

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number **74897**

Trade Name **Acyclovir Sodium for Injection 500mg (base)/**
vial and 1g (base) /vial

Generic Name **Acyclovir Sodium for Injection 500mg (base)/**
vial and 1g (base) /vial

Sponsor **Apothecon, Inc.**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74897

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74897

APPROVAL LETTER

ANDA 74-897

FEB 27 1998

Apothecon, Inc.
Attention: Elaine Cembor
P. O. Box 4500
Princeton, NJ 08543-4500



Dear Madam:

This is in reference to your abbreviated new drug application dated April 30, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Sodium for Injection, 500 mg (base)/vial and 1 g (base)/vial.

Reference is also made to your amendments dated December 1, 1997, and January 29, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Sodium for Injection, 500 mg (base)/vial and 1 g (base)/vial to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zovirax® Sterile Powder, 500 mg (base)/vial and 1 g (base)/vial, respectively, of Glaxo Wellcome Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

Page 2

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

2/27/98
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74897

FINAL PRINTED LABELING

Wiley

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Preparation of solution: Inject 10 mL Sterile Water for Injection into vial. Shake vial until a clear solution is achieved and use within 12 hours. DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING BENZYL ALCOHOL OR PARABENS. Dilute to 7 mg/mL or lower prior to infusion. See package insert for additional reconstitution and dilution instructions.

Exp. Date
Control No.

500 mg NDC 59772-4161-2

**ACYCLOVIR SODIUM
FOR INJECTION**

Active ingredient: vial contains acyclovir sodium equivalent to 500 mg acyclovir

FOR INTRAVENOUS INFUSION ONLY

Store between 15° to 25° C (59° to 77° F).

CAUTION: Federal law prohibits dispensing without prescription.

APOTHECON
A BRISTOL-MYERS SQUIBB COMPANY

Inactive ingredient: Sodium hydroxide has been added to adjust the pH of this product. For indications, dosage, precautions, etc., see accompanying package insert.

APOTHECON
A Bristol-Myers Squibb Company
Princeton, NJ 08540 USA 416120-01

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Preparation of solution: Inject 20 mL Sterile Water for Injection into vial. Shake vial until a clear solution is achieved and use within 12 hours. DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING BENZYL ALCOHOL OR PARABENS. Dilute to 7 mg/mL or lower prior to infusion. See package insert for additional reconstitution and dilution instructions.

Exp. Date
Control No.

1 gram NDC 59772-4160-1

**ACYCLOVIR SODIUM
FOR INJECTION**

Active ingredient: vial contains acyclovir sodium equivalent to 1 gram acyclovir

FOR INTRAVENOUS INFUSION ONLY

Store between 15° to 25° C (59° to 77° F).

CAUTION: Federal law prohibits dispensing without prescription.

APOTHECON
A BRISTOL-MYERS SQUIBB COMPANY

Inactive ingredient: Sodium hydroxide has been added to adjust the pH of this product. For indications, dosage, precautions, etc., see accompanying package insert.

APOTHECON
A Bristol-Myers Squibb Company
Princeton, NJ 08540 USA 416010-01

MA 160

Preparation of solution: Insert 10 ml. Sterile Water for Injection into vial. Shake vial until a clear solution is obtained and use within 12 hours. DO NOT USE BAC-TERIOSTATIC WATER FOR INJECTION CONTAINING BENZYL ALCOHOL OR PARABENS. Dilute to 7 ml. or less with Sterile Water for Injection. See package insert for additional precautions and dilution instructions.

Exp. Date _____
Control No. _____

1 gram NDC 59772-4160-1

ACYCLOVIR SODIUM FOR INJECTION

Active ingredient: vial contains acyclovir sodium equivalent to 1 gram acyclovir
FOR INTRAVENOUS INFUSION ONLY

Store between 7° to 25° C (59° to 77° F).

CAUTION: Federal law prohibits dispensing without prescription.

Inactive ingredient: Sodium hydroxide has been added to adjust the pH of this product. For indications, dosage, precautions, etc., see accompanying package insert.

APOTHECON®
A Bristol-Myers Squibb Company
Princeton, NJ 08540 USA 418010-01

Preparation of solution: Insert 10 ml. Sterile Water for Injection into vial. Shake vial until a clear solution is obtained and use within 12 hours. DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING BENZYL ALCOHOL OR PARABENS. Dilute to 7 ml. or less with Sterile Water for Injection. See package insert for additional precautions and dilution instructions.

Exp. Date _____
Control No. _____

500 mg NDC 59772-4161-2

ACYCLOVIR SODIUM FOR INJECTION

Active ingredient: vial contains acyclovir sodium equivalent to 500 mg acyclovir
FOR INTRAVENOUS INFUSION ONLY

Store between 7° to 25° C (59° to 77° F).

CAUTION: Federal law prohibits dispensing without prescription.

Inactive ingredient: Sodium hydroxide has been added to adjust the pH of this product. For indications, dosage, precautions, etc., see accompanying package insert.

APOTHECON®
A Bristol-Myers Squibb Company
Princeton, NJ 08540 USA 418120-01

10/01/07

10 vials **1 gram each** NDC 59772-4160-1

ACYCLOVIR SODIUM FOR INJECTION

Contains acyclovir sodium equivalent to 1 g acyclovir.

FOR INTRAVENOUS INFUSION ONLY

Store between 15° to 25° C (59° to 77° F).

CAUTION: Federal law prohibits dispensing without prescription.

Dissolve contents of each vial by adding 20 mL of Sterile Water for Injection; shake the vial well to assure complete dissolution. **DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING BENZYL ALCOHOL OR PARABENS.** Inactive Ingredient: Sodium hydroxide has been added to adjust the pH of this product.

For indications, dosage, precautions, etc., see accompanying package insert.

APOTHECON® A Bristol-Myers Squibb Company, Princeton, NJ 08540 USA

Exp. Date
Control No.

10 vials **500 mg each** NDC 59772-4161-2

ACYCLOVIR SODIUM FOR INJECTION

Contains acyclovir sodium equivalent to 500 mg acyclovir.

FOR INTRAVENOUS INFUSION ONLY

Store between 15° to 25° C (59° to 77° F).

CAUTION: Federal law prohibits dispensing without prescription.

Dissolve contents of each vial by adding 10 mL of Sterile Water for Injection; shake the vial well to assure complete dissolution. **DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING BENZYL ALCOHOL OR PARABENS.** Inactive Ingredient: Sodium hydroxide has been added to adjust the pH of this product.

For indications, dosage, precautions, etc., see accompanying package insert.

APOTHECON® A Bristol-Myers Squibb Company, Princeton, NJ 08540 USA

Exp. Date
Control No.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74897

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. ~~CHEMISTRY REVIEW NO. 4~~

2. ANDA# 74-897

3. NAME AND ADDRESS OF APPLICANT

Apothecon® Inc.
A Bristol-Myers Squibb Company
P.O. Box 4500
Princeton, NJ 08543-4500

4. LEGAL BASIS FOR ANDA SUBMISSION

The application is based on the reference listed drug **Zovirax Sterile Powder®** manufactured by Burroughs Wellcome (NDA 18-603). Apothecon certifies that they will not infringe U.S. Patent No. 4,199,574 owned by Burroughs Wellcome. This patent, which covers acyclovir product, composition and method of use, expired on 4/22/97. The firm also certifies that the manufacturing process used by the acyclovir raw material suppliers will not infringe U.S. Patent No. 4,544,634 also owned by Burroughs Wellcome.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Acyclovir Sodium for Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR

N/A

9. AMENDMENTS AND OTHER DATES

Firm:

Original Submission: 4/30/96
Amendment: 6/7/96
Amendment: 6/19/96
Amendment (MAJOR): 2/6/97
Amendment (MINOR): 9/23/97
Amendment (MINOR): 12/1/97
Telephone Amendment: 1/29/98

FDA:

Refusal to File: 5/31/96

Acceptance to File: 7/3/96

Deficiency Letter (MAJOR): 1/8/97

Deficiency Letter (MINOR): 7/11/97

Deficiency Letter (MINOR): 11/7/97

10. PHARMACOLOGICAL CATEGORY

Antiviral

11. HOW DISPENSED

Rx

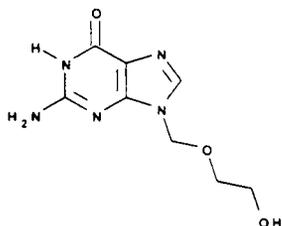
12. RELATED IND/NDA/DMFs13. DOSAGE FORM/ROUTE OF ADMINISTRATION

Sterile Powder/IV

14. STRENGTHS

500 mg/vial

1 gm/vial

15. CHEMICAL NAME AND STRUCTURE

9-[(2-Hydroxyethoxy)methyl]guanine sodium

 $C_8H_{11}N_5O_3 \cdot Na$

Molecular Weight: 247.19

16. RECORDS AND REPORTS

N/A

17. **COMMENTS**

All CMC deficiencies were resolved with the firm's 1/29/98 telephone amendment. Methods validation has been completed, an acceptable EER has been received, labeling has been found acceptable and the bio-waiver has been granted. Issues concerning micro are currently under review by the microbiologist (J.McVey); acceptable 2/6/98.

18. **CONCLUSIONS/RECOMMENDATIONS**

Recommend approval

19. **REVIEWER**

Susan Roséncrance

DATE COMPLETED

12/17/97; revised 2/6/98

2/12/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74897

MICROBIOLOGY REVIEW(S)

OFFICE OF GENERIC DRUGS, HFD640

Microbiologists Review #4

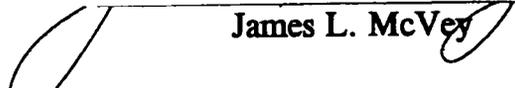
February 6, 1998

- A. 1. **ANDA:** 74-897
APPLICANT: Apothecon Inc.
A Bristol-Myers Squibb Company
Attn. Russell P. Wesdyk
P.O. Box 4500
Princeton, NJ 08543-4500
2. **PRODUCT NAMES:** Acyclovir Sodium for Injection
3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Sterile powder, 500 mg in a 10 mL vial and 1000 mg in a 20 mL vial. For Intravenous Infusion only. Rehydrated with Sterile Water for Injection, 10 mL into the 500 mg vial and 20 mL into the 1000 mg vial. Dilute to 7 mg/mL or lower prior to infusion.
4. **METHOD(S) OF STERILIZATION:**
5. **PHARMACOLOGICAL CATEGORY:** antiviral
- B. 1. **DATE OF INITIAL SUBMISSION:**
May 2, 1996 - Refused to File May 31, 1996
Accepted - June 25, 1996.
2. **DATE OF AMENDMENT:** June 19, 1996.
February 6, 1997.
September 23, 1997
January 29, 1998 - **Subject of this Review**
3. **RELATED DOCUMENTS:**
Submitted November 4, 1992 as a complete replacement.
Complete Revision dated October 19, 1995
Amendment dated May 14, 1997. - Separated from ANDA and sent in

Amendment dated September 22, 1997 - separately reviewed October 2, 1997. Letter sent dated October 11, 1997. One question is outstanding.
Amendment dated December 2, 1997 - information provided found sufficient in Microbiologists review dated December 11, 1997.
4. **ASSIGNED FOR REVIEW:** February 6, 1998.

C. REMARKS: Patent expires April 22, 1997 with no exclusivity. Referenced was reviewed with respect to

D. CONCLUSIONS: The submission is recommend for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes".


James L. McVey

6-98

2/10/98

initialed by F. Fang or F. Holcombe

cc:

Original ANDA
Field Copy
drafted by: J. McVey

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER **74897** _____

BIOEQUIVALENCE REVIEW(S)

SEP 25 1996

Acyclovir Sodium for Injection
500 mg/vial
1 gram/vial
NDA #: 74-897
Reviewer: J. Lee
74897W.496

Apothecon Inc.
Princeton, N.J.
Submission date:
April 30, 1996
May 31, 1996 (refuse to file)
June 25, 1996 (accept for filing)

Review of Two Requests for Waiver

The sponsor has filed an application for acyclovir sodium for injection, 500 mg/vial & 1 gram/vial and is requesting waivers from in-vivo requirements under 21 CFR 320.22 (b)(1). The company claims that their test product contains the identical active and inactive ingredients as currently approved for Zovirax Sterile Powder, the reference listed drug.

The sponsor has provided a comparison between their drug product vs the reference listed drug with respect to conditions of use, active ingredient, dosage form, route of administration, and strengths.

Both drug products are lyophilized products and, when reconstituted, are intended solely for IV infusion.

	<u>Apothecon</u> mg/vial	<u>Zovirax</u> mg/vial
Acyclovir	500	500
NaOH	adj. pH	adj. pH
Acyclovir	1000	1000
NaOH	adj. pH	adj. pH

* NaOH is used both to convert acyclovir to acyclovir sodium and to adjust pH before lyophilization.

Recommendation:

1. The Division of Bioequivalence agrees that the information submitted by Apothecon demonstrates that acyclovir sodium for injection 500 mg/vial and 1 gram/vial fall under 21 CFR 320.22 (b)(1) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. The sponsor's test products are deemed bioequivalent to the corresponding strengths of Zovirax® Sterile Powder, manufactured by Burroughs Wellcome.

9/25/96

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

9/25/96

Concur: _____

Date: _____

9/25/96

Keith Chan, Ph.D.
Director, Division of Bioequivalence

JLee/jl/ 09-12-96

cc: NDA #74-897 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File,
Division File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER **74897** _____

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 74-897

DRUG PRODUCT: Acyclovir Sodium for Injection

FIRM: Apothecon, Inc.

DOSAGE FORM: Sterile Powder/IV **STRENGTHS:** 500 mg/vial; 1 g/vial

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certification provided on page 129 (4/30/96 submission). EER found acceptable 4/21/97.

BIO STUDY: The bio study waiver request was granted by the Division of Bioequivalence on 9/25/96.

METHOD VALIDATION: Methods found suitable by the District on 9/23/97.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): The 3 month accelerated stability data and the 12 month room temperature stability data support the proposed 24 month expiration date for the product. Stability data generated on reconstituted and diluted product show the label claims are met. Containers used in the studies are identical to the proposed market containers.

LABELING: Found acceptable by A.Vezza on 10/30/97.

STERILIZATION VALIDATION (IF APPLICABLE): On the basis of sterility assurance, the application is ready for approval (See Micro Rev #4; 2/6/98).

SIZE OF BIO BATCH: N/A

SIZE OF STABILITY BATCHES: Approval is sought for multiple raw material sources. The firm has manufactured a batch of the proper size for each source. Batch 38341-038 consisted of and batch 38341-042 consisted of

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): Commercial batch sizes of are proposed. The manufacturing process described in the executed batch records is the same as that described in the blank production batch record.

CHEMIST: Susan Rosencrance
TEAM LEADER: U.V. Venkataram

DATE: 2/12/98
DATE: 2/12/98

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74897

CORRESPONDENCE

ANDA 74-897

Apothecon, Inc.
Attention: Russell P. Wesdyk
P.O. Box 4500
Princeton, NJ 08543-4500

MAY 31 1996

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated May 2, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Sodium for Injection, 500 mg/vial and 1 g/vial.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

Although you have provided a statement that your proposed product contains the same inactive ingredients as the reference listed drug, you have failed to provide information to demonstrate that the proposed product is qualitatively and quantitatively the same as the reference listed drug product. Please provide a side-by-side comparison of your formulation with formulation of the reference listed drug which contains information to demonstrate that all inactive ingredients are qualitatively and quantitatively the same. In addition, if any qualitative or quantitative differences do exist between your proposed drug product and the reference listed drug, you must provide information to demonstrate these differences do not affect the safety of the proposed drug product [21 CFR 314.94(a)(9)(iii)].

Certain inactive ingredients for parenteral drug products may vary from the reference listed drug such as preservative, buffer, antioxidant, or substances to adjust pH. However, you must provide information demonstrating that the presence of a new inactive ingredient does not affect the safety of the proposed drug product [21 CFR 314.94(a)(9)(iii)]. This information to demonstrate safety should include, but is not limited to: (a) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients, and that are within the same concentration range, (b) a

description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (c) a comparison of the physical and chemical properties (e.g. pH, osmolarity, tonicity) of the proposed drug product with that of the reference listed drug, and (d) information to show that the inactive ingredients do not adversely affect these properties. Please refer to the Office of Generic Drugs' Interim Inactive Ingredients Policy, dated November 17, 1994.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Also, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Harvey Greenberg
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

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

APOTHECON

P.O. Box 4500 Princeton, NJ 08543

6/17/96
2000

June 7, 1996

RECEIVED

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ANDA ORIG AMENDMENT

N/A/C

JUN 12 1996

GENERIC DRUGS

**Re: Acyclovir Sodium For Injection
ANDA 74-897
5/31/96 Refusal To File Letter (Received 6/7/96)**

Mr. Sporn:

In response to a Refusal To File Letter received this date, and pursuant to 21 CFR 314.96, Apothecon® Inc. respectfully submits this amendment to ANDA 74-897 for Acyclovir Sodium for Injection.

The letter notes that our ANDA was refused for filing solely because, "although you have provided a statement that your proposed product contains the same inactive ingredients as the referenced drug, you have failed to provide information to demonstrate that the proposed product is qualitatively and quantitatively the same as the reference listed drug product. Please provide a side-by-side comparison of your formulation with the formulation of the reference listed drug product."

Please note that neither the innovator's (per the package insert), nor our product contain any inactive ingredients. We provided a side-by-side comparison, noting the active ingredient was the same; the labeling and other text provided clearly notes the lack of a "formulation." Our filing is now amended, with the attached replacement page (replacing page 20) to note in the side-by-side comparison, in addition to the text, that there are no inactive ingredients in either the innovator's or our own Acyclovir Sodium for Injection products.

We are concerned that the CSO was prevented from calling us to resolve this minor detail, thus significantly delaying our filing date and review. If there is anything that the Apothecon organization can do to more easily resolve such matters in the future we re-emphasize our desire to avail ourselves to such options. We further request that due to the minor and debatable nature of the sole issue cited, the Agency reconsider the basis of the May 31, 1996 Refusal to File Letter, accept our original application and place it in queue as of the Agency's receipt date. We do not agree that the application "is not sufficiently complete to merit a critical technical review."



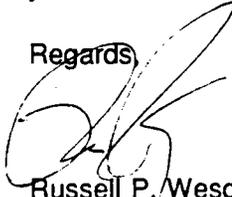
A Bristol-Myers Squibb Company

In addition to the sole matter above, for which our ANDA was refused for filing, we would like to take this opportunity to amend ANDA 74-897 as follows.

1. A DMF reference cover letter is added to clarify structure. This cover letter is numbered for insertion into our ANDA as page 108A and 621A.
2. In keeping with recent agency requests, we are also providing three separate bound copies of the analytics section of our ANDA 74-897.

We trust that you will find this application complete. However, should questions arise during review, please do not hesitate to call me directly (609-897-2407) or to fax your comments (609-897-6005). Apothecon will provide timely responses.

Regards,



Russell P. Wesdyk
Manager, Regulatory Operations

Copy To: FDA Regional Field Office

IV. Comparison Between Generic Drug and Reference Listed Drug

	Burroughs Wellcome Co. Zovirax Sterile Powder®	Apothecon Acyclovir Sodium for Injection (Subject of ANDA)
<i>Conditions of Use</i>	Initial and recurrent mucosal and cutaneous Herpes simplex and varicella-zoster infections in immunocompromised patients. Herpes simplex encephalitis in patients over 6 months of age. Severe initial clinical episodes of herpes genitalis in patients who are not immunocompromised.	Initial and recurrent mucosal and cutaneous Herpes simplex and varicella-zoster infections in immunocompromised patients. Herpes simplex encephalitis in patients over 6 months of age. Severe initial clinical episodes of herpes genitalis in patients who are not immunocompromised.
<i>Active Ingredient</i>	Acyclovir Sodium 549mg* 1098mg*	Acyclovir Sodium 549mg* 1098mg*
	* Label claim is 500 or 1000 mg of acyclovir which is equivalent to 549 or 1098 mg acyclovir sodium. Per the innovator's insert (section V.A.2.), "each 5.49 mg of sterile lyophilized acyclovir sodium is equivalent to 5 mg acyclovir."	
<i>Inactive Ingredient</i>	None*	None
	* based on review of labeling (see Innovator's insert: section V.A.2.)	
<i>Dosage Form</i>	Injection	Injection
<i>Route of Administration</i>	Intravenous	Intravenous
<i>Strengths</i>	500 mg, 1000 mg	500 mg, 1000 mg
<i>Bioequivalency Data</i>	Refer to Section VI for Request for Waiver of <i>In vivo</i> Studies	
<i>Labeling</i>	Refer to Section V of ANDA.	

ANDA 74-897

Apothecon, Inc.
Attention: Russell P. Wesdyk
P.O. Box 4500
Princeton, NJ 08543-4500

JUL 3 1996

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated May 31, 1996, and your amendment dated June 7, 1996.

NAME OF DRUG: Acyclovir Sodium for Injection, 500 mg/vial and 1 g/vial

DATE OF APPLICATION: May 2, 1996

DATE OF RECEIPT: May 2, 1996

DATE ACCEPTABLE FOR FILING: June 25, 1996

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 594-0305

Sincerely yours,

7/3/96

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

NDA ORIG AMENDMENT

NIAL

APOTHECON

P.O. Box 4500 Princeton, NJ 08543-4500 609 897-2000

June 19, 1996

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RECEIVED

JUN 25 1996

GENERIC DRUGS

**Re: Acyclovir Sodium For Injection
ANDA 74-897
6/19/96 FDA Initiated Telephone Conversation**

Mr. Sporn:

In response to a telephone conversation with Mr. Harvey Greenberg, CSO, this date, and pursuant to 21 CFR 314.96, Apothecon® Inc. respectfully submits this amendment to ANDA 74-897 for Acyclovir Sodium for Injection. The phone conversation discussed our filing's presentation of components and composition statements relative to inactive ingredients in the final product. It was requested that we modify our filing with respect to this issue and we hereby do so comply with that request, supplying the attached replacement pages.

We note that our amendment of June 7, 1996, responding to a May 31, 1996 Refusal To File Letter, and this amendment, responding to the telephone conversation of this date, do not alter the content of our filing, but rather the manner and format in which information is presented. The May 31st RTF letter requested a side-by-side comparison of formulations, listing inactive ingredients of which there are none. We further note our telephone discussion with the Agency on June 7, 1996 in which we requested and received specific instruction regarding how to amend our filing to respond to the agency's May 31st RTF letter. As we followed the agency's direction exactly, we were surprised by the June 19 phone call requesting further changes.

We emphasize that throughout these discussions there has been no changes to the basic information presented in the filing. Per the Agency's request we have added to the comparative table "None" for "Inactive Ingredients," information that already existed in the text of the filing. At the Agency's request we have also reformatted our components and composition statements relating to the conversion of Acyclovir Acid to the Sodium Salt using Sodium Hydroxide. Please note that this does not represent a change in content, only reformatting of information already present in the filing. We restate our request that the Agency reconsider the basis of the May 31, 1996 Refusal to File Letter and the June 19, 1996 telephone conversation, and place our original application in queue as of the Agency's original receipt date. We do not agree that the application "is not sufficiently complete to merit a critical technical review." We respectfully suggest that, in fact, the modifications requested to our filing are part of a "critical technical review" and not those of content for acceptance of the filing.



A Bristol-Myers Squibb Company

Thank you for your consideration of the above stated request.

We trust that you will find this application complete. However, should questions arise during review, please do not hesitate to call me directly (609-897-2407) or to fax your comments (609-897-6005). Apothecon will provide timely responses.

Regards,



Russell P. Wesdyk
Manager, Regulatory Operations

Enclosed: Review Copy
 Archive Copy

Copy To: FDA Regional Field Office
 H. Greenberg (desk copy)

APOTHECON

P.O. Box 4500 Princeton, NJ 08543-4500 609 897-2000

February 6, 1997

MAJOR AMENDMENT

Frank O. Holcombe Jr., Ph.D..
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Rm 150
Rockville, MD 20855-2773

AL
NDA ORIG AMENDMENT
AL

**Re: Acyclovir Sodium for Injection
500 mg/vial and 1 g/vial
Response to Deficiency Letter dated 1/8/97
ANDA 74-897**

Dear Dr. Holcombe:

Please refer to our abbreviated new drug application dated April 30, 1996 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Sodium for Injection, 500 mg/vial and 1 g/vial and in particular, to the deficiency letter dated January 8, 1997.

The April 30, 1996 submission is the original filing for the above mentioned product. The Agency's deficiency letter of January 8, 1997 indicates the amendment be designated as a MAJOR AMENDMENT.

We have responded to all deficiencies listed. For ease of review, we have repeated each deficiency on a separate page, verbatim, in italics, followed by our response in plain type.

We have noticed instances in which the information requested by the Agency in the deficiency letter was supplied in the original filing (eg. Chemistry Deficiencies:

and We ask the Agency for advice on how we may better highlight those pieces of information submitted in the original filing to help the Agency in their review.

We trust we have answered all concerns to the satisfaction of the Agency and look forward to the approval of the submission. We have moved our location so should you have any further concerns, please contact me at 609-897-2461 or by fax at 609-897-5515.

Sincerely,
E. B. Cembor
Elaine B. Cembor
Associate Director
Regulatory Affairs

RECEIVED

FEB 10 1997

GENERIC DRUGS



A Bristol-Myers Squibb Company

0000002

ANDA 74-897

Apothecon, Inc.
A Bristol-Myers Squibb Co.
Attention: Russell P. Wesdyk
P.O. Box 4500
Princeton, NJ 08543-4500

JAN 8 1997



Dear Sir:

This is in reference to your abbreviated new drug application dated April 30, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Sodium for Injection, 500 mg/vial and 1 g/vial.

Reference is also made to your amendment dated June 7 and June 19, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

B. LABELING DEFICIENCIES

1. GENERAL COMMENTS:

- a. We acknowledge your comments regarding the established name for this product and request that you revise the established name to read, "Acyclovir for Injection". We refer you to USP 23 General Chapter<1>, Injections, Nomenclature and Definitions and the Pharmacopeial Forum, Volume 22, Number 4, which proposes "Acyclovir for Injection" as the established name of this product. Note that revision of the established name as above will make the "Equivalent to...", statement in the expression of strength unnecessary. Please revise your labels and labeling accordingly.
- b. Revise your storage recommendation to read, "Store between 15° and 25°C (59°and 77°F)".
- c. We note that sodium hydroxide has been used to adjust the pH of this product. Please include sodium hydroxide in your listings of inactive ingredients appearing on the labels and labeling of this product. We refer you to 21 CFR 201.100(a)(5)(iii).

2. CONTAINER (Equivalent to 500 mg and equivalent to 1 g acyclovir)

We encourage the use of boxing, contrasting colors, or other means to differentiate the strengths of your products.

3. CARTON (10's - Equivalent to 500 mg and 1 g acyclovir)

We note (HOW SUPPLIED section of your insert labeling) that your product will be packaged in cartons of 10s for each strength. Please prepare and submit carton labeling, taking note of the above GENERAL comments and the comment under CONTAINER.

4. INSERT

a. GENERAL

Use the abbreviation "mcg" rather than " μ g" throughout your insert labeling.

b. DESCRIPTION

- i. Revise the chemical name of acyclovir to be consistent with the second name appearing in the USP monograph for acyclovir and add "sodium" as follows, "...guanine sodium".
- ii. Include the molecular formula of acyclovir sodium.
- iii. Revise the first sentence of the last paragraph as follows, "...a white to off-white crystalline...".
- iv. We encourage the inclusion of a pH range when listing the pH of this product.
- v. Make the following revision in the penultimate sentence, "...see DOSAGE AND ADMINISTRATION, Method of Preparation)...".
- vi. Delete the word "daltons" where it appears in the last paragraph.
- vii. Revise the second sentence of the last paragraph as follows, "Each vial of acyclovir sodium for injection, containing the equivalent of 500 mg or 1000 mg of acyclovir, when...".

c. INDICATIONS AND USAGE

i. GENERAL

Replace "Vira A" with "adenine arabinoside" throughout this section.

- ii. Replace "acyclovir" with "injectable acyclovir" in the first lines of the Herpes Simplex Infections in Immunocompromised Patients and Varicella-Zoster Infections & Immunocompromised Patients subsections.

d. PRECAUTIONS (General)

Make the following revision in the penultimate sentence, "...patients.¹¹⁻¹⁹ The...".

e. ADVERSE REACTIONS (Observed During Clinical Practice)

Make the following revision in the first line, "...with intravenous acyclovir...".

f. DOSAGE AND ADMINISTRATION

- i. Revise the last sentence of the "CAUTION" statement to read:

For diagnosis - see INDICATIONS AND USAGE.

- ii. Dosage (Herpes Simplex Infections)

Make the following revision in the second line, "...**IMMUNOCOMPROMISED**...", (spelling).

- iii. Make the following revision in the second sentence of the last paragraph, "...administration...", (spelling).

- iv. Include the following text as the last paragraph of this section:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

g. HOW SUPPLIED

- i. Include the established name of your product in this section (see first GENERAL comment above).
- ii. See the second GENERAL comment above, regarding the storage conditions for this product.
- iii. We encourage the inclusion of the "CAUTION: Federal...", statement in this section.

h. REFERENCES

- i. We note that you have deleted reference #28 appearing in the labeling of the listed drug. Please retain this information in your labeling and make the appropriate adjustments to your reference numbering.
- ii. Make the following revision to reference #31, "vidarabine", (spelling).

Revise your container labels and package insert labeling as described above, then prepare and submit final printed (or printers proof) package insert labeling and final printed container labels and carton labeling. Please note that final printed insert labeling is not required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept final "printers proof" for the insert only.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon further 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.

C. Microbiological Deficiencies:

[Faint, illegible text visible on the right edge of the page, possibly bleed-through from the reverse side.]

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

Please provide updated stability data in your next amendment.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Lr *1/7/97*
Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

JUL 11 1997

ANDA/AADA: 74-807



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TO: APPLICANT, Apotheon, Inc. PHONE 609-897-2472
ATTN: Walter Jung FAX 609-897-6005 5515

FROM: Tim Ames, PROJECT MANAGER (301-~~570-0500~~) 827-5849

Dear Sir/Madam:

This facsimile is in reference to your abbreviated new drug/ antibiotic application dated 4/30/96, submitted pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for Acyclovir Sodium for Injection, 500mg and 1g.

Reference is also made to your amendment(s) dated 2/6/97.

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. ~~You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.~~ If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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A. Microbiology Deficiencies: - February 6, 1997 amendment.

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

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES".

Sincerely yours. . .



FRANK O. HOLCOMBE, JR., Ph.D.

Director

Division of Chemistry II

Office of Generic Drugs

Center for Drug Evaluation and Research

JUL 11 1997

1/

10/2/97

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

AADA: 74-897

APPLICANT: Apothecon, Inc.

DRUG PRODUCT: Acyclovir Sodium for Injection

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:

Sincerely yours,


Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTHECON

P.O. Box 4500 Princeton, NJ 08543-4500 609 897-2000

September 23, 1997

*AM noted
to ① Chemistry Review
- for ② labeling Review
for review. JBL
9/20/97*

ORIG AMENDMENT

N/AM

MINOR AMENDMENT

Mr. Tim Ames, R. Ph.
Consumer Safety Officer
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Md 20855-2773

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SEP 24 1997

GENERIC DRUGS

Re: **Acyclovir Sodium for Injection**
500mg/vial and 1g/vial
ANDA 74-897

Dear Mr. Ames:

Please refer to our abbreviated new drug application dated April 30, 1996 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Sodium for Injection, 500mg/vial and 1g/vial and, in particular, to the deficiency letter dated July 11, 1997.

The April 30, 1996 submission is the original filing for the above mentioned product. The Agency's deficiency letter of July 11, 1997 indicates the amendment be designated as a MINOR AMENDMENT. Additionally, the microbiology section, as indicated in the deficiency letter, has been clearly identified as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The other sections have also been appropriately entitled and clearly identified.

We have responded to all deficiencies listed. For ease of review, we have repeated each deficiency on a separate page, verbatim, in italics and underlined, followed by our response in plain type.

We trust we have answered all concerns to the satisfaction of the Agency and look forward to the approval of the submission. Should you have any further concerns, please contact me at 609-897-2461 or by fax at 609-897-5515.

Sincerely,



Elaine B. Cembor
Associate Director
Regulatory Operations



A Bristol-Myers Squibb Company

Handwritten signature

NOV 7 1997

UVJ

21

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

AADA: 74-897

APPLICANT: Apothecon, Inc.

DRUG PRODUCT: Acyclovir Sodium for Injection

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

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

Sincerely yours,

17

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and
Research

MINOR AMENDMENT

NOV 7 1997

ANDA: 74 897



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT Apothecon, Inc PHONE 609-897-2470
ATTN: Walter Jump, Ph.D. FAX 609-897-~~6005~~
5515

FROM: Timothy W. Ames, PROJECT MANAGER (301-827-5849)

Dear Sir/Madam: Walter,

This facsimile is in reference to your abbreviated new drug/ antibiotic application dated 4/30/97, submitted pursuant to Section 505(j)/507 of the Federal Food, Drug, and Cosmetic Act for Acyclovir Sodium for injection 500mg/1ml + 1g/ml.

Reference is also made to your amendment(s) dated September 23, October 9, and October 22, 1997

The application is deficient and, therefore not approvable under Section 505/507 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

It is OK to respond to this fax at some time as you respond (or provide notice of response to

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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APOTHECON

P.O. Box 4500 Princeton, NJ 08543-4500 609 897-2000

*NAI for 12/1/97 BM
Glen
12-0-97*

December 1, 1997

MINOR AMENDMENT

Dr. Frank Holcombe, Ph.D.
Director Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Room 150
Metro Park North II
7500 Standish Place
Rockville, Md 20855-2773

*Am noted
To Chemist for review
JCS 12/8/97
* note pending
micro deficiencies
11/17/97*

Re: **Acyclovir Sodium for Injection**
500mg/vial and 1g/vial
ANDA 74-897

Dear Dr. Holcombe:

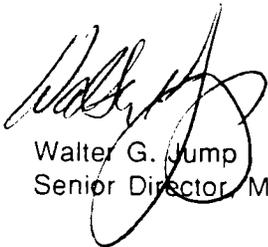
Please refer to our abbreviated new drug application dated April 30, 1996 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Sodium for Injection, 500mg/vial and 1g/vial and, in particular, to the deficiency letter of November 7, 1997.

The April 30, 1996 submission is the original filing for the above mentioned product.

Apothecon has responded to all deficiencies listed in the letter. As is designated in the deficiency letter, our amendment is being submitted concurrent with the DMF amendment and submission by our Worldwide Regulatory Affairs Group. For ease of review, we have repeated each deficiency, verbatim, in italics and underlined, followed by our response in plain type.

I trust we have answered all concerns to the satisfaction of the Agency and look forward to the approval of the submission. Should you have any further concerns, please contact Elaine Cembor at 609-897-2461 or by fax at 609-897-5515.

Sincerely,



Walter G. Jump
Senior Director, Medical and Regulatory Operations

RECEIVED
DEC 02 1997
GENERIC DRUGS



P.O. Box 4500 Princeton, NJ 08543-4500 609 897-2000

January 29, 1998

MINOR TELEPHONE AMENDMENT

Mr. Mark Anderson
Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Room 150
Metro Park North II
7500 Standish Place
Rockville, Md 20855-2773

ORIG AMENDMENT

N/AM

**Re: Acyclovir Sodium for Injection
500mg/vial and 1g/vial
ANDA 74-897**

Dear Mr. Anderson:

Please refer to our abbreviated new drug application dated April 30, 1996 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Sodium for Injection, 500mg/vial and 1g/vial, to the deficiency letter of December 29, 1997 and to the teleconference held on January 26, 1998 with Bristol-Myers Squibb Quality Assurance, Apothecon Regulatory and FDA OGD personnel.

The April 30, 1996 submission is the original filing for the above mentioned product.

Apothecon has responded to all deficiencies listed in the letter. As is stated in the deficiency letter, our amendment is designated as a Minor Telephone Amendment. As requested, we faxed a copy of our response to the Agency followed by hardcopy. For ease of review, we have repeated each deficiency, verbatim, in italics and underlined, followed by our response in plain type.

I trust we have answered all concerns to the satisfaction of the Agency and look forward to the approval of the submission. Should you have any further concerns, please contact me at 609-897-2461 or by fax at 609-897-5515.

Sincerely,

Elaine Cembor
Elaine Cembor
Associate Director
Regulatory Affairs

RECEIVED

JAN 30 1998

GENERIC DRUGS



*Madison
2/4/98*