CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40347

CHEMISTRY REVIEW(S)

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 40-347

FIRM: Bedford Labs
Attention: Shahid Ahmed
270 Northfield Road
Bedford, OH 44146

DOSAGE FORM: Injection

STRENGTH: 10 mg/mL; 30 mL and 50 mL vials

DRUG: Leucovorin Calcium Injection

CGMP STATEMENT/EIR UPDATED STATUS:
EER for all listed facilities (refer to Section #33 of the ANDA review) was found acceptable on 2/12/99.

The drug product is manufactured, processed, packaged, labeled and controlled by:

Ben Venue Laboratories, Inc.
270 Northfield Road
Bedford, Ohio 44146

The Leucovorin Calcium nds is manufactured by :

BIO STUDY: Bedford has requested a waiver from the performance of a biequivalence study, and the request was found acceptable as per the bio review/letter issued to the firm on 1/25/99.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
MV: The drug product is listed in USP 24 (page 957). No MV is necessary.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? Containers used in the stability studies are identical to those listed in container section.

Vials: 30 mL: (DMF

50 mL: (DMF

Closure: [redacted] rubber stopper by

Seal: [redacted] Aluminum, [redacted] (DMF [redacted])

LABELING:
The FPL was found acceptable for approval per T. Watkins's review dated 8/2/99. Refer to the Labeling Approval Summary in the ANDA (Vol. 2.1).

STERILIZATION VALIDATION (IF APPLICABLE):
Micro review: The ANDA has been recommended for approval on the basis of sterility assurance (Micro review dated 4/13/00).

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Bedford has manufactured a [redacted] Liter exhibit batch to support the ANDA submission, and has provided a batch record for a [redacted] Liter maximum batch size. The batch instructions are satisfactory.

The Source of the Leucovorin NDS is [redacted] The referenced DMF [redacted] was found adequate per review completed on 1/19/00.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?) Stability batch was the same as the exhibit batch. The exhibit/stability batch is manufactured via same manufacturing process.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY? Bedford has provided a batch record for a [redacted] Liter maximum batch size. The batch instructions are satisfactory. The manufacturing process for the [redacted] L production batches are the same as the process for the [redacted] L exhibit batches.

Manufacturing process for the intended production size is identical to that used for the exhibit/bio/stability batch.

cc: ANDA #40-347
HFD-600/Reading File
HFD-625/K.Furnkranz/4-17-00
HFD-625/M.Smela TL/4-18-00
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Approval Summary

/S/ 4/21/00 /S/ 4/24/00

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 40-347

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

Leucovorin Calcium

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

N/A

9. AMENDMENTS AND OTHER DATES:

November 19, 1998 Original Submission

December 16, 1998 New Correspondence

10. PHARMACOLOGICAL CATEGORY

Antidote to folic acid antagonists
Antianemic (folate deficiency)

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

NDA 8107 Immunex

DMF

DMF

DMF

13. DOSAGE FORM

Injection

14. POTENCY

10 mg (base)/mL

15. CHEMICAL NAME AND STRUCTURE

See USP 23, pages 872-873.

16. **RECORDS AND REPORTS**

N/A

17. **COMMENTS**

Release and Stability specifications will be based on specifications of approved ANDAs 40-174, 81-277, 81-278 per the acting supervisor, Mujahid Shaikh.

18. **CONCLUSIONS AND RECOMMENDATIONS**

This ANDA is not approvable. Inform the applicant of deficiencies.

19. **REVIEWER:** /S/ Shirley S. Brown

DATE COMPLETED: 4/15/99 April 6, 1999

Redacted 13

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Chem #1

1. **CHEMISTRY REVIEW NO.** 2

2. **ANDA #** 40-347

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**
Leucovorin Calcium

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**
Firm:

November 19, 1998	Original Submission
December 16, 1998	New Correspondence
*July 27, 1999	ANDA Orig Amendment

FDA:

Jan 12, 1999	ANDA Acceptable for Filing
Jan 19, 1999	Labeling Review/Deficiencies
May 26, 1999	Chemistry Review #1: N/A MAJOR

10. **PHARMACOLOGICAL CATEGORY**
Antidote to folic acid antagonists
Antianemic (folate deficiency)

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
NDA 8107 Immunex
DMF
DMF

DMF

13. **DOSAGE FORM**
Injection

14. **POTENCY**
10 mg (base)/mL

15. **CHEMICAL NAME AND STRUCTURE**
See USP 23, pages 872-873.

16. **RECORDS AND REPORTS**
N/A

17. **COMMENTS:** Release and Stability specifications will be based on specifications of approved ANDAs 40-174, 81-277,-81-278.

1. Bedford should clarify the release specifications vs Stability Specifications.(p. 0012 and p. 0025).

18. **CONCLUSIONS AND RECOMMENDATIONS:** This ANDA is not approvable./FAX Amendment (since deficiencies are within the applicant's control). .

19. **REVIEWER:** Kenneth J. Furnkranz

DATE COMPLETED: February 7, 2000
Revised: 2/9/00

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Chem 2

Chemistry Closed

1. **CHEMISTRY REVIEW NO.** 3

2. **ANDA #** 40-347

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**
Leucovorin Calcium

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**

Firm:

November 19, 1998	Original Submission
December 16, 1998	New Correspondence
July 27, 1999	ANDA Orig Amendment
February 16, 2000	New Correspondence
*March 6, 2000	FAX Amendment

FDA:

Jan 12, 1999	ANDA Acceptable for Filing
Jan 19, 1999	Labeling Review/Deficiencies
May 26, 1999	Chemistry Review #1: N/A MAJOR
Feb 10, 2000	Chemistry Review #2: N/A FAX Amend
Mar 3, 2000	Telecon re: Request

10. **PHARMACOLOGICAL CATEGORY**
Antidote to folic acid antagonists
Antianemic (folate deficiency)

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
NDA 8107 Immunex
DMF
DMF

DMF

13. **DOSAGE FORM**
Injection

14. **POTENCY**
10 mg (base)/mL

15. **CHEMICAL NAME AND STRUCTURE**

See USP 23, pages 872-873.

16. **RECORDS AND REPORTS**
N/A

17. **COMMENTS: Bedford Laboratories has submitted an ANDA FAX Amendment as a result of discussion on March 3, 2000 between Ken Furnkranz and Michelle Dillahunt of FDA and Shahid Ahmed and Molly Rapp of Bedford (telecon of 3/3/00) regarding appropriate specifications for impurities in the drug substance and drug product.**

18. **CONCLUSIONS AND RECOMMENDATIONS: Chemistry Closed. Micro Review is pending.**

19. **REVIEWER:** Kenneth J. Furnkranz **DATE COMPLETED:** March 13, 2000

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Chen #3

1. **CHEMISTRY REVIEW NO.** 4

2. **ANDA #** 40-347

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**
Leucovorin Calcium

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**
N/A

9. **AMENDMENTS AND OTHER DATES:**

Firm:

November 19, 1998	Original Submission
December 16, 1998	New Correspondence
July 27, 1999	ANDA Orig Amendment
February 16, 2000	New Correspondence
March 6, 2000	FAX Amendment
*March 30, 2000	ANDA Amendment (FAX Amendment)

FDA:

Jan 12, 1999	ANDA Acceptable for Filing
Jan 19, 1999	Labeling Review/Deficiencies
May 26, 1999	Chemistry Review #1: N/A MAJOR
Feb 10, 2000	Chemistry Review #2: N/A FAX Amend
Mar 3, 2000	Telecon re: Request
Mar 15, 2000	Chemistry Review #3: Chemistry Closed
March 15, 2000	Micro Review: N/A FAX Amend
April 13, 2000	Micro Review; Satisfactory

10. **PHARMACOLOGICAL CATEGORY**
Antidote to folic acid antagonists
Antianemic (folate deficiency)

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
NDA 8107 Immunex
DMF
DMF
DMF

13. **DOSAGE FORM**
Injection

14. **POTENCY**
10 mg (base)/mL

15. **CHEMICAL NAME AND STRUCTURE**
See USP 23, pages 872-873.

16. **RECORDS AND REPORTS**
N/A

17. **COMMENTS:** On March 15, 2000, a Chemistry Closed review was completed indicating that the application was satisfactory for Chemistry, Manufacturing and Controls.

The March 30, 2000 ANDA Amendment (microbiological information) was reviewed and found acceptable on 4/13/00 by Nrapendra Nath, Ph.D. for microbiological aspects.

The Labeling has been found adequate for this ANDA as per the 8/2/99 review of T. Watkins (revisions will be necessary post-approval).

The EER is currently "acceptable"(12-Feb-1999 per Melissa Egas)

18. **CONCLUSIONS AND RECOMMENDATIONS: Approve.**

19. **REVIEWER:** Kenneth J. Furnkranz
DATE COMPLETED: April 17, 2000

cc: ANDA 40-347
DIV FILE
Field Copy
Endorsements:
HFD-617/M.Dillahunt/4-18-00 /S/ 4/19/00
HFD-625/K.Furnkranz/4-17-00 4/21/00
HFD-625/M.Smela, T/L/4-18-00 /S/
V:\FIRMSAM\BEDFORD\LTRS&REV\40347a04.fkf.doc
F/T by: bc/4-19-00

CHEMISTRY REVIEW - Approve /S/ 4/24/00

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Chem #1