CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74914

CORRESPONDENCE

ANDA 74-914 -

Copley Pharmaceutical Inc.
Attention: William E. Brochu, Ph.D.
25 John Road
Canton, MA 02021

DEC 17 1996

Dear Dr. Brochu:

This is in reference to your abbreviated new drug application dated, June 18, 1996 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Capsules 200 mg.

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

Chemistry Deficiencies:

1. Organic Volatile Impurities and Sulfur Dioxide test results were not submitted for Corn Starch NF. Please submit.

2. Sodium Starch Glycollate NF is listed as a component but does not appear in the composition statement (Refer to pp. 2655 & 2656). Please clarify.

3. Please describe in more detail the cap liner used. The information submitted appears to be for the inner safety seal.

4. Please revise the statement on p. 2791 regarding the submission of a Changes Being Effected supplement for the deletion of testing. Please see 21 CFR 314.70 (b)2(v).

5. In regard to the amounts of total related substances found at release testing we feel that the specification of NMT % is too high. Please revise or support with data.

6. Please submit a copy of the method for moisture determination in the finished drug product. Supporting data and documentation should also be submitted.

7. In regard to the stability testing, we have the following comments:

   a. Based on the amounts of guanine and total related substances found during accelerated stability testing, we feel the limits of [redacted] for each are too high. Please revise or support with data.

   b. Specifications should be established for individual related substances and identification should be made where known impurities exist (Refer to p. 2898).

   c. If 25°C - 30°C is used as the room temperature conditions, the humidity conditions should be monitored and reported. Please revise your stability protocol to reflect the changes.

Labeling Deficiencies:

1. CONTAINER: 100s

   Satisfactory in draft.

2. INSERT:

   a. General Comments

      i. When abbreviating micrograms we encourage you to use the abbreviation "mcg" rather than "μg". Please revise your insert labeling accordingly.

      ii. Throughout your labeling print *"in vitro"* and *"in vivo"* in italic print.

      iii. Print "Acyclovir" and "Acyclovir Capsules" in lower case letters, except when it appears at the beginning of a sentence. Please revise accordingly throughout the text of the insert.

   b. DESCRIPTION

      i. Include the molecular formula of acyclovir, $C_8H_{11}N_5O_3$.

      ii. Please note there are now two official USP 23/NF 18 monographs for lactose. Please revise accordingly.

      iii. We note you have listed "sodium starch glycolate" in your Component Statement.

However, it is not listed in the Composition Statement nor in this section. Please comment and/or revise.

iv. Include the dyes in the imprinting ink in the list of inactive ingredients.

v. To be in accord with USP 23/NF 18, make the following revisions in the last paragraph:

...a white to off-white crystalline powder with a molecular weight of 225.21, and ...

c. CLINICAL PHARMACOLOGY (Pharmacokinetics) -

Delete the third paragraph, "A single ... solution".

d. INDICATIONS AND USAGE

i. Genital Herpes Infection (Recurrent Episodes)

Revise the fourth paragraph to read as follows:

... for short periods (see PRECAUTIONS: ...

ii. Chickenpox

In the second paragraph, replace the period with a comma following the words "studies" and "rash".

e. CONTRAINDICATIONS

... of the formulation. [singular]

f. PRECAUTIONS

Pediatric Use

... in pediatric patients less ...

g. DOSAGE AND ADMINISTRATION

Treatment of Chickenpox

Revise this subsection to read as follows:

Children (2 years of age and older): 20 mg/kg **per dose** orally four times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and children over 40 kg: 800 mg four times daily for 5 days.

Therapy should be initiated at the earliest sign or symptom of chickenpox to derive the maximal benefits of therapy.

h. HOW SUPPLIED

i. We note the description of your finished dosage form in the Finished Product Specifications is not consistent with the description of your drug product in this section, (i.e., "Copley 299, Acyclovir 200" verses "Copley Acyclovir 200"). Please comment and/or revise.

ii. Add a "semicolon" following the text "... Acyclovir 200".

i. REFERENCES

i. Reference 4 -

...by 9-(2-...
[Add hyphen after "9"].

ii. Reference 6 -

... acyclovir. *Antimicrob Agents Chemother*. ...

iii. Reference 21 -

...acyclovir. *J Gen Virol*...

iv. Reference 31, revise as follows:

31. Goldberg LH, Kaufman R, Conant MA, et al.Episodic twice daily treatment for recurrent genital herpes. *Am J Med*. 1988; 85:10-13.

v. Reference 38, revise as follows:

38. Rotbart HA, Levin MJ, Hayward AR, Immune responses to varicella zoster virus infections in healthy children. *J Infect Dis*. 1993;167:195-199.

Revise your package insert labeling as described above, then prepare and submit final printed (or printers proof) package insert labeling and final printed container labels. 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 "printers proof" for the insert only for tentative approval of an application.

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.

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. You have been notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 12/16/96

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

ANDA 74-914

Copley Pharmaceutical, Inc.
Attention: William Brochu, Ph.D.
Canton Commerce Center
25 John Road
Canton, MA 02021

AUG 9 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.

NAME OF DRUG: Acyclovir Capsules, 200 mg

DATE OF APPLICATION: June 18, 1996

DATE OF RECEIPT: June 19, 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,

/S/ 8/9/96

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

ANDA 74-914

SEP 25 1996

Copley Pharmaceutical Inc.
Attention: W. E. Brochu
Canton Commerce Center
25 John Road
Canton, MA 02021

Dear Dr. Brochu:

Reference is made to the Abbreviated New Drug Application, submitted on June 18, 1996 for Acyclovir Capsules, 200 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

We advise dissolution testing using the method in the *USP Pharmacopeial Forum*, Volume 22, Number 4, July-August, 1996:

Medium:	900 mL of water
Apparatus:	I (basket) at 100 rpm

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP 29 1997

ANDA 74-914

Copley Pharmaceutical Inc.
Attention: W. E. Brochu
Canton Commerce Center
25 John Road
Canton, MA 02021

Dear Dr. Brochu:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Capsules 200 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs. The dissolution testing should be conducted in 900 mL of water using USP 23 apparatus I (basket) at 100 rpm. The test product should meet the following specification:

   NLT ( )% of labeled amount of the drug in the dosage form is dissolved in 30 minutes

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

May 2, 1997

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER(HFD 600)
Food and Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

Telephone Amendment
Acyclovir Capsules 200 mg
ANDA 74-914

Dear Sir

Reference is made to our above Abbreviated New Drug Application and telephone conversation with Dr. Jacqueline White, FDA, on April 15, 1997.

In our telephone conversation Dr. White advised us that due to a change in the innovator labeling, we should implement additional adverse event information into our package insert labeling. Dr. White inform that in the "Adverse Reaction" section in "Nervous" subsection word "seizure" after "paresthesia" should be added, and we can submit this change as a telephone amendment.

Accordingly, we have revised our insert labeling and have enclosed 12 final printed copies.

Should you have any questions or concerns regarding this amendment, please feel free to contact me at the numbers given below.

Sincerely,

W.E.Brochu, Ph.D.
Director, Regulatory Affairs
617-575-7520 phone, 617-575-7362 fax

RECEIVED
MAY 08 1997
GENERIC DRUGS

AMENDMENT

NAC

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

February 14, 1997

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

MAJOR AMENDMENT
Response to Deficiency Letters of 12/17/96 and 9/25/96
Acyclovir Capsules, 200 mg
ANDA # 74-914

Dear Sir:

Reference is made to our above Abbreviated New Drug Application and to the Agency's Deficiency letters of 12/17/96 from the Division of Chemistry II and 9/25/96 from Division of Bioequivalence.

Bio LETTER

Enclosed are full responses to the questions provided in the deficiency letters of 12/17/96 and 9/25/96, 12 copies of final printed labeling which reflects the requested labeling revisions, and a revised batch record that list the proposed equipment per FDA pre-approval inspection on 10/10/96.

To our knowledge, there are no further outstanding issues related to this application.

We believe we have fulfilled the Agency's requests presented in its deficiency letters of 12/17/96 and 9/25/96. We look forward to an expeditious approval of this product. Please direct any questions related to this submission to me. Thank you.

Sincerely,

William E. Brochu, Ph.D.
Director, Regulatory Affairs
Tel: (617) 575-7520

Enclosures:
Archive Copy (blue folder): 1 copy
Chemistry, Manufacturing, Controls Copy (red folder): 1 copy
Bioequivalence Copy (orange folder): 1 copy

RECEIVED
FEB 18 1997
GENERIC DRUGS

Labels + Labeling satisfactory for approval
Labeling review drafted
11/4/97 A Vega

Copley Pharmaceutical Inc.
25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

FPL

NDA, DRUG AMENDMENT
N/AF

10/29/97

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Response to Labeling Deficiency Letter of 8/14/97
Acyclovir Capsules, 200 mg
ANDA 74-914

Dear Mr. Sporn:

Reference is made to our ANDA# 74-914 and Agency's labeling deficiency letter of 8/14/97. Attached are 12 copies of final printed insert labeling which incorporates the revisions requested by the Agency and the most current brand product labeling approved on 5/29/97. A side-by side comparison of brand labeling vs. our proposed insert labeling is enclosed to facilitate review of the above changes.
Please contact me if any additional information you may require (direct dial: 781-575-7520, FAX: 781-575-7362).

Sincerely

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

File ANDA 74-914

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

8/11/97

Mr. Timothy Ames
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Acyclovir Capsules
ANDA# 74-914
Controlled Correspondence - Dissolution Method

Dear Mr. Ames:

Reference is made to our ANDA #74-91, our major amendment of 2/14/97, and to telephone conversations with Mr. Donald Shostak on 7/18/97 and 8/8/97. The attached is a revision to our communication dated 8/8/97 with the additional modification of the dissolution specification from NLT [redacted] %(Q) at 30 minutes to NLT [redacted] %(Q) at 30 minutes. The dissolution conditions remain the same: paddles at 100 rpm and 0.1N HCl media. We will submit an amendment to our application to include these changes in our finished product specifications and stability testing commitment.

We trust this trust this is consistent with the Agency's expectations and requirements. Please advise if there are any questions or comments.

Sincerely,

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

cc: Mr. David Shostak

File ANDA 74-914

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

8/8/97

Mr. Timothy Ames
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Acyclovir Capsules
ANDA# 74-914
Controlled Correspondence - Dissolution Method

Dear Mr. Ames:

Reference is made to our ANDA #74-91, our major amendment of 2/14/97, and to a telephone conversation with Mr. Donald Shostak on 7/18/97. The attached reflects Copley's understanding of the Agency's expectation for a dissolution method and specification for Acyclovir Capsules and Copley's choice of method among the two (2) methods that were submitted.

Mr. Shostak advised that both the original dissolution method and specification included in our ANDA as well as that included in our major amendment of 2/14/97 would be acceptable to the Agency. The method included in our amendment was in response to a comment made to us by the Bioequivalence Division that Mr. Shostak indicated had apparently been overstated and misinterpreted. Mr. Shostak asked that since either method was acceptable, that Copley pick among the two methods and advise the Agency of the choice. The only other requirement he added is that whatever method is selected that the specification be NLT % dissolved in 30 minutes. Our interpretation of that requirement is as stated in the attached, i.e. "Not less that % (Q) of the labeled quantity of $C_8H_{11}N_5O_2$ is dissolved in 30 minutes. This translates to NLT % dissolved in 30 minutes as requested.

We trust this trust this is consistent with the Agency's expectations and requirements. Please advise if there are any questions or comments.

Sincerely,

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

cc: Mr. David Shostak

RECEIVED
NOV 26 1997
GENERIC DRUGS

Copley Pharmaceutical Inc.
25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

June 18, 1996

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Acyclovir Capsules 200mg
ANDA Submission

Dear Mr. Sporn:

Pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, Copley Pharmaceutical, Inc. respectfully submits for your Division's review and approval our Abbreviated New Drug Application (ANDA) for Acyclovir Capsules 200 mg. Copley's Acyclovir Capsules 200 mg (reference product) is the same as Burroughs Wellcome's ZOVIRAX® Capsules 200 mg, NDA 18-828 (listed product), with regard to active ingredient, dosage form, strength, route of administration and conditions for use. It is our intent to market this product following approval of this application and upon expiration of patent 4,199,574 (April 22, 1997) which claims the listed drug. Section III of this application contains the required patent certification and exclusivity statement pertaining to the listed drug.

In support of this filing, Copley has manufactured a biobatch of Acyclovir Capsules, 200 mg (Lot 299Z01) which was used to conduct our bioequivalence studies (fed and Fasted) contained in Section VI of this application. As with our biobatch, our scale-up batch sizes (capsules) will be manufactured at our facility located at 25 John Road, Canton, MA 02021. Our bulk active drug, Acyclovir USP, is supplied by (DMF

This application is submitted in accordance with the guidelines set forth in 21 CFR 314.94 and OGD's Policy and Procedure Guide 30-91. The application consists of seven (7) volumes which is provided to the Agency in a "blue folder" for FDA's archival files, a "red folder" for the chemistry review (volumes 1-2), and

an "orange folder" (containg relevant chem/pharm data and the bioequivalence studies) for the bioequivalence review (volumes 3-7). Also provided are two copies of the methods validation section of this application to support FDA's analytical testing of our product.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are (617) 575-7520 (direct dial) and (617) 575-7362 (fax).

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to our District FDA Office.

Thank you for your prompt handling of this submission.

Sincerely,

William E. Brochu, Ph.D.
Director, Regulatory Affairs

Enclosures:

Archive Copy (blue folder): 7 volumes
Bioequivalence Copy (orange folder): 5 volumes
Chemistry, Manufacturing, Controls Copy (red folder): 2 volumes
Methods Validation (2 copies, separate binders)