CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75405

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 75-405	CHEMIST: Eugene L. Schaefer, Ph.D.	DATE: 8/10/1999
DRUG PRODUCT: Cladribine Injection		
FIRM: Bedford Laboratories		
DOSAGE FORM: Injection	STRENGTH: 1 mg/mL, 10 mL per vial	

cGMP:

The facilities were found acceptable on 8/24/98. **A new EER might be needed, if the approval package does not get all the required signatures by 8/24/99.** An EER was re-issued & is acceptable per Aug. 11, 1999 Bing Cá

BIO:

A waiver was granted 9/24/98.

VALIDATION - (Description of dosage form received by FDA lab same as in firm's ANDA?): Yes

Methods Validation has been started at PRL-NW, Seattle, **but not completed,** per E-mail from Tom Savage 8/10/99.

STABILITY:

The containers in the stability studies are identical to those in the container section.

LABELING:

Container, carton, and insert labeling were tentatively approved on 4/5/99.

STERILIZATION VALIDATION (If applicable):

Satisfactory per review of Lynne Ensor, Ph.D. on 8/6/99.

SIZE OF BIO BATCH (Firm's source of NDS ok?):

DMF satisfactory 5/20/99.

SIZE OF STABILITY BATCHES (If different from bio batch, were they manufactured via the same process?):

The size of the stability batch was L.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:

The maximum size of production batches will be L. The manufacturing process is identical to the exhibit batch.

Signature of chemist: /S/ 8/10/99 Eugene L. Schaefer, Ph.D.	Signature of supervisor: /S/ 8/11/99 Michael Smela

\\CDV008\WP51F99\FIRMSAM\BEDFORD\LTRS&REV\75405ap.sum

1. **CHEMISTRY REVIEW NO.** 1 Cycle Number: 1

2. ANDA # 75-405 **FIRST GENERIC**

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10 mL fill in 20-mL vial

10. PHARMACOLOGICAL CATEGORY

Synthetic Antineoplastic agent for treatment of Hairy Cell Leukemia

11. Rx or OTC

Rx

4. LEGAL BASIS FOR SUBMISSION

Leustatin Inj, NDA 20229, RW Johnson (Ortho Biotech Inc.). No patents. NCE exclusivity expired 2/26/98. Orphan Drug Exclusivity will expire 2/26/2000.

5. SUPPLEMENT(s)

N/A

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

N/A

9. AMENDMENTS AND OTHER DATES:

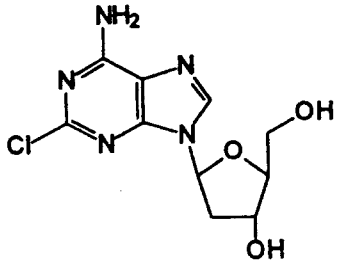
Vol. A1.1 and A1.2:

06/29/98 Original submission
06/30/98 Acceptable for filing
07/14/98 NC - Side-by-side labeling
09/24/98 Bio "no further questions" letter

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

15. CHEMICAL NAME AND STRUCTURE

Cladribine. Adenosine, 2-chloro-2'-deoxy-. $C_{10}H_{12}ClN_5O_3$. 285.69. 4291-63-8. Antineoplastic.



16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points:

22, 23.A, 28.B, and 29.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

The review of processing has not been completed, as of 1/26/99.

31. SAMPLES AND RESULTS

Cladribine is not in USP 23 through Supp 9. Methods Validation will be scheduled when the analytical issues have been resolved.

32. LABELING

Not satisfactory 9/23/98, but FPL requested.

33. ESTABLISHMENT INSPECTION

EER submitted 7/31/98.

34. BIOEQUIVALENCE STATUS

Waiver granted 9/24/98.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 75-405 is **NOT APPROVED - MINOR AMENDMENT** requested.

19. REVIEWER:	DATE COMPLETED:	REVISED:
Eugene L. Schaefer, Ph.D.	1/26/99	1/28/99

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Chem Review #1

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-405 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Cladribine Injection, 1 mg/mL, 10 mL fill in 20 cc vial

The deficiencies presented below represent MINOR deficiencies.

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Chem

Sincerely yours,

/S/ 7/1/99

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

1st generic exhibit not needed per F.H.

cc: ANDA 75-405
ANDA DUP
DIV FILE
Field Copy

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

MS Word

1. CHEMISTRY REVIEW NO. 2 Cycle Number: 2

2. ANDA # 75-405 **FIRST GENERIC**

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10 mL fill in 20-mL vial

10. PHARMACOLOGICAL CATEGORY

Synthetic Antineoplastic agent for treatment of Hairy Cell Leukemia

11. Rx or OTC

Rx

4. LEGAL BASIS FOR SUBMISSION

Leustatin Inj, NDA 20229, RW Johnson (Ortho Biotech Inc.). No patents. NCE exclusivity expired 2/26/98. Orphan Drug Exclusivity will expire 2/26/2000.

5. SUPPLEMENT(s)

N/A

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

N/A

9. AMENDMENTS AND OTHER DATES:

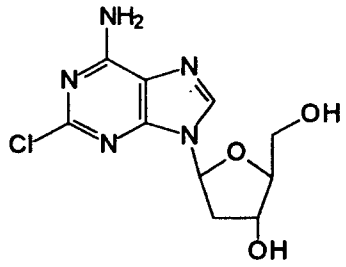
Vol. A1.1 and A1.2:
06/29/98 Original submission
06/30/98 Acceptable for filing
07/14/98 NC - Side-by-side labeling
09/24/98 Bio "no further questions" letter
02/12/99 NA Minor fax from FDA

Vol. A2.1:
03/23/99 Minor amendment

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

15. CHEMICAL NAME AND STRUCTURE

Cladribine. Adenosine, 2-chloro-2'-deoxy-. $C_{10}H_{12}ClN_5O_3$. 285.69. 4291-63-8. Antineoplastic.



16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points:

22, 28.B, 29.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

The review of processing has not been completed, as of 3/31/99.

31. SAMPLES AND RESULTS

Cladribine is not in USP 23 through Supp 9. The analytical issues have been resolved, and Methods Validation is being scheduled.

32. LABELING

Not satisfactory 9/23/98. FPL submitted 3/23/99. Not reviewed, as of 4/1/99.

33. ESTABLISHMENT INSPECTION

Facilities were found acceptable 8/24/98.

34. BIOEQUIVALENCE STATUS

Waiver granted 9/24/98.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 75-405 is **NOT APPROVED - MINOR AMENDMENT** requested.

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 4/1/99

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Chem Review #2

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-405 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Cladribine Injection, 1 mg/mL, 10 mL fill in 20-cc vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

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

The labeling portion of your amendment is pending review.

Sincerely yours,

/S/ 4/22/99

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

1. CHEMISTRY REVIEW NO. 3 Cycle Number: 3

2. ANDA # 75-405 **FIRST GENERIC**

3. NAME AND ADDRESS OF APPLICANT

CHEMISTRY CLOSE

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10 mL fill in 20-mL vial

10. PHARMACOLOGICAL CATEGORY

Synthetic Antineoplastic agent for treatment of Hairy Cell Leukemia

11. Rx or OTC Rx

4. LEGAL BASIS FOR SUBMISSION

Leustatin Inj, NDA 20229, RW Johnson (Ortho Biotech Inc.). No patents. NCE exclusivity expired 2/26/98. Orphan Drug Exclusivity will expire 2/26/2000.

5. SUPPLEMENT(s)
N/A

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

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 and A1.2:
06/29/98 Original submission
06/30/98 Acceptable for filing
07/14/98 NC - Side-by-side labeling
09/24/98 Bio "no further questions" letter
02/12/99 NA Minor fax from FDA

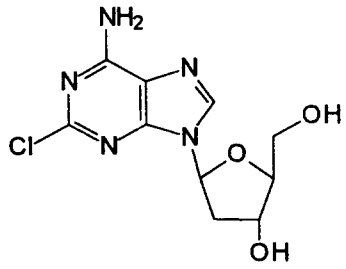
Vol. A2.1:

03/23/99 Minor amendment
04/27/99 NA Minor fax from FDA
05/10/99 Minor amendment

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

15. CHEMICAL NAME AND STRUCTURE

Cladribine. Adenosine, 2-chloro-2'-deoxy-. $C_{10}H_{12}ClN_5O_3$. 285.69. 4291-63-8. Antineoplastic.



16. RECORDS AND REPORTS N/A

17. COMMENTS

All chemistry deficiencies in Points 20 through 30 have been resolved.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

The review of processing has not been completed, as of 5/21/99.

31. SAMPLES AND RESULTS

Cladribine is not in USP 23 through Supp 10. Methods Validation has been scheduled. **Samples were transferred from PHI-DO to PRL-NW, Seattle, 5/6/99.**

32. LABELING

FPL submitted 3/23/99. Tentatively approved 4/5/99.

33. ESTABLISHMENT INSPECTION

Facilities were found acceptable 8/24/98.

34. BIOEQUIVALENCE STATUS

Waiver granted 9/24/98.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 75-405 is **ready for approval except for microbiology and methods validation.**

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 5/21/99

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Chem Review #3

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-405 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Cladribine Injection, 1 mg/mL, 10 mL fill in 20-cc vial

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

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

1. CHEMISTRY REVIEW NO. 3 Cycle Number: 3

2. ANDA # 75-405 **FIRST GENERIC**

3. NAME AND ADDRESS OF APPLICANT

ADDENDUM

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10 mL fill in 20-mL vial

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 and A1.2:
06/29/98 Original submission
06/30/98 Acceptable for filing
07/14/98 NC - Side-by-side labeling
09/24/98 Bio "no further questions" letter
02/12/99 NA Minor fax from FDA

Vol. A2.1:

03/23/99 Minor amendment
04/27/99 NA Minor fax from FDA
05/10/99 Minor amendment

17. COMMENTS

This review was CHEMISTRY CLOSED on 5/24/99, awaiting a microbiology review, and MV by an FDA lab.

The processing was found **not satisfactory** 6/11/99 by Lynne A. Ensor, Ph.D. Deficiencies are being faxed to Bedford.

Samples were transferred from PHI-DO to PRL-NW, Seattle, 5/6/99. I called Tom Savage in Seattle 7/13/99. He estimated the lab work **might be done in another three weeks.**

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 75-405 is **ready for approval except for microbiology and methods validation.** A **facsimile amendment** is being requested.

19. REVIEWER:	ADDENDUM COMPLETED:
Eugene L. Schaefer, Ph.D.	7/13/99

38. Comments to be Provided to the Applicant

ANDA: 75-405 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Cladribine Injection, 1 mg/mL, 10 mL fill in 20-cc vial

The deficiencies presented below represent FACSIMILE deficiencies.

Sterility Assurance for this product has not been demonstrated. The deficiencies are attached.

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

A satisfactory Methods Validation is needed to support the ANDA. The study has been scheduled.

Sincerely yours,

/S/

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

1. CHEMISTRY REVIEW NO. 4 Cycle Number: 3

2. ANDA # 75-405 **FIRST GENERIC**

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10 mL fill in 20-mL vial

10. PHARMACOLOGICAL CATEGORY

Synthetic Antineoplastic agent for treatment of Hairy Cell Leukemia

11. Rx or OTC Rx

4. LEGAL BASIS FOR SUBMISSION

Leustatin Inj, NDA 20229, RW Johnson (Ortho Biotech Inc.). No patents. NCE exclusivity expired 2/26/98. Orphan Drug Exclusivity will expire 2/26/2000.

5. SUPPLEMENT(s)
N/A

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

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 and A1.2:

06/29/98 Original submission
06/30/98 Acceptable for filing
07/14/98 NC - Side-by-side labeling
09/24/98 Bio "no further questions" letter
02/12/99 NA Minor fax from FDA

Vol. A2.1:

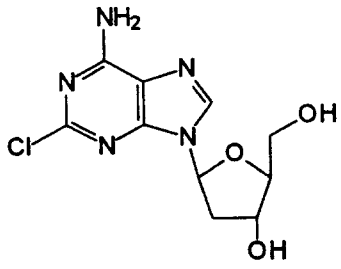
03/23/99 Minor amendment
04/27/99 NA Minor fax from FDA

05/10/99 Minor amendment
07/21/99 NA Facsimile fax from FDA
08/02/99 Facsimile amendment - micro response

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

15. CHEMICAL NAME AND STRUCTURE

Cladribine. Adenosine, 2-chloro-2'-deoxy-. $C_{10}H_{12}ClN_5O_3$. 285.69. 4291-63-8. Antineoplastic.



16. RECORDS AND REPORTS N/A

17. COMMENTS

All chemistry deficiencies in Points 20 through 30 have been resolved.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

The processing was found **satisfactory** by Dr. Lynne Ensor 08/06/99 per email. The review is waiting signature.

31. SAMPLES AND RESULTS

Cladribine is not in USP 23 through Supp 10. Methods Validation has been started, but not completed, per E-mail from Tom Savage 8/10/99.
If an MV report has not been received from the Seattle lab by the time the approval package is ready for final sign-off, the following New Comment should be sent to Bedford Labs: Please provide a commitment to cooperate fully with the Agency regarding any issues which might arise during FDA validation of your analytical methods.

32. LABELING

FPL submitted 3/23/99. Tentatively approved 4/5/99.

33. ESTABLISHMENT INSPECTION

Facilities were found acceptable 8/24/98. **A new EER should be requested, because the approval package will probably not get all the required signatures by 8/24/99.**

34. BIOEQUIVALENCE STATUS

Waiver granted 9/24/98.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 75-405 is **ready for approval.** Methods validation has not been completed, as of 8/10/99.

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 8/10/99

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Chem Review #4

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-405 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Cladribine Injection, 1 mg/mL, 10 mL fill in 20-cc vial

The deficiencies have been remedied.

cc: ANDA 75-405
ANDA DUP
DIV FILE
Field Copy

CHEMISTRY REVIEW - APPROVED - METHODS VALIDATION NOT COMPLETED

MS Word

1. CHEMISTRY REVIEW NO. 4 Cycle Number: Out of Cycle

2. ANDA # 75-405

ADDENDUM FOR METHODS VALIDATION DEFICIENCIES

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10-mL fill in 20-mL vial

4. LEGAL BASIS FOR SUBMISSION

Leustatin Inj, NDA 20-229, RW Johnson (Ortho Biotech Inc.). No patents. NCE exclusivity expired 2/26/98. Orphan Drug Exclusivity will expire 2/26/2000.

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 and A1.2:

06/29/98 Original submission

Vol. A2.1:

03/23/99 Minor amendment

17. COMMENTS

31. SAMPLES AND RESULTS

ANDA 75-405 was tentatively approved 8/31/99 in the absence of methods validation. An MV Report dated 10/22/99 was received from the FDA Pacific Regional Laboratory Northwest, Seattle, on 10/27/99. The lab considered Bedford's methods **satisfactory with modifications (lab classification 2)**.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 75-405 is **NOT APPROVED - MINOR AMENDMENT** requested, because of deficiencies in analytical methods.

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 11/19/99

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Chem Review # 4 Addendum

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-405

APPLICANT: Bedford Laboratories,
A Division of Ben Venue Laboratories, Inc.

DRUG PRODUCT: Cladribine Injection, 1 mg/mL, 10 mL vial

The deficiencies presented below represent MINOR deficiencies.

ANDA 75-405 was tentatively approved before methods validation by an FDA laboratory had been completed.

Methods validation has now been completed. Based on the observations by the chemist and the supervisory chemist at the Pacific Regional Laboratory Northwest, Seattle, we have the following concerns:

1. Regarding analytical method which was submitted in the original ANDA on pages 0691 to 0709:

   a. In the Calculations on page 9 of the method, the term "Conc. of Drug found (mg)" should be replaced with the term "Amount of Drug found (mg)".

   b. The percent of each individual known impurity should be calculated with respect to the area of that known impurity's standard, rather than the total area.

2. Regarding analytical method which was submitted in Attachment VII of the minor amendment of March 23, 1999: The calculation on page 0046 of that amendment gives a result in terms of ppm / µg/g, whereas the specification on page 0005 is in terms of percent. The method or the specification should be revised to be consistent with the other.

3. Please describe the results of your investigation of the black particle that was found in one of the finished drug product vials at the FDA laboratory.

Sincerely yours,

/S/ 12/3/95

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 Cycle Number: N/A (ANDA has been tentatively approved)

2. ANDA # 75-405

METHODS VALIDATION DEFICIENCIES

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
300 Northfield Road
Bedford, OH 44146

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Cladribine

13. DOSAGE FORM
Injection Solution

14. STRENGTH
1 mg/mL, 10-mL fill in 20-mL vial

4. LEGAL BASIS FOR SUBMISSION
Leustatin Inj, NDA 20-229, RW Johnson (Ortho Biotech Inc.). No patents. NCE exclusivity expired 2/26/98. Orphan Drug Exclusivity will expire 2/26/2000.

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 and A1.2:

06/29/98 Original submission

Vol. A2.1:.

03/23/99 Minor amendment - included revised analytical methods
04/01/99 MVP was submitted
08/31/99 ANDA 75-405 was tentatively approved in the absence of methods validation.
10/27/99 An MV Report dated 10/22/99 was received from the FDA Pacific Regional Laboratory Northwest, Seattle. The lab considered Bedford's methods satisfactory with modifications.
12/06/99 Minor amendment in response to tentative approval letter of 8/31/99 - no changes in CMC or labeling, 12 copies of FPL submitted
12/08/99 NA Minor facsimile for MV deficiencies
12/09/99 Telecon re Deficiency #1.b of 12/08/99
12/16/99 Minor amendment in response to 12/08 **(the subject of this review)**

17. COMMENTS

31. SAMPLES AND RESULTS

The responses to the MV deficiencies are **satisfactory.**

32. LABELING

The labeling submitted 12/6/99 was found **satisfactory** by Teresa Watkins 12/10/99.

18. CONCLUSIONS AND RECOMMENDATIONS

On 08/31/99, ANDA 75-405 was tentatively approved in the absence of methods validation. ANDA 75-405 **can be TENTATIVELY APPROVED** again, or it appears it can be fully approved on 2/26/2000.

Note: The DS and DP continue to lack inclusion in USP 24. DMF for the DS has not been amended since the ANDA was tentatively approved.

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 12/30/99

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Chem Review #5

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-405

APPLICANT: Bedford Laboratories,
A Division of Ben Venue Laboratories, Inc.

DRUG PRODUCT: Cladribine Injection, 1 mg/mL, 10 mL vial

None

cc: ANDA 75-405
ANDA DUP 75-405
DIV FILE
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Reading file (for facsimiles only)

2/1/11/2000

CHEMISTRY REVIEW - TENTATIVE APPROVAL - A SECOND TIME

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-405

APPLICANT: Bedford Laboratories,
A Division of Ben Venue Laboratories, Inc.

DRUG PRODUCT: Cladribine Injection, 1 mg/mL, 10 mL vial

The deficiencies presented below represent MINOR deficiencies.

ANDA 75-405 was tentatively approved before methods validation by an FDA laboratory had been completed.

Methods validation has now been completed. Based on the observations by the chemist and the supervisory chemist at the Pacific Regional Laboratory Northwest, Seattle, we have the following concerns:

1. Regarding analytical method which was submitted in the original ANDA on pages 0691 to 0709:

   a. In the Calculations on page 9 of the method, the term "Conc. of Drug found (mg)" should be replaced with the term "Amount of Drug found (mg)".

   b. The percent of each individual known impurity should be calculated with respect to the area of that known impurity's standard, rather than the total area.

2. Regarding analytical method which was submitted in Attachment VII of the minor amendment of March 23, 1999: The calculation on page 0046 of that amendment gives a result in terms of ppm / µg/g, whereas the specification on page 0005 is in terms of percent. The method or the specification should be revised to be consistent with the other.

3. Please describe the results of your investigation of the black particle that was found in one of the finished drug product vials at the FDA laboratory.

Sincerely yours,

/S/

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

JUL 21 1999

38. Comments to be Provided to the Applicant

ANDA: 75-405 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Cladribine Injection, 1 mg/mL,
10 mL fill in 20-cc vial

The deficiencies presented below represent FACSIMILE deficiencies.

Sterility Assurance for this product has not been demonstrated. The deficiencies are attached.

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

A satisfactory Methods Validation is needed to support the ANDA. The study has been scheduled.

Sincerely yours,

/S/

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