the tests, specifications and methods used in the testing of Sodium Hydroxide, NF and is provided in **Attachment 4**. All compendial tests are routinely performed for raw material release.

6. **The description of the manufacturing process**

Baxter manufactures products utilizing well-established processing controls. These controls can be found throughout the description of the manufacturing process for milrinone. Although adjustments are infrequent and minor, it is not the intent to allow for repeated adjustments to dextrose and milrinone.

Therefore, the manufacturing process

[3] As described in the original application, where the heavy metals test is required, it is performed using sodium sulfide to generate the sulfide ions required for this test.

Baxter

A revised **Section XI.1.c.(1), Solution Mixing Procedure**, is included as **Attachment 5**. **Table XII-1, In-Process Controls and Specifications** (page 142, as submitted 03/31/00) was revised to reflect the changes in the mixing procedure and is included as **Attachment 6**. A revised Material Specification, Document Number D3-15-13-108, a component of the Master Production Record, is included as **Attachment 7**.

Premixed intravenous drug solutions, such as milrinone, are ready to use solutions and are thus formulated in 100 mL or higher volumes. Due to these large formulation volumes, the batch size volumes for premixed drug solutions are large, typically ( )liters. Baxter formulates large batch size volumes on a weight/volume basis. During the mixing of the solution, the accuracy of weight and volume measurements and the raw material assay value, which is used to calculate the amount of raw material required, will be within a small range and contribute to minor variability in the resulting drug concentration.

Based on the probability of normal distribution, it should be expected that the individual variabilities discussed above could be occasionally cumulative and result in dextrose and/or milrinone concentrations slightly lower or higher that the established target concentration range. Therefore, an occasional minor adjustment during the solution mixing may be needed.

7. **The product formulation (page 84 and 97) assumes that the 'as is' potency of milrinone is always %; but the equation for calculating the actual amount is provided for 100% potency. The amount of milrinone in the formula table should include the amount of milrinone at 100% potency and the equation should be used to calculate the required amount of milrinone. Please revise and resubmit.**

The product formulation described on page 84 and page 97 states that the quantity shown in the table is the value that would be obtained in the event the "as is" potency was %. It was not the intention to portray that the potency is always %. The % value was chosen for illustrative purposes only and was used in the denominator

Baxter

of the equation to determine the amount of milrinone required for formulation. The 100% in the numerator of the equation is a conversion factor. If the potency were 100.0%, no calculation would be needed.

However, since the calculation is for illustrative purposes, we have revised **Table XI-1** (page 84) to use 100.0% "as is" potency in the calculation as you have requested. The revised **Table XI-1** is provided in **Attachment 8** of this correspondence.

8. **We request that you specify in the batch record the maximum bulk solution holding time for pre and post filtration.**

The milrinone solution batch is formulated and filled per established procedures. Once the solution in the mix tank is determined to be within specification, the tank is released for filling. The solution leaves the mix tank through filling lines and filtered.

Established procedures

An increase in the holding time of the solution filled containers is acceptable provided that there is a corresponding reduction in the tank hold time (pre-filtration).

These holding times will be included as key parameters during the chemical process validation. The chemical process validation will be performed concurrently with the production of the first three commercial batches.

Baxter

9. **We request you to provide data comparing your Drug Product impurity/degradant profile with the innovator's impurity/degradant profile.**

Data comparing our Drug Product impurity/degradant profile with the innovator's impurity/degradant profile were provided in **Section XVI, Stability of the Finished Dosage Form** of the original application. **Section XVI**, pages 1257-1281 (as submitted 03/31/00) contains stability data for our Drug Product and **Section XVI**, pages 1282-1284 (as submitted 03/31/00) contains stability data for the innovator's drug product. **Section XVI**, page 1285 (as submitted 03/31/00) contains a comparative chromatographic profile for our Drug Product and the innovator's Drug Product. The chromatograms demonstrate the similar impurity profiles for the two products and are provided in **Attachment 9** of this correspondence to facilitate your review.

10. **Please include a limit for individual known and unknown impurities/degradants at release and stability.**

Based on currently available drug product stability data and the impurity limits in the drug substance, we have determined that it is appropriate to establish the following limits for individual known and unknown impurities/degradates at release and stability for the drug product:

Limit: NMT % (
NMT %(
NMT %(
( )
NMT _% Other Individual Impurities/Degradates

These limits provide for the amount of impurities in the drug substance and the possible formation of impurities in the drug product over shelf-life, while allowing appropriate latitude to account for normal manufacturing, analytical, and stability profile variation. **Table XIV-1** (page 1196, as submitted 03/31/00) has been revised to incorporate these new specifications and is included in **Attachment 3** of this correspondence.

Baxter

11. The limit for total impurities/degradants is not justified by data. Please include a tighter limit.

Baxter has determined that it is appropriate to lower the limit for Total Impurities in the proposed drug product from Not More Than _ % to Not More Than _ %. Please refer to the response to Comment 4.

12. The forced degradation study should be repeated on samples of the drug product solution in order to evaluate interference from potential excipient interaction. Please submit results.

For clarification, the forced degradation study was performed on drug product solution (containing 100% of the formulation) as well as on blanks (container, water and matrix). The drug product solution (prepared to contain 100% of the proposed formulation) was described in **Section XV, Addendum 1.B** (page 1214, as submitted 03/31/00) of the original application. The drug product solution was exposed to acid, base, oxidation, UV and fluorescent light. The test solutions were assayed and the chromatograms were evaluated to determine the formation of unknown peaks as well as to ensure that no peaks interfering with the peaks were present. The chromatograms were presented in **Figures 7 - 10** (pages 1227-1230, as submitted 03/31/00) of the original application for the Milrinone test article and the three blank solutions. Copies of these chromatograms are also provided in **Attachment 10** of this correspondence.

Baxter

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

1. **DMF # [redacted] has been reviewed and found deficient. This ANDA cannot be approved until these deficiencies have been resolved.**

   Baxter Healthcare Corporation acknowledges that DMF [redacted] has been reviewed and found deficient and that ANDA 75-834 cannot be approved until these deficiencies have been resolved. Baxter was notified by [redacted] in December 2000 that they have submitted an amendment to their DMF to address the deficiencies.

2. **Methods validation will be performed on the drug substance and drug product by FDA field Laboratory.**

   Baxter Healthcare Corporation acknowledges that methods validation will be performed on the drug substance and drug product by FDA field Laboratory. Samples for Methods Validation have been requested by FDA field Laboratory and Baxter Healthcare Corporation has responded to that request.

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

   Baxter Healthcare Corporation acknowledges that the Establishment Evaluation Request is pending.

Baxter

Additional Information:

1. Baxter is revising **Section IX.1** (pages 71 - 72, as submitted 03/31/00) to delete our facility at Aibonito, Puerto Rico as a site for plastic container assembly. A revised **Section IX.1** is included as **Attachment 11**.

2. Baxter is correcting the description of the manufacturing process for the PL 146® membrane tubing supplied in **Section XI** (page 77, as submitted 03/31/00). The PL 146® membrane tubing is manufactured using

Baxter

Responses to Labeling Deficiencies of November 17, 2000:

Baxter Healthcare Corporation is also responding to the Agency's November 17, 2000 labeling deficiencies on the referenced drug product. The Agency's comments are restated in bold and are followed by Baxter's response:

1. **CONTAINER (200 mcg/mL) 100 mL and 200 mL**

   a. **Delete the parentheses from "20 mg/100 mL" and "40 mg/200 mL"**

      These terms were only in parentheses on the overwrap labels and have been deleted.

   b. **Revise the secondary expression of strength to read "200 mcg (0.2 mg) per mL*"**

      Baxter has revised its container and overwrap labels consistent with the Agency's recommendations.

   c. **Place an asterisk before the "Each mL contains..." statement.**

      Baxter has revised its container and overwrap labels consistent with the Agency's recommendations.

   d. **Put periods at the end of the sentences in the text.**

      Baxter has revised its container labels to improve readability of the text by using a combination of large and small capital letters instead of simply using all upper case letters. Baxter does not put periods at the end of the sentences in the text for labels on flexible plastic containers due to the risk of leakage caused by small perforations in the plastic film during the labeling hot stamping process. This labeling convention is used for numerous Baxter products in flexible plastic containers, such as 0.9% Sodium Chloride Injection, USP (ANDA 16-677, approved December 9, 1970) and 5% Dextrose Injection, USP (ANDA 16-673, approved March 4, 1971).

Baxter

e. Increase the prominence of "Rx only".

Baxter has revised its container labels consistent with the Agency's recommendations.

2. OVERWRAP (200 mcg/mL) 100 mL and 200 mL

a. See comments (a), (b) and (c) under CONTAINER.

Refer to responses (a), (b) and (c) under CONTAINER. Baxter has revised its overwrap labels consistent with the Agency's recommendations.

b. Capitalize the statement "MUST NOT BE USED IN SERIES CONNECTIONS."

Baxter has revised its overwrap labels consistent with the Agency's recommendations.

3. INSERT

a. GENERAL COMMENT

Improve the overall print quality.

The print quality of the insert is comparable to that used in numerous other inserts for various approved Baxter products. The photocopy of the draft insert supplied in the March 31, 2000 submission was apparently of poor quality. An improved copy of the insert is supplied in **Attachment 14.**

b. DESCRIPTION

"a molecular formula" rather than "an empirical formula"

Baxter has revised its product insert consistent with the Agency's recommendations.

Baxter

c. CLINICAL PHARMACOLOGY

Sixth paragraph, last sentence - "...or shortly..." rather than "...of shortly..."

Baxter has revised its product insert consistent with the Agency's recommendations.

d. PRECAUTIONS

Carcinogenesis, Mutagenesis, Impairment of Fertility, penultimate sentence - "*in vivo*" (*italics*)

Baxter has revised its product insert consistent with the Agency's recommendations.

e. DOSAGE AND ADMINISTRATION

i. **Add the following text to immediately follow the first table:**

The loading dose may be given undiluted, but diluting to a rounded total volume of 10 or 20 mL (see appropriate package insert for diluents) may simplify the visualization of the injection rate.

Baxter has revised its product insert consistent with the Agency's recommendations.

ii. **Paragraph after second table - "...an improvement..." rather than "...and improvement..."**

Baxter has revised its product insert consistent with the Agency's recommendations.

Baxter

f. **DIRECTIONS FOR USE**

Preparation for Administration - "WARNING: DO NOT USE IN SERIES CONNECTIONS." (all upper case)

Baxter has revised its product insert consistent with the Agency's recommendations.

g. **HOW SUPPLIED**

If this drug product will be available in cases please specify how many per case in this section and also submit the case label.

Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container is packaged one unit per foil overwrap and will not be available in cases.

Additional Labeling Revisions:

1. Baxter has changed the following statement on the overwrap labels (100 mL and 200 mL):

   from: "...discard unit as sterility may be impaired."

   to: "...discard bag as sterility may be impaired."

   This change was made for consistency with the container labels.

2. Baxter has added the following statement to the **Contraindications** section of the insert:

   "Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products."

   This addition is in conformance with Baxter's initiative to add a contraindication concerning corn allergy to the inserts of products that contain dextrose, because dextrose may be derived from corn.

Baxter

3. Baxter has added the following sentence to the end of the **Dosage and Administration** section of the insert:

> "Milrinone Lactate in 5% Dextrose Injection is a clear, colorless to pale yellow solution."

This descriptive statement adds clarification to the preceding sentence concerning the inspection of parenteral drug products for discoloration prior to administration.

Four draft copies each of the revised container labels, overwrap labels, and insert are included in **Attachments 12, 13, and 14**, respectively, for tentative approval. Baxter acknowledges that submission of 12 final printed copies of all labels and labeling will be required at least 60 days prior to for full approval of this application. Baxter intends to submit final printed labeling in a separate correspondence when available.

To facilitate review, and in accordance with 21 CFR §314.94(a)(8)(iv), a side-by-side comparison of the proposed labeling with our last submission (March 31, 2000), with all differences annotated and explained, is provided in **Attachment 15**.

Baxter

A field copy of this submission has been sent to the Chicago District office on the date of this letter in compliance with 21 CFR §314.94(d)(5). A field copy has also been forwarded to the San Juan District Office to facilitate, as necessary, the pre-approval inspection process for Baxter's Jayuya, Puerto Rico manufacturing facility. Baxter certifies that the field copies are true copies of the archival and review copies of the application submitted to FDA headquarters.

Please contact Mr. Stacey Thompson at (847) 270-2577 if you have comments or questions regarding this application. Thank you for your time and consideration in its review.

Sincerely,

Stacey L. Thompson
FOR

Marcia Marconi
Vice President
Regulatory Affairs
(847) 270-4637 (phone)
(847) 270-4668 (fax)

Attachments

I.V. Systems Division
Regulatory Affairs

Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

Fax: 847.270.4668

Baxter

November 28, 2000

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

NEW CORRESP

NC

Re: ANDA 75-834: Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container

Intent to File Amendment

Dear Sir or Madam:

Per 21 CFR §314.120(a), we are notifying you of our intent to file an amendment to the above-referenced ANDA, in response to your FAX correspondence dated November 17, 2000. Thank you for incorporating this information into the file. If you have any questions, please contact Mr. Stacey Thompson at (847) 270-2577.

Sincerely,

Stacey L. Thompson

FOR

Marcia Marconi
Vice President, Regulatory Affairs
(847) 270-4637 (Phone)
(847) 270-4668 (Fax)

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV 29 2000
OGD

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Regulatory Affairs

Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

847.270.4637
Fax: 847.270.4668

75834

AP

Baxter

April 25, 2000

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

NEW CORRESP
NC

Re: ANDA for Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container

CMC ESD Electronic Submission

Dear Sir or Madam:

Baxter Healthcare Corporation is providing a CMC ESD electronic submission with regard to the above referenced application. The paper ANDA was submitted on March 31, 2000. A copy of the original application cover letter is included as **Attachment 1**. The ESD submission is being made within 30 days of submission of the paper ANDA as provided for in FDA's Guidance for Industry: *Preparing Data for Electronic Submission in ANDAs*, issued September, 1999.

Baxter certifies that the information contained in the April 25, 2000 electronic submission for Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container is not different from the information contained in the March 31, 2000 hard copy submission for Milrinone Lactate in 5% Dextrose Injection in PL 2408 Plastic Container.

The Entry and Validation Application (EVA), Version 4.14, was used in the preparation of this submission. Microsoft Word 97 was used to prepare the CMC Companion Document. The CD-ROM has been virus scanned using Norton AntiVirus.

Baxter

For clarification purposes, we would like to make note of the following:

- Trademark symbols were not included in the EVA files, although they were appropriately utilized in the paper submission.
- The ANDA number was not included in the *CMC Submission Info* screen because we have not yet received notification from the Agency of the ANDA number assigned to the submission.
- On the *Drug Information* screen, N/A was entered in the fields for *Pharmacological Class* and *Chemical Class* because this information is not required on the 356h form.
- The *Material Specifications* screen under *Packaging Systems* has been intentionally left blank. In the paper submission, this information is provided via cross-reference to Baxter's DMF.
- On the *CMC Batch, General* screen, N/A was entered in the field for *Expiration Date*. Baxter does not typically assign expiration dates to experimental batches manufactured solely for the purpose of stability evaluation.
- Also on the *CMC Batch, General* screen, N/A was entered in the field for *Quantity Units*. The batch is defined as the volume in the Mixing Tank, which is measured in liters, as identified on the *Submission Info* screen. Formulation components that are added to the mix tank are measured in kilograms.
- On the *Test Profiles* screen, N/A was entered in the cells under the column headed "Dissolution Testing". Dissolution testing is not applicable to premixed solutions.
- On the *Equipment* screen, N/A has been entered for the equipment manufacturer. This information is generally not documented in the batch records but is available in equipment characterization files at the manufacturing facility.

We also have the following general comments about the EVA program. We hope our comments facilitate further development of the EVA program:

- On the *Auxiliary Firms* screen, it was required to enter information in the "State" and "Zip" fields for foreign suppliers. Although entering N/A was an option, data entry would have been facilitated if blank fields were allowed. This observation also applied to Comments fields in general.

Baxter

- On the *CMC Manufacturing Steps* screen, we noted that the manufacturing step identifiers and descriptions did not carry over from the first batch entered to subsequent batches. Since the manufacture of multiple batches is common and manufacturing processes are typically identical between these batches, this capability would have been useful.
- On the *CMC Raw Material* screen, the Ingredient ID only is shown. It would be helpful to include both the ingredient ID and name.

Please contact Mr. Stacey Thompson at (847) 270-2577 if you have any comments or questions regarding this submission.

Sincerely,

Stacey L. Thompson
FOR

Marcia Marconi
Vice President
Regulatory Affairs
(847) 270-4637 (Phone)
(847) 270-4668 (Fax)

Enclosed: Two copies of a CD-ROM containing files of the CMC ESD and the CMC Companion Document