CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75405

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

ANDA 75-405 was tentatively approved 8/31/99 in the absence of methods validation. A 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). The firm received a not approvable minor facsimile because of deficiencies in analytical methods on December 8, 1999. The firm requested a telecon to discuss 1.(b) of the chemistry comments.

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

Mr. Ahmed wanted to know if the percent for each known impurity should be calculated against the standard peak area, or could the peak area of the known impurity be corrected by use of its response factor.

Dr. Schaefer informed him that either approach would be O.K.

DATE
December 9, 1999

ANDA NUMBER
75-405

IND NUMBER

TELECON

INITIATED BY

SPONSOR X

FDA

PRODUCT NAME
Cladribine Injection, 1 mg/mL, 10 mL vial

FIRM NAME
Bedford Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Shahid Ahmed

TELEPHONE NUMBER
(440) 232-3320 EXT 333

SIGNATURE
M.Dillahunt 12/14/1999
E. Schaefer
2/10/99

V:\FIRMSAM\BEDFORD\TELECONS\75405.TC.002.DOC
CC: ANDA 75-405
Chem Div I, T-con Notebook

MINUTES OF PHONE CALL

DATE: 8/25/99

SUBJECT: ANDA 75-405 , Cladribine Inj

ORGANIZATION: **Bedford labs**

PARTICIPANTS: Allen Rudman
Dr. Shahed Ahmed

Dr Ahmed was asked if there was a protocol to extend expiry in the application. He said that there was none. He acknowledged that if Bedford wanted to extend the expiry without a protocol they would have to submit a pre-approval supplement.

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-405 **Date of Submission: December 6, 1999**
Applicant's Name: Bedford Laboratories
Established Name: Cladribine Injection, 1 mg/mL
APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (10 mL) Satisfactory as of March 23, 1999 submission.
Carton Labeling: (1 x 10 mL) Satisfactory as of March 23, 1999 submission.
Professional Package Insert Labeling: Satisfactory as of December 6, 1999 submission.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Leustatin®
NDA Number: 20-229
NDA Drug Name: Cladribine Injection
NDA Firm: R.W. Johnson
Date of Approval of NDA Insert and supplement #: February 26, 1993. S-004 and S-007 (SSCBE's)
Pending approval. New Drug expects to approve soon.
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator carton labeling in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X

Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. ODE- Expires 2-26-2000, Will not market before this time.	X		

FOR THE RECORD:

1. The reference listed drug for this product is R.W, Johnson Pharmaceutical Research Institute□s Leustatin□(Approved February 26, 1993). However, the firm has submitted a side-by-side compared to a revised insert which appears in the PDR. Team Leader, John Grace, states that new drugs anticipates approval of this revised labeling. Therefore, we will not request the firm to return to the originally approved labeling. ~~NOTE: Full approval for this application can not be granted until we receive documentation from new drugs stating the proposed innovator revisions have been approved. The Orange book name is Cladribine Injectable; Injection. This is not a USP item. The applicant uses Cladribine Injection, 1 mg/mL.~~
   NOTE: The original labeling differs in DOSAGE AND ADMINISTRATION. ~~IV was never in the marketplace~~. 0.1 mg/Kg/day was original dose. The RLD was requested to submit SSCBE Δing to 0.09/mg/Kg/d. by New Drug
2. The applicant certifies that the New Chemical Entity Exclusivity expired on 2-16-98 and that it will not market until the Orphan Drug Exclusivity expires on 2-26-2000.
   See Vol. 1.1, page 6.
3. The product is manufactured by BenVenue Laboratories, Inc, 270 Northfield Road, Bedford, Ohio 44146, for Bedford Laboratories. No outside firms are utilized. See Vol. 1.1, page 174 & 176.
4. Container/Closure Statement

   Container: Molded.
   Closure: mm Gray plug
   Seal: mm Aluminum Flip off seals.
   See Vol. 1.2, page 583.
5. Fished Product-Clear, colorless, sterile, preservative free, isotonic solution. See Vol. 1.1, page 24.
6. Product Line-10 mg(1 mg/mL) of Cladribine as 10 mL filled in a single-use clear Flint glass 20 mL vial individually boxed. See Vol. 1.1, page 45.
7. Components/Composition Statement
   Innovator:
   Active: Cladribine
   Inactive: Sodium Chloride
   Phosphoric acid
   and/or Dibasic Sodium Phosphate to adjust pH

   Applicant:
   Active: Cladribine
   Inactive: Sodium Chloride
   Phosphoric acid
   and/or Dibasic Sodium Phosphate to adjust pH
   Water for Injection qs to 1 mL
   See Vol. 1.1, page 74.
8. Storage/Dispensing Conditions
   NDA: Store Refrigerated 2□ to 8□C(36□ to 46□F). Protect from light during storage.
   ANDA: Same as NDA.

Date of Review: December 10, 1999
Date of Submission: December 6, 1999

Reviewer: /S/ **Date:** 12-10-99

Team Leader: /S/ **Date:** 12-13-1999

cc:
ANDA: 75-405
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
V:\FIRMSAM\BEDFORD\LTRS&REV\75405.apl
Review

Concur: /S/ 12/13/99

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-405 **Date of Submission: March 23, 1999**

Applicant's Name: Bedford Laboratories

Established Name: Cladribine Injection, 1 mg/mL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes
If no, list why:

Container Labels: (10 mL) Satisfactory as of March 23, 1999 submission.

Carton Labeling: (1 x 10 mL) Satisfactory as of March 23, 1999 submission.

Professional Package Insert Labeling: Tentatively Satisfactory as of March 23, 1999 submission. See FOR THE RECORD.

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Leustatin®

NDA Number: 20-229
NDA Drug Name: Cladribine Injection
NDA Firm: R.W. Johnson

Date of Approval of NDA Insert and supplement #: February 26, 1993. S-004 and S-007 (SSCBE's) Pending approval. New Drug expects to approve soon.
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator carton labeling in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., bensyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. ODE- Expires 2-26-2000, Will not market before this time.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. The reference listed drug for this product is R.W, Johnson Pharmaceutical Research Institute's Leustatin™(Approved February 26, 1993). However, the firm has submitted a side-by-side compared to a revised insert which appears in the PDR. Team Leader, John Grace, states that new drugs anticipates approval of this revised labeling. Therefore, we will not request the firm to return to the originally approved labeling. NOTE: Full approval for this application can not be granted until we receive documentation from new drugs stating the proposed innovator revisions have been approved. The Orange book name is Cladribine Injectable; Injection. This is not a USP item. The applicant uses Cladribine Injection, 1 mg/mL.
NOTE: The original labeling differs in DOSAGE AND ADMINISTRATION. IV was never in the marketplace.

2. The applicant certifies that the New Chemical Entity Exclusivity expired on 2-16-98 and that it will not market until the Orphan Drug Exclusivity expires on 2-26-2000. See Vol. 1.1, page 6.

3. The product is manufactured by BenVenue Laboratories, Inc, 270 Northfield Road, Bedford, Ohio 44146, for Bedford Laboratories. See Vol. 1.1, page 174.

4. No outside firms are utilized. See Vol. 1.1, page 176.

5. Container/Closure Statement

Container: Molded.
Closure: mm Gray plug
Seal: 20 mm Aluminum Flip off
seals.

See Vol. 1.2, page 583.

6. Finished Product

Clear, colorless, sterile, preservative free, isotonic solution.

See Vol. 1.1, page 24.

7. Product Line

10 mg(1 mg/mL) of Cladribine as 10 mL filled in a single-use clear Flint glass 20 mL vial individually boxed.

See Vol. 1.1, page 45.

8. Components/Composition Statement

Innovator:
Active: Cladribine
Inactive: Sodium Chloride
Phosphoric acid
and/or Dibasic Sodium Phosphate to adjust pH

Applicant:
Active: Cladribine
Inactive: Sodium Chloride
Phosphoric acid
and/or Dibasic Sodium Phospate to adjust pH
Water for Injection qs to 1 mL

See Vol. 1.1, page 74.

9. Storage/Dispensing Conditions

NDA: Store Refrigerated 2° to 8°C(36° to 46°F). Protect from light during storage.

ANDA: Same as NDA.

Date of Review: March 26, 1999
Date of Submission: March 23, 1999

Reviewer: /S/ **Date:** 4/5/99

Team Leader: /S/ **Date:** 4-5-1999

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cc:

ANDA: 75-405
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)

Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-405 **Date of Submission: June 29, 1998**

Applicant's Name: Bedford Laboratories

Established Name: Cladribine Injection, 1 mg/mL

Labeling Deficiencies:

1. GENERAL COMMENTS:

2. CONTAINER

   a. Revise "For IV Infusion" to read "MUST BE DILUTED PRIOR TO IV INFUSION".

3. CARTON

   a. Revise "For IV Infusion" to read "MUST BE DILUTED PRIOR TO IV INFUSION".

4. INSERT

   a. TITLE

      We encourage the inclusion of "℞ only".

   b. We encourage the relocation of "℞ only" to the TITLE section.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of final printed carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Carton Labeling:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No

What is the RLD on the 356(h) form:

NDA Number:

NDA Drug Name:

NDA Firm:

Date of Approval of NDA Insert and supplement #:
Has this been verified by the MIS system for the NDA?
Yes No

Was this approval based upon an OGD labeling guidance? Yes No

If yes, give date of labeling guidance:
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
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Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
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Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			X
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. ODE- Expires 2-26-2000, Will not market before this time.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. The reference listed drug for this product is R.W, Johnson Pharmaceutical Research Institute's Leustatin™(Approved February 26, 1993). However, the firm has submitted a side-by-side compared to a revised insert which appears in the PDR. Team Leader, John Grace, states that new drugs anticipates approval of this revised labeling. Therefore, we will not request the firm to return to the originally approved labeling. NOTE: Full approval for this application can not be granted until we receive documentation from new drugs stating the proposed innovator revisions have been approved. The Orange book name is Cladribine Injectable; Injection. This is not a USP item. The applicant uses Cladribine Injection, 1 mg/mL.
   NOTE: The original labeling differs in DOSAGE AND ADMINISTRATION. IT was never in the marketplace.

2. The applicant certifies that the New Chemical Entity Exclusivity expired on 2-16-98 and that it will not market until the Orphan Drug Exclusivity expires on 2-26-2000. See Vol. 1.1, page 6.

3. The product is manufactured by BenVenue Laboratories, Inc, 270 Northfield Road, Bedford, Ohio 44146, for Bedford Laboratories. See Vol. 1.1, page 174.

4. No outside firms are utilized. See Vol. 1.1, page 176.

5. Container/Closure Statement

   Container: Molded.
   Closure: mm Gray plug
   Seal: mm Aluminum Flip off
   seals.

   See Vol. 1.2, page 583.

6. Finished Product

   Clear, colorless, sterile, preservative free, isotonic solution.

   See Vol. 1.1, page 24.

7. Product Line

   10 mg(1 mg/mL) of Cladribine as 10 mL filled in a sinle-use clear Flint glass 20 mL vial individually boxed.

See Vol. 1.1, page 45.

8. Components/Compossition Statement

Innovator:
Active: Cladribine
Inactive: Sodium Chloride
Phosphoric acid
and/or Dibasic Sodium Phosphate to adjust pH

Applicant:
Active: Cladribine
Inactive: Sodium Chloride
Phosphoric acid
and/or Dibasic Sodium Phospate to adjust pH
Water for Injection qs to 1 mL

See Vol. 1.1, page 74.

9. Storage/Dispensing Conditions

NDA: Store Refrigerated 2° to 8°C(36° to 46°F). Protect from light during storage.

ANDA: Same as NDA.

Date of Review: September 23, 1998
Date of Submission: June 29, 1998

Reviewer: /S/ **Date:** 9/23/98

Team Leader: /S/ **Date:** 9/23/98

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cc:
ANDA: 75-405
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace 9-23-98 (no cc)

Review

Telecon

Date: 071498

Time: 1400 H

ANDA #: 75-405

Firm: Bedford Labs.

Drug: Cladribine Injection, 1 mg/mL, 10 mL vial

Participants: Gregg Davis, FDA and Shahid Ahmed

Phone #: 440-232-3320 ext. 333

Agenda:

I called Shahid and asked for an additional piece of info. The application did not contain a side-by-side labeling comparison for the carton and vial labels. It only contained this comparison for the insert. He said it was an oversight in copying and he will fax the info and follow with a hard copy.