CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-567

CORRESPONDENCE

BEDFORD LABORATORIES™

Reviewed Satisfactorily 3/26/01 DRL (Initial)

March 23, 2001

TELEPHONE AMENDMENT

N/Am

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 75-567/Telephone Amendment**
Product: **Levocarnitine Injection, USP; 200 mg/mL, 2.5 mL and 5 mL vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-567, for Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5.0 mL vials, to remove the deficiency communicated to Mr. Shahid Ahmed of Ben Venue Laboratories, Inc., by Mr. Rashmikant Patel of the Agency, in his voice mail message of March 22, 2001. FDA Form 356h is attached.

Bedford Laboratories™ is revising the Active Drug Substance specifications for Levocarnitine, USP, as follows:

Test	Specification	Test Method
Bioload	Response Level 1	Current USP

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

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 26 2001
OGD

Sincerely,
for Bedford Laboratories™

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

BEDFORD LABORATORIES™

March 14, 2001

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

ORIG AMENDMENT
N/Am

RE: **ANDA 75-567/Telephone Amendment**
Product: **Levocarnitine Injection, USP; 200 mg/mL, 2.5 mL and 5.0 mL vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-567, for Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5.0 mL vials, to clarify the issue discussed between Mr. Greg Davis of the Agency and Mr. Shahid Ahmed on March 14, 2001. Please find FDA Form 356h attached.

Bedford Laboratories™ acknowledges the existence of Exclusivity for Indication I-280 (Use of Carnitor Injection for the Prevention and Treatment of Carnitine Deficiency in Patients with End Stage Renal Desease who are Undergoing Dialysis), which expires December 15, 2002. Bedford Laboratories™ is not claiming this indication in its package insert labeling, as submitted in the Minor Amendment of January 3, 2001.

We trust this meets with your approval. If there are any further questions or comments, do not hesitate to contact the undersigned at (440) 201-3333 or facsimile at (440) 232-2772.

Sincerely,
for Bedford Laboratories™

MWandine for

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

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 15 2001
OGD

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

BEDFORD
LABORATORIES™

March 14, 2001

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

ORIG AMENDMENT
N/Am

RE: **ANDA 75-567/Telephone Amendment**
Product: **Levocarnitine Injection, USP; 200 mg/mL, 2.5 mL and 5.0 mL vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-567, for Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5.0 mL vials, to clarify the issue discussed between Mr. Greg Davis of the Agency and Mr. Shahid Ahmed on March 14, 2001. Please find FDA Form 356h attached.

Bedford Laboratories™ acknowledges the existence of Exclusivity for Indication I-280 (Use of Carnitor Injection for the Prevention and Treatment of Carnitine Deficiency in Patients with End Stage Renal Desease who are Undergoing Dialysis), which expires December 15, 2002. Bedford Laboratories™ is not claiming this indication in its package insert labeling, as submitted in the Minor Amendment of January 3, 2001.

We trust this meets with your approval. If there are any further questions or comments, do not hesitate to contact the undersigned at (440) 201-3333 or facsimile at (440) 232-2772.

Sincerely,
for Bedford Laboratories™

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

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 15 2001
OGD

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

BEDFORD
LABORATORIES™

NDA ORIG AMENDMENT
N/Am1

March 9, 2001

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 75-567/Telephone Amendment**
Product: **Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5.0 mL vials**

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-567, for Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5.0 mL vials, to remove the deficiencies cited in the telephone communication of March 9, 2001, between Ms. Michelle Dillahunt, Ms. Shirley Brown and Dr. Bing Cai of the Agency and Mr. Shahid Ahmed and Ms. Margaret VanDine of Ben Venue Laboratories, Inc. Please note, Form FDA 356h is attached.

Bedford Laboratories™ commits to reviewing the APHA color data for Finished Product and Stability after three production batches have been manufactured and tested. At that time, the specifications will be revised accordingly. To reiterate, Bedford Laboratories™ proposes APHA Color Specifications of for Finished Product and r Stability. Unfortunately, due to the age of the exhibit lots, APHA Color testing was not practicable.

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

Sincerely,
for Bedford Laboratories™

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

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 12 2001
OGD

February 21, 2001

BEDFORD LABORATORIES™

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

MINOR AMENDMENT

RE: ANDA 75-567/Minor Amendment
Product: Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5.0 mL vials

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-567, for Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5.0 mL vials, to remove the deficiencies cited in the Minor Deficiency of January 29, 2001.

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

A. Deficiencies

1. The holder of Drug Master Fi[illegible] is responded to their deficiencies as of February 15, 2001. Please refer to Attachment II for a copy of [illegible] response.

2. Due to the age of the exhibit lot of Levocarnitine Injection, Ben Venue Laboratories, Inc., manufactured another pilot batch of Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5 mL vials and terminally sterilized the vials in accordance with the master production records. The APHA color results are as follows:

mL	APHA Results
2.5	
2.5	
2.5	
5.0	
5.0	
5.0	
Lot Number JC020701, sterilized for 22 minutes at 123°C	

Therefore, Bedford Laboratories™ proposes a Final Product Specification of [illegible] APHA Units and a stability specification of [illegible] APHA Units.

Acknowledgments:

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB 23 2001
OGD

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

BEDFORD LABORATORIES™

1. There were no labeling deficiencies to be addressed at this time.

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

Sincerely,
for Bedford Laboratories™

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

BEDFORD
LABORATORIES™

January 3, 2001

MINOR AMENDMENT/Chemistry and Labeling Deficiencies

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

NDA ORIG AMENDMENT
N/Am1

RE: ANDA 75-567/Minor Amendment
Product: Levocarnitine Injection, USP, 200 mg/mL, 2.5 mL and 5.0 mL vials

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-567, for Levocarnitine Injection, USP, 200 mg/mL, 2.5 mL and 5.0 mL vials, to remove the deficiencies cited in the Minor Deficiency of November 13, 2000.

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

A. Chemistry Deficiencies

The holder of Drug Master File [redacted], has responded to their deficiencies as of December 21, 2000. A copy of the correspondence letter from [redacted] is provided in this amendment.

B. In addition:

1. All deficiencies have been corrected and twelve copies of final printed package insert labeling is provided in this amendment for the Agency's review. Also located in this amendment is annotated side-by-side comparison of the proposed final printed package insert labeling with the previously submitted package insert labeling.

   Also, please note that Bedford Laboratories omits the indication for "The treatment of manifestations of carnitine deficiency in patients with end stage renal disease who require dialysis" from the proposed labeling. Revised Statement of Exclusivity is provided in this amendment.

2. 24-months stability data were provided in the response to Minor Deficiency Letter October 6, 2000. The copies of stability data are provided in this amendment for your review.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 04 2001
OGD

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

BEDFORD
LABORATORIES™

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

Sincerely,
for Bedford Laboratories™

P. Patel for

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

A DIVISION OF BEN VENUE LABORATORIES, INC.

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

BEDFORD LABORATORIES™

October 6, 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

MINOR AMENDMENT

ORIG AMENDMENT
N/AM

RE: ANDA 75-567/Minor Amendment
Product: Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5.0 mL vials

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-567, for Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5.0 mL vials, to remove the deficiencies cited in the Minor Deficiency of April 11, 2000 and the Microbiological Deficiency of June 13, 2000.

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

A. Chemistry Deficiencies

1. The holder of Drug Master File has responded to their deficiencies as of June 20, 2000. Please refer to Attachment II for a copy of Lonza Group's response.

2. The specification for Specific Rotation has been amended to "-29° to -32°" as recommended by the Agency. Please refer to Attachment III for the Finished Product Specification and Stability Protocol #SP-98087, which have been revised to reflect this change.

Acknowledgments:

1. Bedford Laboratories™ has received the microbiological review of this application on June 13, 2000. The deficiencies have been responded to in this amendment.

2. Bedford Laboratories™ acknowledges that the approval of this application is dependent upon the satisfactory evaluation of cGMP compliance of all the facilities listed in the application.

3. The labeling deficiencies have been corrected and final printed labels and labeling are contained in this amendment.

4. Please refer to Attachment IV for updated stability data.

5. Bedford Laboratories™ acknowledges that the regulatory method for the assay of the product is the USP method, should a conflict arise.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 10 2000
OGD

10/11/00

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

BEDFORD LABORATORIES™

B. Labeling Deficiencies

All deficiencies have been corrected. Please refer to Attachment V for twelve copies of final printed vial labels, shelf carton labeling and package insert labeling for review. Also located in Attachment V are annotated side-by-side comparisons of the proposed final printed labels and labeling with the draft labeling submitted in the application.

C. Microbiological Deficiencies

1. In accordance with current Ben Venue Laboratories' Standard Operating Procedure, the maximum hold time from the time the first component is added to the compounding vessel to the time the last vial is filled and stoppered, cannot exceed ıours. A maximum time period until ſ has not been established as products which are ɛd are also filled, thus reducing the opportunity for increased bioburden, the major concern with extended hold times. Ben Venue's practice of ı products provides additional assurance of a sterile product.

2. Please refer to Attachment VI for the validation report, specific to Levocarnitine Injection.

3. Please refer to Attachment VII for the report, "Validation Verification of the LAL Test for Detection of Bacterial Endotoxins in Levocarnitine Injection Using the ɔ System."

Acknowledgments:

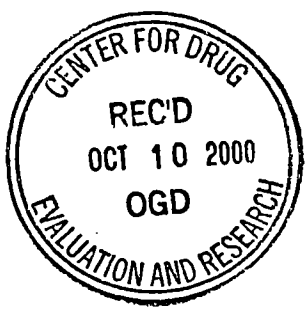
Bedford Laboratories™ acknowledges the Agency's comment and commits to providing pertinent and complete information to the Agency in support of each application, as necessary.

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

Sincerely,
for Bedford Laboratories™

NWanDeu for

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



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

BEDFORD
LABORATORIES™

September 10, 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

NDA ORIG AMENDMENT
N/AC

RE: **ANDA 75-567/Major Amendment**
Product: **Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5.0 mL vials**

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-567, for Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5.0 mL vials, to remove the deficiencies cited in the Major Deficiency of July 21, 1999.

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

A. Chemistry Deficiencies

1. No comment.

2. As stated on Page 046 of the original application, Levocarnitine, USP, is tested to current USP specifications and test methods, including the tests for Limit of n and Limit of . The methods referred to, 999-00-295 and 999-00-297, are Ben Venue Laboratories' General Test Methods fo m Limit Test and imit Test, respectively, extracted from the USP XXIII and supplements, thereto.

3. Please refer to response to A. 2.

4. Please refer to Attachment II which contains a current Certificate of Analysis for Water for Injection, USP, which includes testing as specified in the Tenth Supplement.

5. The filling machines utilized in the filling of Levocarnitine Injection, have certain accuracies or tolerances. The accuracy or tolerance value is documented in gravimetric units in the batch record (Pages 344 and 345). The listed values for tolerance are g/unit and for the 2.5 mL and 5.0 mL, respectively. The target fill is set as the limit specified in the USP XXIII, Supplement 10, plus the tolerance value to ensure that each vial is filled with the appropriate withdrawable amount of drug product. For example, for the 5.0 mL vial, the USP recommended volume is 5.30 mL. The target fill is set at

CENTER FOR DRUG EVALUATION AND RESEARCH
SEP 13 1999
OGD

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

mL) with a minimum action level of

If the accuracy or tolerance of the filling machines are not compensated for in the target fill, then there is a potential that some of the vials may be below the minimum fill volume.

6. Please refer to Page 546 of the original application, in which the results of the USP Elution Cytotoxicity testing are presented. This testing was completed in accordance with USP Method <87>, Biological Reactivity Tests, In Vitro.

7. Please refer to Attachment III for the revised Controls for the Finished Dosage Form, in which testing for Identification (Chemical) is included and a limit for "Any Other Individual Impurity" under Chromatographic Purity is added.

8. Please refer to the response to A.7.

9. Please refer to Attachment III for the revised Controls for the Finished Dosage Form, which states the correct USP reference for Bacterial Endotoxins.

10. Please refer to Attachment III for the revised Controls for the Finished Dosage Form, which states the correct USP reference for Particulate Matter.

11. Please refer to Attachment IV for the equivalency study between the USP monograph assay and the in-house method for the drug product. The methods yielded results within of each other, thereby proving equivalency.

12. Please refer to Attachment V for the revised Post-Approval Stability Protocol, which includes a limit for "Any Other Individual Impurity" for Chromatographic Purity.

13. The error referred to is located on Page 654, not 645, as listed in the deficiency letter. The vial size has been corrected on the revised data summary sheet, located in Attachment VI.

14. The data summary sheet for 0917-86-37734B, 12 month-inverted data has been revised to include the sterility test results. Please refer to Attachment VI for this data.

15. The limit listed for Related Compound A was incorrect on the data summary sheets. The correct limit is as listed in the stability protocols. Please refer to Attachment VI for the revised data summary sheets with the correct limit for Related Compound A.

Acknowledgments:

1. Bedford Laboratories™ notes that the microbiological review is pending.

2. Bedford Laboratories™ acknowledges that the approval of this application is dependent upon the satisfactory evaluation of cGMP compliance of all the facilities listed in the application.

3. Bedford Laboratories™ has revised the product to "USP", in accordance with the current monograph.

4. The labeling deficiencies have been corrected and final printed labels and labeling are contained in this amendment.

5. Please refer to Attachment VI for updated stability data.

B. Labeling

All deficiencies have been corrected. Please refer to Attachment VII for twelve copies of final printed vial labels, shelf carton labeling and package insert labeling for review. Also located in Attachment VIII are annotated side-by-side comparisons of the proposed final printed labels and labeling with the draft labeling submitted in the application.

Please note in Attachment VIII is an Environmental Impact Analysis revised to cite the correct 21 CFR reference.

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.