

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-567

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 75-567

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
270 Northfield Road
Bedford, Ohio 44146

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Levocarnitine

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

January 12, 1999	Original Submission
February 16, 1999	NC
September 10, 1999	Amendment (responding to deficiencies dated 7/21/99)
October 6, 2000	Amendment (responding to deficiencies dated 4/11/00)
January 3, 2001	Amendment (responding to deficiencies dated 4/11/00)
*February 21, 2001	Amendment (responding to deficiencies dated 1/29/01)
*March 9, 2001	Amendment (resounding to deficiencies per the 3/9/01 telecon)

*subject of this review

10. PHARMACOLOGICAL CATEGORY

Mammalian Energy Metabolism

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Injection

14. POTENCY

200 mg/mL

15. CHEMICAL NAME AND STRUCTURE

See USP 24, page 961.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

The applicant was asked to note and acknowledge the following in the 1/29/01 deficiencies:

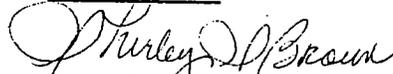
Labeling deficiencies, if any, must also be addressed in your response.

Response per the 2/21/01 amendment: There were no labeling deficiencies to be addressed at this time.

18. CONCLUSIONS AND RECOMMENDATIONS

Deficiencies are satisfied. Approval recommended.

19. REVIEWER:


Shirley S. Brown

DATE COMPLETED:

March 29 2001
March 12, 2001

Page(s) 9

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

Chem Rev 5

3/12/01

JAN 29 2001

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-567 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Levocarnitine Injection, 200 mg/mL, 2.5 mL and
5.0 mL vials

The deficiencies presented below represent MINOR deficiencies:

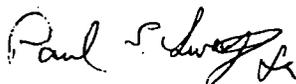
A. Deficiencies:

1. Drug Master File for the drug substance remains deficient. The Drug Master File Holder has been notified. Please do not respond until the DMF has been amended.
2. Please add a quantitative color test (e.g. APHA) to the release and stability specifications and provide data from your current stability samples.

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

Labeling deficiencies, if any, must also be addressed in your response.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 13 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-567 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5.0 mL vials

The deficiency presented below represents a MINOR deficiency.

A. Deficiency:

Drug Master File for the drug substance remains deficient. The Drug Master File Holder has been notified. Please do not respond until the DMF has been amended.

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

1. Your response must also address the labeling deficiencies.
2. Please provide any additional stability data that may be available.

Sincerely yours,


Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 75-567

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
270 Northfield Road
Bedford, Ohio 44146

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Levocarnitine

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

January 12, 1999	Original Submission
February 16, 1999	NC
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*subject of this review

10. PHARMACOLOGICAL CATEGORY

Mammalian Energy Metabolism

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

NDA 20-172

Sigma-Tau

13. DOSAGE FORM

Injection

14. POTENCY

200 mg/mL

15. CHEMICAL NAME AND STRUCTURE

See USP 24, page 961.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

The applicant was asked to note and acknowledge the following in the 1/29/01 deficiencies:

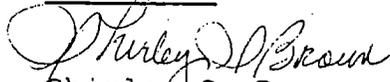
Labeling deficiencies, if any, must also be addressed in your response.

Response per the 2/21/01 amendment: There were no labeling deficiencies to be addressed at this time.

18. CONCLUSIONS AND RECOMMENDATIONS

Deficiencies are satisfied. Approval recommended.

19. REVIEWER:


Shirley S. Brown

DATE COMPLETED:

March 29, 2001
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Page(s) 9

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Chem Rev 5
3/12/01

JAN 29 2001

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-567 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Levocarnitine Injection, 200 mg/mL, 2.5 mL and
5.0 mL vials

The deficiencies presented below represent MINOR deficiencies:

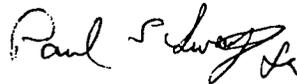
A. Deficiencies:

1. Drug Master File for the drug substance remains deficient. The Drug Master File Holder has been notified. Please do not respond until the DMF has been amended.
2. Please add a quantitative color test (e.g. APHA) to the release and stability specifications and provide data from your current stability samples.

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

Labeling deficiencies, if any, must also be addressed in your response.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APR 11 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-567 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Levocarnitine Injection, 200 mg/mL, 2.5 mL and
5.0 mL vials

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The Drug Master File Holder has not responded to the deficiencies communicated in July, 1999. The Drug Master File for the drug substance remains deficient. Do not respond to this communication until the DMF has been amended.
2. Several of the stability test results for Specific Rotation are reported as "-32°". Your proposed specification states "between ", and fails this specification. Please revise your specification to so that the extremes of the range are included in the limits. This change should be made to your release and stability limits.

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

1. The microbiologist's review of the submission for sterility assurance is pending.
2. A satisfactory compliance evaluation of facilities referenced in the ANDA is required for approval. We have requested an evaluation from the Office of Compliance.
3. Your response must also address the labeling deficiencies.
4. Please provide any additional stability data that may be available.

5. As requested in our July 21, 1999 facsimile (Deficiency #11), please note the USP method is considered the regulatory method for assay of the drug product.

Sincerely yours,


R. Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

JUL 21 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-567 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Levocarnitine Injection, 200 mg/mL, 2.5 mL and 5.0 mL

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Drug Master File for the active ingredient is deficient. The Drug Master File Holder has been notified.
2. Method No. for " " testing is not described. The method should be updated per USP 23, Supplement 10 (official May 15, 1999).
3. Method No. " testing is not described. The method should be updated per USP 23, Supplement 10 (official May 15, 1999).
4. The specifications for Water for Injection, USP should be revised per USP 23, Tenth Supplement and a current Certificate of Analysis should be provided.
5. The drug product fill targets (pages 344-345) should be justified with data per the reference listed drug. Please refer to USP 23 <1151> as your overfill greatly exceeds the recommendation.
6. The container stopper should also be tested per USP <87>, Biological Reactivity Tests, In Vitro, and the results should be submitted to the ANDA.
7. The USP specifications for identification of the drug product also include a color test. Please add to your specifications.
8. The drug product release test for Chromatographic Purity should also include a limit for "Any Other Individual Impurity".
9. Your reference for the USP Bacterial Endotoxins test is stated as <788> (page 585). The correct reference is <85>.
10. Your reference for the USP Particulate Matter test is stated as <85> (page 585). The correct reference is <788>.

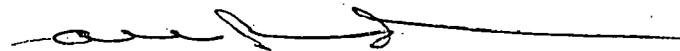
11. Per your cover letter, an equivalency study between the USP monograph assay and the in-house assay for the drug product will be performed. Data per this study and a Certificate of Analysis for the drug product tested per the USP methods should be provided. Please also note the USP method is considered the regulatory method.
12. The drug product stability test for Chromatographic Purity should also include a limit for "Any Other Individual Impurity".
13. The container on page 645 is listed as a 2.5-mL container, but the container description is for the 5.0-mL container. Please clarify.
14. Regarding stability studies: Result for Sterility testing for the 12-month room temperature inverted station for the study on page 650 is not provided.
15. The stability reports list the limit for related compound A as Please clarify as this differs on page 643.

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

1. The microbiologist's review of the submission for sterility assurance is pending.
2. A satisfactory compliance evaluation of facilities referenced in the ANDA is required for approval. We have requested an evaluation from the Office of Compliance.
3. You state that your proposed drug product is non-USP in your cover letter. Note that the product is considered an official article in the USP whether you label it "USP" or not.

4. Your response must also address the labeling deficiencies.
5. Please provide any additional stability data that may be available.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research