# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**40347**

# CORRESPONDENCE

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NEW
V/C

December 16, 1998

Ms. Carol Holquist
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 40-347; New Correspondence**
**Product:** **Leucovorin Calcium Injection, USP – 10 mg/mL; 30 mL/vial and 50 mL/vial**

Dear Ms. Holquist,

We would like to amend our unapproved Abbreviated New Drug Application by responding to your telephone request dated 12/10/98.

Please find attached revised Section I thru Section VII. These sections contain the revision to the listed drug product and listed drug product holder (Immunex's Leucovorin Calcium for Injection).

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

The revised sections are provided in the format suggested by your office and contains a copy of the package insert of the "listed drug" (Immunexs' Leucovorin Calcium for Injection; 350 mg/vial and approved citizen petitions for Gensia Laboratories) as well as copies of the relevant pages of the **Approved Prescription Drug Products List with Therapeutic Equivalence Evaluations and Supplements.**

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 (Leucovorin Calcium Injection, USP – 10 mg/mL). The drug product is intended for intravenous or intramuscular administration which is the same Route of Administration as the drug product that is the subject of Approved New Drug Applications.



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

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 (440) 232-3320, ext. 333 (direct dial) and (440) 232-2772 (fax).

Sincerely,
for Bedford Laboratories™

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

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November 19, 1998

N 40-347

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:** **Leucovorin Calcium Injection, USP – 10 mg/mL; 30 mL/vial and 50 mL/vial**

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 Luecovorin Calcium Injection, USP- 10 mg/mL. 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 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" (Abbotts' Leucovorin Calcium Injection, USP; 10 mg/mL and approved citizen petitions for Gensia Laboratories) as well as copies of the relevant pages of the **Approved Prescription Drug Products List with Therapeutic Equivalence Evaluations and Supplements.**

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 (Leucovorin Calcium Injection, USP – 10 mg/mL). The drug product is intended for intravenous or intramuscular administration and contains an active ingredient in the same concentration as the drug product that is the subject of Approved New Drug Applications.



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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 (440) 232-3320, ext. 333 (direct dial) and (440) 232-2772 (fax).

Sincerely,
for Bedford Laboratories™

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

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July 27, 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

**RE: ANDA 40-347/Major Amendment (dated 5/26/99)**
**Product: Leucovorin Calcium Injection, USP; 10 mg/mL; 30 mL and 50 mL vials**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 40-347, for Leucovorin Calcium Injection, USP 10 mg/mL; 30mL and 50mL vials, to remove the deficiencies cited in the Major Amendment dated May 26, 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. Major deficiencies.

1. The proposed specification for Bacterial Endotoxins for Leucovorin Calcium, USP (page 0062) was in error. The correct specification should have been identical to that as listed on page 0064, the Certificate of Analysis of BVL lot # 98-0282, Leucovorin Calcium, USP. Please refer to Attachment II for corrected specifications of Leucovorin Calcium, USP.

2. We have revised the proposed specifications for individual and total related substances to % respectively to be consistent with the manufacturer of active ingredient, This change has been reflected in the active drug substance specifications and Certificate of Analysis of BVL lot # 98-0282. Please refer to Attachment II for revised specifications of active drug substance and Attachment III for corrected Certificate of Analysis of BVL lot # 98-0282.

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3. The filling machine used to manufacture Leucovorin Calcium drug product has a certain accuracy or tolerance. This accuracy or tolerance value is documented in gravimetric units in the batch record. The listed value for tolerance is g/unit as documented on page 455 and 522 in the original application. The target fill is set as the limit specified in the USP XXIII, supplement 10, page 5057, plus the tolerance to value to assure that each vial is filled with the right amount of drug product. For example, for the 30 mL vial, the USP recommended volume is mL. the target fill is set at g ( mL with a density of , plus g/unit which equals g ( mL) with a minimum action level of g ( mL) and a maximum action of g mL).

   If the accuracy or tolerance of the filing machine is not compensated in the target fill, then there is a likely hood that some of the vials may be filed with lower amounts of drug product.

4. The Membrane Filtration/Bioload test result of zero (0), as listed on page 0769 of the original application, meets the specifications as stated. To better clarify the specifications please refer to the following:

   a. Should a test result exceed Response Level 1 (Greater than 10 CFU's/mL) written notification and a brief description of the nature of the event shall be recorded on an official Notification of Atypical Bioload Result form. Other activities will include, but not limited to a review of other bioload test results, review of sterile filtration results, re-test of the retain sample and review of viable data associated with the Water for Injection used in the bulk solution formulation, as well as identification of the microbiological species.

   b. Should a test result exceed Response Level 2 (Greater than 25 CFU's/mL), in addition to the items listed above in 4.a., testing of raw materials used, a review of previous viable data, review of sterile filtration process and a decision by the Material Review Board as to the disposition of the material in question takes place.

5.

| | Drug Product Release (Page 862) | Drug Product -Stability (Page 896) |
|---|---|---|
| pH | 7.4 to 8.2 | 6.5 to 8.5 |
| Assay | % | % |

Tests and Specifications on page 862 are specifications for Drug Product release, where as Tests and Specifications on Page 896 are Stability Specifications for drug product which should meet through its shelf-life. Ben Venue uses a pyramid approach such that the specifications for pH and assay are more stringent for In-Process and gradually widen through Product release and Stability due to possible degradation of the active moiety in the aqueous medium over a period of time.

6. Ben Venue Laboratories, Inc. is committed to perform color testing using an APHA test method.

The reference listed drug samples (Abbott – 25 mL, exp. August, 2000), BVL's twelve month stability samples stored under 5° ± 3°C and 25°± 2°C/60 ± 5% RH were analyzed using APHA test method 151-00-020A with the following test results:

| Mean APHA Color Value | | | |
|---|---|---|---|
| | BVL Product - 30 mL | BVL Product - 50 mL | Abbott – 25 mL |
| 5° C – Upright | 141.5 | 125 | 388 |
| 5° C – Inverted | 137.7 | 130.2 | |
| 25° C – Upright | 255.3 | 169.8 | |
| 25° C – Inverted | 227.5 | 179.8 | |

Based on the above data, we would like to propose the following APHA color specifications for finished product and stability testing:

Drug Product Release: NMT 200 APHA units
Drug Product -Stability: NMT 300 APHA units

Please refer to Attachment IV for APHA color test method, Attachment V for revised drug product specifications and pre- and post-stability protocols.

7. Ben Venue's stability samples, which were stored under 5° ± 3°C and 25°± 2°C/60 ± 5% RH respectively and reference listed drug samples were analyzed for individual known, unknown and total impurities using BVL's test method Detailed data summary of testing is provided in Attachment IX. Based on available data, we would like to propose the following related substance specifications for drug product release and stability samples. Due to the specification change in the impurities, all the stability data and finished product test data were recalculated for known-unknown/total impurities. Please refer to Attachment V for an addendum to the finished product Certificate of Analysis, stability data summary sheets and revised pre- and post-approval stability protocols.

| | Drug Product Release | Drug Product (Stability) |
|---|---|---|
| | NMT % | NMT % |
| | NMT % | NMT % |
| Highest unknown individual impurity: | NMT % | NMT % |
| Total known and unknown impurities: | NMT % | NMT % |

8. We have corrected the oversight regarding the Categorical Exclusion for Environmental Impact Consideration to 21 CFR 25.31. Please refer to Attachment VI for a revised copy of Section XX - Environmental Impact Analysis.

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B. In addition to:

1. We acknowledge that the Microbiological review for the sterility assurance is pending. Please find we have included an additional copy of the filter validation report for the Microbioloby reviewer.

2. Based on your comments, we have updated our vial labels, carton and package insert labeling . Twelve copies of final printed labels and labeling are provided in Attachment VII. Also, in accordance with 21 CFR 314.94 (a) (8) (iv), we have included side-by-side comparison of our proposed final printed label and labeling with our last submission, with all differences highlighted, provided in Attachment VII.

3. Twelve month stability data for the exhibit batch has been provide in Attachment V for your review.

C. Additional Data:

As we have committed in the original application of Section XI, appendix II, our filter manufacturer has completed the microbial validation retention study using actual drug product. The report of this microbial validation retention study is provided in Attachment VIII.

Labeling Deficiencies:

Please refer to above response B.2.

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.

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March 6, 2000

**FAX AMENDMENT**
**CHEMISTRY DEFICIENCY**

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/FA

**RE: ANDA 40-347/Facsimile Amendment**
**Product: Leucovorin Calcium Injection, USP; 10 mg/mL; 30 mL and 50 mL vials**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 40-347 for Leucovorin Calcium Injection 10 mg/mL; 30 mL and 50 mL per vial, to remove the deficiencies cited in the Fax Deficiency dated February 10, 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 drug substance manufacturer has revised their impurity specifications since the time of the original application. Their specifications now include a limit of _% for each of 7 known impurities and a sum of all impurities of NMT %. A copy of the recent certificate of analysis from the API manufacturer is provided in Attachment II for your review.

   In light of these revised specifications from the drug substance manufacturer, we would like to propose the following limits for drug substance, drug product and stability:

| Impurity | Drug Substance Manufacturer | BVL Drug Substance | Final Product Release | Stability |
|---|---|---|---|---|
| | % | % | % | % |
| | % | % | % | % |
| | % | % | % | % |
| | % | % | % | % |
| | % | % | | |
| | % | % | % | % |
| | % | % | % | % |
| | | % | % | % |
| | | % | % | % |
| Total | % | % | % | % |

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Furthermore, will not be monitored at the final product release or throughout the shelf-life as it is a synthetic precursor and not a possible degradant of Leucovorin Calcium. The drug product is formulated in an aqueous medium, and the possibility of aromatization of the piperazine ring to form is highly unlikely in an aqueous medium. All of the other known impurities are possible degradants as well as synthetic precursors in some cases. The revised drug substance specifications are provided in Attachment II and the final product and stability specifications are provided in Attachment III.

2. The specifications listed on page 0012 of the July 27, 1999 response letter were the drug product limits throughout the shelf life, consisting of the stability protocol specifications, as well as any kinetically independent testing such as volume in container, identification, etc. The limits presented on page 0011 of the July 27, 1999 response letter are the final product release limits, and those were the limits given on the Certificates of Analysis on pages 13-15. The release and drug product shelf life specifications have been clarified, revised, and are provided in Attachment III. The revised Stability protocols are also provided in Attachment III.

3. We acknowledge the Agency's comment that the related substance specifications for the drug product should not be more stringent than those applied to the drug substance itself. The limits for the drug product were set in error in the last amendment sent on July 27, 1999. Revised limits for the drug substance, final product, and stability are given in the table under item #1.

B. Acknowledgements

1. Bedford Laboratories™ acknowledges that the microbiology review for sterility assurance is still pending.

2. The current stability data is provided in Attachment IV.

We trust this meets with your approval. If there are any questions or comments, please feel free to call me at 440-232-330 ext 333 for any additional information.

Sincerely
for Bedford Laboratories™

Shahid Ahmed
Director of Regulatory Affairs

| | |
|---|---|
| Attachment I | 356H |
| Attachment II | Drug Substance Manufacturer Certificate of Analysis and BVL specifications |
| Attachment III | Final Product Release Specifications, Drug Product Specifications and Stability Protocols |
| Attachment IV | Current Stability Data |

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March 30, 2000

**FAX AMENDMENT**
**MICROBIOLOGY DEFICIENCY**

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 40-347/Facsimile Amendment**
**Product:** **Leucovorin Calcium Injection, USP; 10 mg/mL; 30 mL and 50 mL vials**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 40-347 for Leucovorin Calcium Injection 10 mg/mL; 30 mL and 50 mL per vial, to remove the deficiencies cited in the Fax Deficiency dated March 24, 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. Microbiology Deficiencies

1. The completed B/F testing Report is provided in Attachment II. It was completed in accordance with the current compendial requirements.

2. The bulk drug solution maximum holding time will be 72 hours under refrigeration or 30 hours at room temperature, and not 102 hours combined. If the drug product is removed from refrigerated storage, then the hold time is reduced by four hours for every one hour it is held at room temperature. Also, when the bulk solution is held for longer than 24 hours, samples are pulled for biolad testing prior to the filling operation. The information given on page 130 of the original application was regretfully incomplete. In the Standard Operating Procedure governing bulk solution hold times, Rule Number 3 specifically states that an additional 30 hours are not added to the intial 72 hours.

3. It is possible that the subject drug product could support microbial growth as it is formulated at a pH of 7.6 – 8.0, and Leucovorin Calcium itself does not possess bacteriocidal properties. A bioload prep test was performed in which organisms were innoculated into the drug product solution. The innoculated organisms did survive in the drug product medium. The preparation test report is presented in Attachment III.



4. If a pre-filter bulk solution exceeded 25 CFU's/ml on repeat testing, a full investigation would ensue which would include but is not limited to a review of other bioburden test

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results, re-test of the retain sample, review of viable data associated with the Water for Injection used for the formulation of bulk solutions, and an identification of the microbial organisms present in the solution to the genus and species level. Additionally, the following activities may be performed: testing of raw materials used for the formulation of bulk solutions, review of recent raw material test results, and a management decision as to the acceptance of the material in question. Because the levels listed on page 168 of the original application are response levels, and are not drug product specifications, conditions under which a lot would be rejected are dependent on the investigation results and are decided on a case by case basis.

B. Acknowledgements

1. The statement concerning the viable count of isolates from the gloves and the raw data has been reviewed and the mean remains unchanged, however, we are evaluating statistical tools other than the normal distribution to analyze historical data for meaningful and scientifically valid interpretation.

We trust this meets with your approval. If there are any questions or comments, please feel free to call me at 440-232-330 ext 333 for any additional information.

Sincerely
for Bedford Laboratories™

Shahid Ahmed
Director of Regulatory Affairs

| | |
|---|---|
| Attachment I | 356H |
| Attachment II | B/F Report |
| Attachment III | Bioload Preparation Test |