CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76018

CORRESPONDENCE

ANDA 76-018

MAY 7 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 October 27, 2000,, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Amiodarone Hydrochloride Injection, 50 mg/mL, packaged in 3 mL vials.

Reference is also made to your amendments dated September 25, November 19, and December 19, 2001; and January 18, January 22, February 20, and February 21, 2002.

We have completed the review of this abbreviated application. Based upon the information you have presented to date, we have concluded that 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, Cordarone I.V. Injection of Wyeth Ayerst Laboratories, is currently subject to a period of orphan drug market exclusivity (ODE). 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 this exclusivity period has expired, i.e., currently August 3, 2002.

In order to reactivate this application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED between 60 to 90 days prior to the date you believe your application will be eligible for final approval. 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 August 3, 2002, you should amend your application accordingly.

At the time you submit any amendments, you should contact Stanley Shepperson, Pharm.D., Project Manager, at 301-827-5789, for further instructions.

Sincerely yours,

/S/ for

5/1/2002

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-018

Bedford Laboratories
Attention: Shahid Ahmed
270 Northfield Road
Bedford, Ohio 44146

NOV 30 2000

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: Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials

DATE OF APPLICATION: October 27, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 1, 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:

Bonnie McNeal
Project Manager
(301) 827-5849

Sincerely yours,

/S/ for

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

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July 12, 2002

1 of 1
faxed copy already received

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

Telephone Amendment

NEW CORRESP
NC

RE: Telephone Amendment

Product: ANDA 76-018 Amiodarone Hydrochloride Injection; 50 mg/mL, 3 mL vials

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 76-018, for Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials, in response to a July 12, 2002 telephone conversation between Mr. Ubrani Venkataram of the Agency and Ms. Molly Rapp regarding the active pharmaceutical ingredient manufacturer, Attached is FDA Form 356h.

Amiodarone Hydrochloride is currently manufactured at location. In the event that wishes to transfer production of Amiodarone Hydrochloride drug substance to a different manufacturing site, Bedford Laboratories™ commits to submit a supplement to the Agency for such a change.

We trust this meets with your approval. Should you have any further questions, please don't hesitate to contact me directly at 440-201-3576.

Sincerely,

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

RECEIVED
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July 10, 2002

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

Telephone Amendment

NEW CORRESP
NC

RE: ANDA 76-018/Telephone Amendment
Product: Amiodarone Hydrochloride Injection; 50 mg/mL, 3 mL vials

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 76-018, for Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials, in response to a July 8, 2002 telephone conversation between Mr. Stan Shepparson of the Agency and Ms. Molly Rapp regarding the active pharmaceutical ingredient manufacturer, Attached is FDA Form 356h.

On September 21, 2001, an explosion took place at the No explosion took place inside the facility, nor was there any extensive damage done to this plant. Please note that this explosion did not take palce in any of the facilities that manufacture active pharmaceutical ingredients.

Amiodarone Hydrochloride is currently manufactured at location. None of the active drug substance used in support of this ANDA was produced at the facility, facility that suffered the explosion. In addition, there are no plans to manufacture Amiodarone Hydrochloride at the

We trust this meets with the Agencys approval. If there are any questions or comments, please call the undersigned at (440) 201-3576.

Sincerely,

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

RECEIVED
JUL 2002

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noted NAI
A. Vezza
10/17/02

NEW CORRESP
NC

July 9, 2002

Gratuitous Amendment

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

RE: **ANDA 76-018/Gratuitous Amendment**
Product: **Amiodarone Hydrochloride Injection; 50 mg/mL, 3 mL vials**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 76-018, for Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials, in response to a telephone conversation between Mr. Adolph Vezza from the Agency and Ms. Molly Rapp on July 9, 2002. Attached is FDA Form 356h.

Bedford Laboratories™ commits to add "3 mL" on the container label immediately prior to the "Single Use Vial" text. This change will be implemented prior to the commercial launch of Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL.

We trust this meets with the Agency's 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.

Sincerely,
for Bedford Laboratories™,

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

RECEIVED
JUL 10 2002
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labeling review
drafted 7/8/02
A. Vega

ORIG AMENDMENT
N/A M

June 27, 2002

Minor 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

RE: **ANDA 76-018/Minor Amendment**
Product: **Amiodarone Hydrochloride Injection; 50 mg/mL, 3 mL per vial**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 76-018, for Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials, as requested in the Tentative Approval letter of May 7, 2002. Form 356H is provided.

There have been no changes to the Chemistry and Manufacturing Controls or to the Microbiology Section that were tentatively approved on May 7, 2002.

There was a minor revision to the package insert labeling; the reference to the dosage form has been removed from the "How Supplied" section of the insert. There have been no changes to the labels or to the shelf carton labeling that was tentatively approved. Twelve final printed copies of the label and labeling are provided for review.

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

Sincerely,
for Bedford Laboratories™

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

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JUL 0 1 2002
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300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

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ORIG AMENDMENT
N/HH.

February 21, 2002

Gratuitous Amendment

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

RE: ANDA 76-018/Gratuitous Amendment
Product: Amiodarone Hydrochloride Injection; 50 mg/mL, 3 mL vials

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 76-018, for Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials, to provide a Gratuitous Amendment with regards to the active pharmaceutical ingredient manufacturer,
Attached is FDA Form 356h.

On September 21, 2001, an explosion took place at the

No explosion took place inside the facility, nor was there any extensive damage done to this plant. did not yet manufacture any raw materials at this location, including Amiodarone Hydrochloride. Amiodarone Hydrochloride is currently manufactured at location.

We trust this meets with the Agency's 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.

Sincerely,
for Bedford Laboratories™,

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

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N/AF

ORIG AMENDMENT

February 20, 2002

Labeling Amendment

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

RE: **ANDA 76-018/Labeling Amendment**
Product: **Amiodarone Hydrochloride Injection; 50 mg/mL, 3 mL vials**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 76-018, for Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials, to remove the deficiencies cited in the Labeling Deficiency of February 12,2002. Attachment I provides FDA Form 356h.

All deficiencies cited in the package insert labeling have been corrected. Please note, 12 final printed package inserts are attached for review. Also, in accordance with 21 CFR 314.94(a)(8)(iv). Attachment II contains a side-by-side comparison of the currently proposed labeling versus that which was previously submitted.

We trust this meets with the Agency's 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.

Sincerely,
for Bedford Laboratories™,

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

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Labeling review
drafted 2/11/02
A. Vega

N/AF

DRUG AMENDMENT

FPL

January 22, 2002

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

Labeling Amendment

RE: **ANDA 76-018/Labeling Amendment**
Product: **Amiodarone Hydrochloride Injection; 50 mg/mL, 3 mL vials**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 76-018, for Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials, to remove the deficiencies cited in the Labeling Deficiency of December 26, 2001. Attachment I provides FDA Form 356h.

All deficiencies cited in the package insert labeling have been corrected. Please note, 12 final printed package inserts are attached for review. Also, in accordance with 21 CFR 314.94(a)(8)(iv). Attachment II contains a side-by-side comparison of the currently proposed labeling versus that which was previously submitted.

We trust this meets with the Agency's 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.

Sincerely,
for Bedford Laboratories™,

Marianne for

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

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JAN 23 2002

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N/AM

ORIG AMENDMENT

January 18, 2002

TELEPHONE 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

RE: **ANDA 76-018/Telephone Amendment**
Product: **Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials**

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application, 76-018 for Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials, to remove the deficiencies cited in telephone communication of January 18, 2002, between Ms. Bonnie McNeal, Ms. Lynn Ensor, and Ms. Marla Stevens of the Agency and Ms. Molly Rapp and Ms. Margaret VanDine of Ben Venue Laboratories. Attached is FDA Form 356h.

Bedford Laboratories™ submits current Process Simulation Testing Data for Both of these mm vials.

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™

MMVanDine for

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

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2 2 2002
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December 19, 2001

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

TELEPHONE AMENDMENT

NEW CORRESP
N/AM.

RE: ANDA 76-018/Telephone Amendment
Product: Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application, 76-018 for Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials, to remove the deficiencies cited in telephone communications of December 14, 2001 and December 19, 2001, between Mr. Stan Shepardson of the Agency and Ms. Molly Rapp of Ben Venue Laboratories. Attached is FDA Form 356h.

Bedford Laboratories wishes to revise the stability specification for Chromatographic Purity for Amiodarone Hydrochloride Injection, 50 mg/mL, 3 mL vials, to the following:

NMT %
Individual Unknown Impurities: NMT %
Total Impurities: NMT %

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™

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 20 2001
OGD

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

BEDFORD LABORATORIES™

NC

NEW CORRESP

November 19, 2001

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 76-018/Amendment to a Minor Amendment
Product: Amiodarone Hydrochloride Injection; 50 mg/mL, 3 mL vials

Dear Mr. Shepardson,

We would like to amend our September 25, 2001 Minor Amendment which was sent with regards to our unapproved Abbreviated New Drug Application for Amiodarone Hydrochloride Injection; 50 mg/mL, 3 mL vials. This request is based on a telephone conversation between Mr. Stan Shepardson from the Agency and Mrs. Molly Rapp from Ben Venue Laboratories on November 19, 2001. FDA Form 356h is attached.

A withdrawal letter was submitted on November 5, 2001 for the minor amendment to this application (submitted September 25, 2001) based on a telephone conversation with Ms. Beth Fritsch of the Regulatory Support Group. The minor amendment contained defieciency responses, as well as the introduction of a new strength, . **We do not wish to withdraw the entire amendment, only the additional dosage.** This amendment to the minor amendment is being submitted to clarify that the September 25, 2001 response should be considered for the information and responses concerning the 3 mL per vial dosage only.

The November 5, 2001 Withdrawal letter is being withdrawn under separate cover.

Sincerely,
for Bedford Laboratories,

Molly Rapp
Supervisor Regulatory Affairs
Ben Venue Laboratories, Inc.

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November 5, 2001

NEW CORRESP

NC

Attn: Ms. Beth Fritsch
Regulatory Support Group
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 76-018/Letter of Withdrawal of Minor Amendment**
Product: **Amiodarone Hydrochloride Injection; 50 mg/mL, 3 mL vials**

Dear Ms. Fritsch,

Reference is made to the above Minor Amendment to ANDA 76-019, submitted September 25, 2001. In accordance with 21 CFR 314.96, Bedford Laboratories, Inc., is hereby withdrawing this Minor Amendment for consideration of review. FDA Form 356h is attached.

As discussed in the telephone communication between Ms. Fritsch of the Agency and Ms. Molly Rapp of Ben Venue Laboratories, a Minor Amendment will be submitted to answer the deficiencies cited in ANDA 76-018 in the Agency's communications of March 27, 2001 and July 3, 2001. Furthermore, a new Abbreviated New Drug Application will be submitted to provide the Agency data regarding Amiodarone Hydrochloride Injection, 50 mg/mL, which was erroneously supplied in the Minor Amendment of September 25, 2001.

Bedford Laboratories™ understands that such withdrawal is without prejudice to refiling.

Sincerely,
for Bedford Laboratories,

MVanDine

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

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Control).

2.b. Please refer to Page 514 of the original application for the Before Filtration results of the In-Process testing included in of the Compounding Record.

2.c. Bulk yield accountability limits and results are presented on Page 501 of the original application, Page 1 of 2 of the Batch Reconciliation section of the exhibit batch record; in error, Page 2 of 2 of the Batch Reconciliation section was omitted. Please refer to Attachment VI of this amendment for the packaged vial yield limits and results.

3.a. Please refer to Attachment VII for the revised Specifications for the Release of the Drug Product which includes tests and specifications for Content and pH. The method, "Limit Test for in the Amiodarone HCl Drug Substance, Drug Product and Stability Samples," is also included in this attachment.

3.b. Please refer to Attachment VIII for the comparison of data and chromatograms between Amiodarone Hydrochloride Injection and the Reference Listed Drug, Cordarone®.

4.a. The stability specifications for Related Substance Limits have been revised as presented in the Post Approval Stability Protocol, SP# 200038.01, located in Attachment IX. Also located in Attachment IX are the revised Stability Testing Summary Sheets, reflecting the new Related Substance Limits.

4.b. Please refer to Attachment IX for the revised Post Approval Stability Protocol, SP #200038.01, which includes tests, methods and specifications for Free Iodide Content and pH.

B. Acknowledgments

a. Please refer to Attachment X for the revised Components and Composition Statement, which has been revised to include the functionality of the excipients.

b. Bedford Laboratories™ has been informed by the holder of DMF : that the deficiencies to their DMF were responded to in March, 2001.

c. Bedford Laboratories™ acknowledges that methods validation is being performed by the FDA Laboratory in Philadelphia.

C. Labeling

All labeling deficiencies have been corrected and side-by-side comparisons of the proposed vial label, carton labeling and package insert labeling versus that last submitted are provided in Attachment XI. Also, 12 copies of all final printed vial labels and carton labeling are also provided in Attachment XI. Draft labeling is provided for the package insert.

D. Microbiological

1.a. The D-values for the BIs used for the sterilization validation of the stoppers and equipment are as follows:

D-VALUES (min.)	Stoppers		Equipment
	Bags	Trays	
	1.9	2.43	1.35
	2.0	1.9 1.5	1.8

All concentrations of the biological indicator suspensions were confirmed by Ben Venue prior to use, except the BI for the utilized in the equipment validation study; at the time of the validation (1987) it was not current Ben Venue practice to confirm the concentration of the suspension.

1.b. Please refer to Attachment XII for the Equipment Sterilization Information which outlines the validation parameters for the equipment sterilization.

1.c. Please refer to Response D.1.a. for the remaining information regarding the biological indicators omitted from the equipment sterilization validation description. Please note, the information provided on Page 121 of the original application regarding the description of the BI utilized in the Equipment Challenge Study for is erred; the correct Equipment Challenge Study is No. V01590S, not V15396S. Below is the BI information for the appropriate challenge study (V01590S):

BI:	*Bacillus stearothermophilus*
Vehicle:	Spore Strip
Quantity:	12/run
Manufacturer:	
BVL Lot No.:	S05
Spore Population:	1.2 x E6
Qualification Date:	1/24/90
D-Value:	1.7 minutes
Qualification Date:	2/1/90

The question is posed as to why the biological indicators are not the same; the biological indicators presented in the text (Page 121 of the original application and above) are for the validation studies, performed in 1987 , and 1990 , those biological indicators presented on Pages 229 and 260 are for the annual routine performance audits of these same Therefore, different BIs were utilized as there were 13 years and 10 years between these studies, respectively.

Please refer to Attachment XIII for

these test summaries include three consecutive minimum and maximum biological challenge runs.

2.a. Ben Venue Laboratories, Inc., has revised the SOP D-29, to include challenge runs using the smallest vial size and the fastest filling speed. The SOP has been revised in accordance with USP General Chapter <1116>, which provides for performing the process at the extremes with regards to vial size and filling speed. Ben Venue Laboratories, Inc., is currently performing The most current Process Simulation Testing for the largest vial/slowest fill speed is provided in Attachment XIV and is summarized below:

Test No.	Date Performed	Filling Room	Vial Size/ Opening	Fill Volume	Test Status	Contamination Rate
1017-57-277940	2/26/01	111	100 cc/20 mm	50 mL	Pass	0/17,810
1017-57-277947	2/27/01	111	100 cc/20 mm	50 mL	Pass	0/12,510
1017-57-277951	2/28/01	111	100 cc/20 mm 60 cc/20 mm	50 mL	Pass	0/15,432
1018-57-277945	2/26/01	112	100 cc/28 mm	50 mL	Pass	0/15,209
1018-57-277949	2/27/01	112	100 cc/28 mm	50 mL	Pass	0/12,976
1018-57-277953	3/1/01	112	100 cc/28 mm	50 mL	Pass	0/12,873

Please note, the smallest vial/fastest fill speed Process Simulation Testing will be performed as the second stage of the bi-annual media.

2.b. The presented in response to Question 2.a., have durations of fills ranging from 724 minutes to 876 minutes; the time to fill the maximum batch size of Amiodarone Hydrochloride Injection L into 3 mL vials) has been estimated at 10 hours or 600 minutes. The duration of the clearly supports the production parameters of this product.

3. The purpose of the filter validation is to provide

4. The validation of the LAL Test for Bacterial Endotoxins in the Amiodarone Hydrochloride Injection has been repeated utilizing the following dosage: 30 mg/min for 10 minutes, then 1 mg/mL for the following fifty minutes for a total dosage of 350 mg/70 kg/hour. Based upon this dosage, the calculation: 5 EU/kg ÷ (350 mg/70 kg/hour) = 1.0 EU/mg, sets the limit for the Bacterial Endotoxins at NMT 1.0 EU/mg for raw material,

final product and stability. The re-validation report is located in Attachment XV.

Microbiological Acknowledgments:

Please refer to Attachment XVI which illustrates the Acceptance Criteria for the Process Simulation Testing with revised Failure Limits based upon the total number of contaminated units.

As previously stated, Bedford Laboratories™ is submitting for review an additional dosage size, a multiple-dose vial. This dosage form was proposed in the Citizen Petition 00P-1352/CP1, filed by and subsequently approved by the Agency on January 16, 2001. The approval letter for this petition is located in Attachment XVII. Information specific to this dosage size is provided for review in Attachment XVII. Please note, the manufacturing process is identical to that of the 3 mL dosage form, including the sterilization process validation information.

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.

SEP 2 7 2001
EVALUATION AND RESEARCH

BEDFORD
LABORATORIES™

76-018

505(j)(2)(A) OK
30-NOV-2000

October 27, 2000

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: Amiodarone Hydrochloride Injection, 50 mg/mL, 3 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 Amiodarone Hydrochloride Injection, 50 mg/mL; 3 mL vial. Please note that the field copy has been sent directly to the 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, and contains a copy of the package insert of the "listed drug" (Wyeth Ayerst's Cordarone® Injection.) The application consists of three volumes.

In accordance with Title 21 CFR 320.22 Bedford Laboratories requests a waiver of the requirement for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence for the drug product that is the subject of this application (Amiodarone Hydrochloride Injection, 50 mg/mL; 3 mL per vial). The drug product is a solution intended solely for intravenous administration and it contains the active ingredient in the same concentration as in the listed drug.

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 current Good Manufacturing Practices in accordance with Title 21 CFR 210 and 211. Ben Venue's signed statement is provided in Section IX (MANUFACTURING FACILITY) Subsection 3 (cGMP Certification).

Bedford Laboratories commits to provide full cooperation to resolve any problem which may arise during the methods validation testing as part of the "Post-Approval" process for the above listed drug product.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV - 1 2000
OGD

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

Two copies of analytical methods, which were used to test this product, as well as an analytical method validation package are enclosed separately along with this application.

Please note, the proposed drug product is presented in vials instead of ampules, unlike the listed drug. No Citizen Petition is required for changing the container/closure system, in accordance with Section 505 (j) (c) of the Food, Drug and Cosmetic Act.

Section XXII of this application, located in Volume 3, contains the Sterilization Assurance Data and Information as well as the following: a copy of the labeling and package insert, a summary 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.

This application will include a CMC ESD electronic submission. The diskettes will be sent as a New Correspondence within 30 days.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440)-232-3320, ext. 3333 (direct) and (440)-232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

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