CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-217

CORRESPONDENCE

BEDFORD
LABORATORIES™

September 16, 1999

ORIG 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 64-217/Telephone Amendment
Product: Rifampin for Injection USP; 600 mg per vial

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 64-217, for Rifampin for Injection USP, 600 mg per vial, to provide the requested information per the telephone conversation between Mark Anderson and Susan Rosencrance of the Agency and Pratima Patel of Ben Venue Laboratories, Inc. on September 14, 1999.

Form 356H is provided in Attachment I.

Please refer to Attachment II for the Constituted Solution Study data which was conducted at the T=0 test point.

The test data for Clarity and Completeness of solution was inadvertently left out of the previous amendment. Please refer to Attachment III for 24 months stability data, as well as 18 months and 24 months data for Clarity and Completeness of solution.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333 or by facsimile (440) 232-2772, for any additional information.

Sincerely,
for Bedford Laboratories™

P. Patel for

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

RECD
SEP 17 1999
CSD

A DIVISION OF BEN VENUE LABORATORIES, INC.

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

NDA ORIG AMENDMENT

N/Am

June 28, 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: ANDA 64-217/Ammendment to the Minor Amendment (submitted 6/15/99)
Product: Rifampin for Injection USP; 600 mg per vial

Dear Sir/Madame:

As committed in our Minor Amendment, submitted 6/15/99, we wish to amend our unapproved Abbreviated New Drug Application, ANDA 64-217, for Rifampin for Injection USP, 600 mg per vial with the following information:

1. Attachment I: 356h
2. Attachment II: Stability Data sheets (LAL, particulate and sterility have been updated for the 24 month time period)

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333, for any additional information.

Sincerely,
for Bedford Laboratories™

P. Patel for

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 29 1999
OGD

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June 15, 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: ANDA 64-217/Minor Amendment
Product: Rifampin for Injection USP; 600 mg per vial

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 64-217, for Rifampin for Injection USP, 600 mg per vial, to remove the deficiencies cited in the Minor Amendment dated April 27, 1999.

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:

B. Acknowledgments

Ben Venue Laboratories, Inc. acknowledges that updated stability data need to be submitted. Please refer to Attachment VI for the updated stability data. LAL, particulate and sterility testing is in-progress for 24 month test point. As soon as stability data is completed, this application will be amended.

C. Labeling

All deficiencies cited have been corrected. Please refer to Attachment VII for twelve copies of final printed labels and labeling. Also located in Attachment VII are side by side comparisons of the final printed labels and labeling.

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We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333, for any additional information.

Sincerely,
for Bedford Laboratories™

P. Patel for

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

JUN 9 1998

38. **CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 64-217

APPLICANT: Bedford Laboratories™

DRUG PRODUCT: Rifampin for Injection USP

The deficiencies presented below represent MAJOR deficiencies

A. Deficiencies:

1. Your testing protocol for the active ingredient should include a test for residual solvents, namely
Please revise your protocol accordingly and provide a copy in your next amendment.

2. Please clarify how often check weights are to be determined throughout the filling operation. Frequent monitoring (e.g., every 15 minutes) is recommended since this is a product and a low or high fill volume would not be readily apparent after

3. There is a discrepancy in the finished product release limits proposed for purity. Page 630 of the submission lists one set of limits for impurities, while page 632 lists another set. Please clarify this discrepancy and clearly define the purity limits you intend to use. Also please provide a rationale which briefly discusses how your purity limits were determined.

4. The finished product release protocol does not include a test for solution completeness and clarity. This test is recommended for constituted solutions under USP <1> *Injections*. The test provides quality assurance of the prepared injection as it is actually administered. Please include this test in your protocol and provide a copy of the revised protocol in your next amendment. Also include any data you have available to support the solution completeness and clarity of your product.

5. Your proposed shelf life limits for individual and total impurities are tighter than the limits proposed for the bulk drug substance. For example, the limit for individual impurities in the bulk drug substance is while the shelf life limit for individual impurities in the product is The same is true for total impurities. The total impurity limit for the bulk drug substance is while the product's shelf life total impurity limit is According to the methodology, it appears percent impurities are calculated in the same manner for both the bulk drug substance and finished product. Percentages are determined by comparing the analytical response (peak area) for the impurity with the analytical response (peak area) for rifampin. Please provide a rationale which explains how you have established these shelf life limits for purity.

6. Please include a test for solution completeness and clarity in your stability testing protocol. A copy of the revised protocol should be provided in your next amendment. Also include any data you have available to support the solution completeness and clarity of your product throughout its shelf life.

7. We note that samples subjected to accelerated stability conditions were tested for moisture content at each test station, whereas your room temperature stability protocol specifies moisture test points at 0, 12, 24, and 30 months. This provides 4 data points and is sufficient for statistical analysis, but since this product has a proposed expiration date of 24 months we recommend you have test stations for moisture content at 6 month intervals (e.g., 0, 6, 12, 18, 24, (30) months). Revised room temperature protocols (pre & post-approval) should be provided in your next amendment.

8. The following comments pertain to your constitution and dilution studies done in support of the label claims:

   a. Please specify the age of the samples used in conducting the constitution and dilution studies. More specifically, please clarify whether or not the data from these studies were generated from sample that had been stored for 3 months under accelerated conditions in order to simulate a worse case scenario.

   b. Your constitution and dilution studies monitored only appearance, pH and assay. Testing to determine the degradation levels was not included. We consider degradation monitoring a valuable component of any constitution/dilution study. Please repeat your studies with respect to purity and provide the data in your next amendment.

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

1. If available, updated room temperature stability data should be provided in your next amendment.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS

ANDA: 64-217 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Rifampin Injection, 600 mg/vial

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale Conner

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APR 27 1999

38. **CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 64-217

APPLICANT: Bedford Laboratories

DRUG PRODUCT: Rifampin for Injection USP

The deficiencies presented below represent facsimile deficiencies

A. Deficiencies:

1. We note you have included limits for residual solvents in your acceptance/release testing protocol for the drug substance; however, you need to also provide the test methodology and appropriate validation data. In addition, due to inherent toxicity we feel a ppm limit is too high. Data reported in the certificate of analysis (COA) suggests a much tighter limit is possible. We have addressed this issue with your supplier, We advise nothing greater than ppm for but strongly recommend an even tighter limit if possible. Please address this issue.

2. We have the following comments in regard to your finished product release/shelf life acceptance criteria for impurities. The limits you have proposed for rifampin quinone, total impurities and the structurally related substance, 25-desacetyl rifampin, are all in accord with those limits recommended by the USP for the drug substance, hence they appear acceptable for your drug product. However, you have also proposed an additional limit of NMT for an unknown impurity. Since this species may not necessarily be a related substance (structurally related to rifampin), release and shelf life limits for its control should not necessarily be set based on the USP's limit for individual related substances. Rather the limit should be based on available data. Based on the release and stability data provided thus far, levels no higher than have been observed. Additionally the

levels do not appear to increase with time, thus it appears tighter controls need to be imposed. Please address this issue.

3. Test results from your constitution/dilution study show the degradant rifampin quinone exceeds the limit at 24 hours when dilutions are done in saline. Levels as high as 3% rifampin quinone are reported. These data do not support your label claims that the product is stable in saline for 24 hours. Please address this issue.

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

Updated room temperature stability data needs to be provided in the next amendment. We are particularly concerned about seeing data for sterility and bacterial endotoxins since these test results have not yet been reported for exhibit batch 21014.

Sincerely yours,

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

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September 16, 1998

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

N/AC

RE: **ANDA 64-217/Major Amendment**
Product: **Rifampin for Injection USP; 600 mg per vial**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 64-217, for Rifampin for Injection USP, 600 mg per vial, to remove the deficiencies cited in the Major Amendment dated June 9, 1998.

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. Our testing protocol for the active ingredient has been [illegible]

B. Acknowledgments

Please refer to Attachment IV for revised stability protocols and supporting label temperature stability data.

C. Labeling

All deficiencies cited have been corrected. Please refer to Attachment VI for twelve copies of final printed labels and labeling. Also located in Attachment VI are side by side comparisons of the final printed labels and labeling.

BEDFORD LABORATORIES™

D. Microbiology

1.

2.

3.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333, for any additional information.

Sincerely,
for Bedford Laboratories™

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

BIOEQUIVALENCY COMMENTS

ANDA: 64-217 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Rifampin Injection, 600 mg/vial

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale Conner

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 64-217

Bedford Laboratories, Inc.
Attention: Robert V. Kasubick, Ph.D.
300 Northfield Road
Bedford OH 44146

NOV 24 1997

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: Rifampin for Injection USP, 600 mg/vial

DATE OF APPLICATION: October 17, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 21, 1997

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

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

Should you have questions concerning this application contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

Jerry Phillips
Director,
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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October 17, 1997

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 Antibiotic Drug Application
Product: Rifampin for Injection, USP - 600 mg/vial

Dear Sir/Madam:

In accordance with Section 507 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 Antibiotic Drug Application for Rifampin for Injection, USP - 600 mg/vial. Please note that the field copy is being sent directly to the FDA District Office in Cincinnati, Ohio.

The drug products subject to this application will be manufactured by Ben Venue Laboratories, Inc., located at 300 Northfield Road, Bedford, Ohio, 44146.

This abbreviated antibiotic drug application contains the information required by Section 507 (b)(1)(2)(4). The application is provided in the format suggested by your office, and contains a copy of the package insert of the "listed drug" (Hoechst Marion Roussel's Rifadin I.V.; NDA 50-627) as well as copies of the relevant pages of the Approved Prescription Drug Products List with Therapeutic Equivalence Evaluations.

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 products that are the subject of our application (Rifampin for Injection, USP - 600 mg/vial). The drug product is a powder, that when reconstituted, is intended solely for intravenous administration and contains an active ingredient in the same solvent and concentration as the drug product that is the subject of Approved New Drug Application (Hoechst Marion Roussel's Rifadin I.V.; NDA 50-627).

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300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

Bedford Laboratories™ certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug products are in conformity with current Good Manufacturing Practices in accordance with Title 21 CFR 210 and 211. Ben Venue Laboratories, Inc., signed statement is provided in Section IX (Manufacturing Facility) Subsection 3 (cGMP Certification).

The analytical methods which were used to test these products are current compendial methods.

One copy of the Microbiological Validation, along with the drug products' specifications, stability protocols and the package insert is enclosed separately with this application. The drug product was aseptically filled.

If the Agency has any comments or further requests or if we could be of any assistance in your review, we welcome direct and immediate telephone contact at (216) 232-3320, ext. 218 (direct dial) and (216) 232-2772 (fax).

Sincerely,
for Bedford Laboratories™

Robert V. Kasubick, Ph.D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.