

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75101

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 75-101 Date of Submission: March 28, 1997

Applicant's Name: Chelsea Laboratories, Inc.

Established Name: Acyclovir Capsules, 200 mg

Labeling Deficiencies:

1. CONTAINER 100s, 500s, 1000s
 - a. We encourage you to differentiate your container labels from those for your acyclovir tablet application (ANDA 74-938).
 - b. Delete "Controlled Room Temperature".
2. INSERT
 - a. GENERAL COMMENTS
 - i. Revise your insert labeling to be in accord with the enclosed copy of the insert labeling of the reference listed drug, Zovirax® (Glaxo Wellcome Inc.; revised March 1997 and approved May 29, 1997).

Note: The following comments, except those for the HOW SUPPLIED section, refer to the enclosed insert labeling of the reference listed drug.
 - ii. Italicize "in vitro" and "in vivo" throughout the text of the insert.
 - b. DESCRIPTION

Revise the molecular weight to be 225.21 per USP 23.
 - c. PRECAUTIONS
 - i. Include the entire paragraph beginning "There are no adequate ... and ending ...risk to the

fetus. As the second paragraph of the **Pregnancy: Teratogenic Effects:** Pregnancy Category B subsection.

- ii. Delete the subsection entitled "**Pregnancy Exposure Registry**".

d. **DOSAGE AND ADMINISTRATION**

- i. **Treatment of Chickenpox: (Adults and Children over 40 kg)**, Retain as the second paragraph -

Intravenous acyclovir is indicated for the treatment of varicella zoster infections in immunocompromised patients.

- ii. **Bioequivalence of Dosage Forms** - Retain the entire paragraph "Acyclovir suspension was shown to be ... capsules (n=24)".

e. **HOW SUPPLIED**

- i. See comment b under CONTAINER.
- ii. We note that Chelsea Laboratories is listed as the manufacturer yet on page 329 of this submission Hoechst Marion Roussel, Inc. is listed as the manufacturer. Please comment and/or revise.

Please revise your container labels and insert labeling, as instructed above, and submit final printed container labels and draft 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.



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

Enclosure: Insert labeling of the reference listed drug

ANDA APPROVAL SUMMARY

ANDA: 75-101

DRUG PRODUCT: Acyclovir Capsules

FIRM: Chelsea Laboratories, Inc.

DOSAGE FORM: Capsules **STRENGTH:** 200 mg

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certifications and debarment statements provided. EER found acceptable 5/30/97.

BIO STUDY: The bio study was found acceptable by the Division of Bioequivalence on 2/17/98.

METHOD VALIDATION: Methods found suitable by the District on 11/6/97.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): The 3 month accelerated stability data and the 18 month room temperature stability data support the proposed 24 month expiration date for the product. Containers used in the studies are identical to the proposed market containers.

LABELING: Found acceptable by the Division of Labeling on 1/7/98.

STERILIZATION VALIDATION (IF APPLICABLE): Not Applicable

SIZE OF BIO BATCH: The bio batch (R57720) consisted of capsules (approximately

SIZE OF STABILITY BATCHES: The bio batch (R57720) was also used in generating stability data.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The proposed commercial batch size is also capsules (approximately The manufacturing process described in the executed batch record is the same as that described in the production batch record.

CHEMIST: Susan Rosencrance

DATE: 3/11/98

TEAM LEADER: John Harrison

DATE: 3/11/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75101

CORRESPONDENCE

21
inclusion

BIOEQUIVALENCY COMMENTS

NDA:75-101

APPLICANT: Chelsea Laboratories Inc.

DRUG PRODUCT: Acyclovir Capsule, 200 mg

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

Please acknowledge that the following dissolution testing specifications have been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of Deaerated water, at 37°C using USP Apparatus (I), basket at 100 rpm. The test product should meet the following specifications:

Not less than .Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please refer to the acceptance table in the USP for the acceptance criteria.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



CHELSEA LABORATORIES, INC.
Regulatory Affairs Department



P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

Mail No. 98-029

March 5, 1998

Dale Conner, Pharm D.
Director, Division of Bioequivalence
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

BIOAVAILABILITY

ORIG AMENDMENT

10/13

**RE: Acyclovir Capsules 200 mg
ANDA 75-101
Bioequivalence and Chemistry - Minor Telephone Amendment**

Dear Dr. Conner,

This is in response to the FDA facsimile deficiency letter dated February 18, 1998 for the above mentioned ANDA. For ease of review, your comments are in bold text followed by our response.

Please acknowledge that the following dissolution testing specifications have been incorporated into your stability and quality programs:

The dissolution testing should be conducted in 900 mL of Deaerated water, at 37°C using USP Apparatus (I), basket at 100 rpm. The test product should meet the following specifications:

Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please refer to the acceptance table in the USP for the acceptance criteria.

The following testing specifications have been incorporated into our stability and quality control program as directed by the bioequivalence division of OGD. Using the FDA requested dissolution system, the release specification has been revised to Not Less Than (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes. Please see **Attachment 1** for Stability Data and Comparative Dissolution Results.

RECEIVED

MAR 06 1998

GENERIC DRUGS

000001

As can be seen from the summaries in Attachment 1, all the data submitted in the application meet the original specification of "Not Less Than (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes." In addition, all stability data (i.e. accelerated and controlled room temperature) for the 100 count container/closure system meets the revised specification of NLT (Q). Therefore, we are providing only new 18 month CRT data. The next test station (24 months) for this container/closure system will be provided when the date is available.

Unlike the 100 count container/closure system data, the data for the 1000 count container/closure system has two (2) capsule data points (88.9%, 89.1%) at the 18 month controlled room temperature sample (30 minutes), which meet the original specification but, do not meet the newly proposed specification for individual values ($Q + 5\%$ i.e. unless samples are tested at the S2 level. Samples were tested at 21 months (CRT 28°C) and meet the newly proposed requirement at the S2 level. Similarly, the 3 month accelerated (40°C/75%RH) samples for the 1000 count container/closure also meet the newly proposed requirement (See page 000011). Unfortunately, one capsule value at 2 months accelerated conditions (30 minute time point) will not meet the newly proposed specification unless additional samples are tested at the S3 level. Since this sample has aged (2 months at accelerated conditions and 19 months at controlled room temperature) and as the 2 month data has been superceded by the 3 month accelerated condition acceptable data, retest at this point in time would be inappropriate.

The individual stability data points for initial, 1, 2 and 3 month accelerated samples (1000 count) and the initial, 3, 6, 9, 12, 18 and 21 month (1000 count) controlled room temperature sample at the 30 minute time point are provided on page 000012. All stability data presented in the application was performed on hard gelatin capsules without the use of enzymes (pepsin and pancreatin) in the dissolution medium.

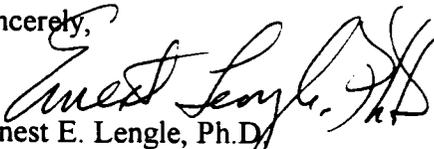
In the Twentieth Interim Revisions Announcement (Pharmacopeial Forum Volume 23 #6 - Effective date 12/1/97, <711> Dissolution, see Attachment 2), the use of enzymes (pepsin and pancreatin) in the dissolution medium is now permissible for hard gelatin capsules that do not conform to the dissolution specification. If future production batch samples do not meet release specifications, the sample will be retested according to the recommendations in the Announcement.

Additionally, Pre-Approval Stability Specifications and Test Methods (see Attachment 3); Certificate of Analysis and Finished Product Specifications and Test Methods (see Attachment 4) and the Commercial Stability Protocol (see Attachment 5) have been revised and are provided in this amendment. Chelsea also notes that the bioequivalency comments provided in this communication are preliminary and are subject to revision after review of the entire application.

This 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 manufacturing facility's district office (Cincinnati). This "Field Copy" was contained in burgundy binders.

We believe that all comments made by the FDA have been addressed. If there are any questions regarding this response, please call me at (513) 948-3149.

Sincerely,



Ernest E. Lingle, Ph.D.
Director, Regulatory Affairs

000003



CHELSEA LABORATORIES, INC.
Regulatory Affairs Department



P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

Mail No. 97-220

December 3, 1997

*PI's subject
for approval - Review
revised - drafted 11/6/98
so*

Frank O. Holcombe, Jr. Ph.D.
Director, Division of Chemistry II
HFD-621, Room 204, Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**RE: Acyclovir Capsules 200 mg
ANDA 75-101
Minor Amendment**

Dear Dr. Holcombe,

This is in response to the FDA deficiency letter dated November 12, 1997 for the above mentioned ANDA. For ease of review, your comments are in bold text followed by our response.

A. Deficiencies:

- 1. Please note that your finished product release and stability testing protocol will need to be revised to incorporate the dissolution specification recommended by the Division of Bioequivalence. The revised protocols should be submitted in your next amendment.**

Chelsea's testing protocols have been revised to incorporate the dissolution specification recommended by the Division of Bioequivalence. Dissolution testing will be performed at NLT (Q) in 30 minutes, which is effectively equivalent to your requested (Q) is NLT dissolved in 30 minutes (i.e. a result below μ ails S1). Revised Finished Product Specifications along with a Certificate of Analysis are provided in Attachment 1. Revised Stability Specifications, Post Approval Stability Protocol and Stability Test Methods are provided in Attachment 2.

RECEIVED

DEC 05 1997

000001

GENERIC DRUGS

*M. O'Neil
12-8-97*

B. Additional comment:

We await the response to our letter dated October 9, 1997 which contained deficiencies related to the bioequivalence studies submitted in support of your application. Any changes made to the chemistry, manufacturing and controls sections of your deficiencies must be submitted and could result in the response being considered a MAJOR Amendment.

Chelsea submitted, on Nov. 20, 1997, an amendment in response to the Agency's letter dated October 9, 1997. The deficiencies relating to the bioequivalence studies submitted in support of our application were answered in this amendment.

**Labeling Deficiencies:
INSERT**

**Revise the second sentence of the DESCRIPTION section to read:
Each capsule, for oral administration, contains 200 mg of acyclovir.**

The DESCRIPTION section of the insert has been revised to read:
"Each capsule, for oral administration, contains 200 mg of acyclovir."

A total of twelve [eight copies for the Archival submission and four copies for the Review submission] copies of Final Printed Labels are provided in Attachment 3.

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 manufacturing facility's district office (Cincinnati). This "Field Copy" was contained in burgundy binders.

We believe that all comments made by the FDA have been addressed. If there are any questions regarding this response, please call me at (513) 948-3149.

Sincerely,


Ernest E. Lenge, Ph.D.
Director, Regulatory Affairs

000002

SEP 22 1991

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-101

APPLICANT: Chelsea Laboratories, Inc.

DRUG PRODUCT: Acyclovir Capsules (200 mg)

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. The submission did not include USP <661> physicochemical test data for the HDPE bottles. Please include this information.
2. It was noted that the packaging and labeling records did not include yield limits. Please revise the records accordingly and resubmit them in your next amendment.
3. Please provide updated room temperature stability data in your next amendment, if available.

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

1. Please note that the Division of Bioequivalence will determine the acceptability of your dissolution specifications. If changes are requested you should revise your release and stability protocols accordingly and resubmit them in a subsequent amendment.
2. Your analytical methods for the drug product will be submitted for validation by our district laboratories.

Sincerely yours,



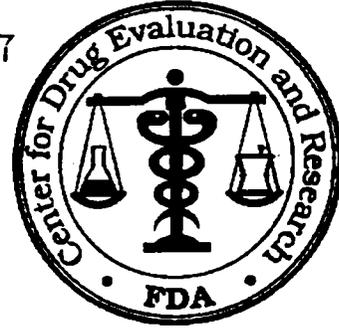
Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

FACSIMILE AMENDMENT

SEP 22 1997

ANDA 75-101

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



TO: APPLICANT: Chelsea Laboratories, Inc.
ATTN: Ernest Lengle, Ph.D.

PHONE: 513-948-3149
FAX: 513-948-7083

FROM: Mark Anderson

PROJECT MANAGER (301) 827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 28, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Acyclovir Capsules, 200 mg..

Reference is also made to your amendment dated July 18, 1997.

Attached are 4 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. 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.

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..

X:\new\ogdadmin\macros\faxfax.frm

Pro Admin
S. J. ...
11-21-97



CHELSEA LABORATORIES, INC.
Regulatory Affairs Department



P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

NDA ORIG AMENDMENT

N/AB

Mail No. 97-216

November 20, 1997

Rabindra Patnaik Ph.D.
Director, Division of Chemistry II
HFD-621, Room 204, Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: Acyclovir Capsules 200 mg
ANDA 75-101
Minor Amendment

Dear Dr. Patnaik,

This is in response to the FDA deficiency letter dated October 9, 1997 for the above mentioned ANDA. For ease of review, your comments are in bold text followed by our response.

- 1. The study results of study P96-127, indicate that the 90% confidence intervals of the log transformed C_{MAX} mean parameter (n=32) fails, being outside the regulatory limits of 80-125%.

It is important to note that the aberrant C_{MAX} value in the initial study (P96-127) was exhibited by the Reference Drug Product and NOT Chelsea's Test Drug Product (Refer to Page 001199-001201 and page 001204 in the bioequivalency report from Bioassay).

Furthermore, the following has been cited in the book entitled "Generics and Bioequivalences"¹ edited by Andre J. Jackson, Office of Generic Drugs, Center of Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland:

¹ Ormsby, E.D., Statistical Methods in Bioequivalence. in Generics and Bioequivalences, Andre J. Jackson, Ed., CRC Press, Ann Arbor, MI, 1994, p.22.

RECEIVED

NOV 21 1997

000001

GENERIC DRUGS

“As with any other types of studies, there are always values that do not compare well with other results in the bioequivalence study. These curious values which cannot be attributed to missing concentrations in the profile or any extreme concentration in the profile are called outliers. There are many tests to identify outliers, but routine removal from the study is not valid because such outliers can indicate two important and real possible outcomes. One, the profile is a result of a product failure; or, two, this could be the realization of a subject-by-formulation interaction. The main point is that the observation could be very meaningful and should not be discarded unthinkingly.

The only legitimate way of removing a subject's results is to bring the subject back to the study center and repeat both formulations. It is far cheaper to have one subject return than to redo the whole study. If the results are different again we probably have a real subject-by-formulation interaction. Further study of this would be required by the agency. If the two repeated results are similar for the two formulations, then one of the formulations of the initial pair failed and can be identified by comparison with its respective repeat. **If it was the reference product that failed, then the test formulation should not be penalized and the subject's results should be removed.** Usually no more than 5% of the subjects should be considered outliers before the quality of the study would be questioned. If the test formulation failed, then another study may be warranted although it may be wise to do more in-vitro formulation development before any in-vivo repeat. Results with and without these outliers should be submitted for review. It should be noted that an a prior test for outlier screening should be part of the study protocol and followed even if the study indicates bioequivalence.”

The purpose of the redosing study (P96-363) was to determine if there was a subject-by-formulation interaction that caused the Reference Drug Product to exhibit low bioavailability in Subject #8 relative to the Test Drug Product. The results of the redosing study confirmed the lack of subject-by-formulation interaction since the Test and Reference Drug Products performed similarly. Thus, the elimination of the data for Subject #8 should be allowed from the database. The validity of the redose study was shown by the data obtained for other two subjects (“control”), namely Subject #22 and #36, whose Test/Reference ratios were similar for the initial and redose studies, i.e., 0.77 vs 0.79 and 1.29 vs 0.97, respectively. Furthermore, a comparison of the C_{MAX} values in the redose study for the 3 subjects for both the Test and Reference Drug Products, based on the expected within subject CV of 0.27 observed in the initial study, showed all values to be within expectation except for the change of the Reference value for Subject #8 from 193 ng/mL to 506 ng/mL from initial study to redosing study ($p < 0.02$).

000002

- 2. The study results for P96-363, indicated that subject #8 levels following the redosing of the test and reference products were similar to each other, as opposed to study P96-127, where test treatment levels of subject #8 were considerably greater than the reference. It is interesting to note, however, that the test and reference levels of all the repeated subjects in study P96-363 show less differences than those seen for study P96-127. It may be argued that, based on the large inter-subject variability, it would have been possible that some other subject would have shown more differences, had the study P96-363 been conducted by redosing all 32 subjects. It also could be argued that, since there is large inter-study variation in levels, the redosed subjects might possibly give still different levels if dosed for a third time. Based on the provided information and failure of the 90% confidence interval for the log transformed C_{MAX} , the test product cannot be considered bioequivalent to the reference.**

There are only 3 subjects in the redosing study. Subject #8 was expected to show less of a difference because of the aberrant C_{MAX} results for the Reference Drug Product. Subject #22 showed values of 0.79 and 0.77 in the initial and redosing studies, virtually identical. Subject #36 showed a ratio of 1.20 and 0.97 for the initial and redosing study, respectively, which are not very different, certainly, within statistical expectations. We believe that the data in the redosing study are not unusual in this regard.

The inter-study variability based on the 3 subjects does not seem to be very large. Even including the aberrant results in the initial study for C_{MAX} for Subject #8, the average results are 477 and 580 for initial and redosing studies, respectively. This is only about a 21% difference, which cannot be considered a very large difference. Furthermore, this difference of 21% is attributed primarily due to aberrant results of subject #8 for Reference Drug Product observed in the initial study (P96-127). Even if the studies showed a large difference in response, the ratios of the two products should not be significantly affected.

Chelsea would like to note and acknowledge FDA's recommendation for dissolution. Dissolution testing will be performed at NLT (Q) in 30 minutes, which is effectively equivalent to your requested (Q) is NLT dissolved in 30 minutes (i.e. a result below fails S1). Regarding the Agency's note about the unacceptability of the fasted bioequivalence study vs the electronic submission (EVA), reference is made to the Oct. 24, 1997 and Oct. 27, 1997 telephone conversations in which the Agency explained that their note was in error.

We believe that all comments made by the FDA have been addressed. If there are any questions regarding this response, please call me at (513) 948-3149.

Sincerely,


Ernest E. Lengle, Ph.D.
Director, Regulatory Affairs

000003



CHELSEA LABORATORIES, INC.
Regulatory Affairs Department



P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

Mail No.: 97-184

October 10, 1997

Dr. Frank O. Holcombe, Director
Division of Chemistry II
Office of Generic Drugs
CDER, Food & Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

Subject: Acyclovir Capsules 200 mg
ANDA 75-101
Facsimile Amendment

ORIGINAL AMENDMENT

N/FA

*Labeling review drafted
(labeling ok except one,
8 PIs & 9 container labels)
10/16/97*

*Noted:
To Susan R
Adolph V*

10/15/97

RECEIVED
OCT 14 1997
GENERIC DRUGS

Dear Dr. Holcombe:

This is in response to an FDA Facsimile deficiency letter dated September 22, 1997 for the Acyclovir Capsules 200 mg ANDA (75-101). For ease of review, your comments are in bold text followed by our responses.

Chemistry Deficiencies

1. The submission did not include USP <661> physicochemical test data for the HDPE bottles. Please include this information.
Please see Attachment 1 for copies of the USP <661> physicochemical test data for the HDPE bottles.
2. It was noted that the packaging and labeling records did not include yield limits. Please revise the records accordingly and resubmit them in your next amendment.

3. **Please provide updated room temperature stability data in your next amendment, if available.**

The updated room temperature stability data are provided in Attachment 2.

We would also like to acknowledge that the Division of Bioequivalence will determine the acceptability of our dissolution specifications and if changes are requested, we will revise the release and stability protocols accordingly and resubmit them in a subsequent amendment.

The analytical methods for the drug product are currently under review by the district laboratories. Samples, standards and columns were sent to Nicholas Falcone of the Philadelphia District Laboratory at his request on September 24, 1997.

Labeling Deficiencies:

1. **CONTAINER 100s, 500s, 1000s**

- a. **We encourage you to differentiate your container labels from those for your acyclovir tablet application (ANDA 74-938)**

Acyclovir Capsules and Acyclovir Tablets are two different products. The labels are differentiated by the product form (Tablet versus Capsule). The size of the text of "Capsules" and "Tablets" is sufficient for distinguishing between the two products. Also, upon examination of the product, the difference is very apparent.

- b. **Delete " Controlled Room Temperature".**

"Controlled Room Temperature" has been removed.

1. **INSERT**

- a. **GENERAL COMMENTS**

- i. **Revise your insert labeling to be in accord with the enclosed copy of the insert labeling of the reference listed drug, Zovirax® (Glaxo Wellcome Inc.; revised March 1997 and approved May 29, 1997.**

The insert labeling has been revised in accord with the copy of the insert labeling of the reference listed drug, Zovirax® (Glaxo Wellcome Inc.), revised March 1997 and approved May 29, 1997.

Note: The following comments, except those for the HOW SUPPLIED section, refer to the enclosed insert labeling of the reference listed drug.

- ii. **Italicize "*in vitro*" and "*in vivo*" throughout the text of the insert.**

The words "*in vitro*" and "*in vivo*" have been italicized throughout the text of the insert.

b. DESCRIPTION

Revise the molecular weight to be 225.21 per USP 23.

The molecular weight statement has been revised to read 225.21.

c. PRECAUTIONS

- i. Include the entire paragraph beginning "There are no adequate ... and ending ...risk to the fetus. As the second paragraph of the Pregnancy: Teratogenic Effects: Pregnancy Category B subsection.**

The text has been revised to have the sentence "Acyclovir should be used ...risk to the fetus." as part of the second paragraph under PRECAUTIONS: PREGNANCY: *Teratogenic Effects*

- ii. Delete the subsection entitled "Pregnancy Exposure Registry".**

The subsection titled "Pregnancy Exposure Registry" has not been included in the insert labeling.

d. DOSAGE AND ADMINISTRATION

- i. Treatment of Chickenpox: (Adults and Children over 40 kg), Retain as the second paragraph**

Intravenous acyclovir is indicated for the treatment of varicella zoster infections in immunocompromised patients.

The text "Intravenous acyclovir is ...in immunocompromised patients." has been included in the second paragraph under Treatment of Chickenpox: (Adults and Children over 40 kg).

- ii. Bioequivalence of Dosage Forms - Retain the entire paragraph "Acyclovir suspension was shown to be ... capsules (n=24)".**

The text "Bioequivalence of Dosage Forms: Acyclovir ...to four Acyclovir 200-mg capsules (n=24)." has been included in the insert labeling.

e. HOW SUPPLIED

- i. See comment b under CONTAINER.**

The text "Controlled Room Temperature" has been deleted from the temperature storage statement.

- ii. We note that Chelsea Laboratories is listed as the manufacturer yet on page 329 of this submission Hoechst Marion Roussel, Inc. is listed as the manufacturer. Please comment and/or revise.

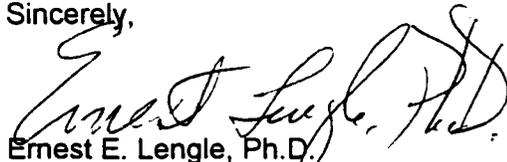
Chelsea Laboratories Inc. is a wholly owned subsidiary of Hoechst Marion Roussel, and according to CFR 201.1 (f) the name of the subsidiary can appear on the label.

The container labels and the insert labeling have been revised as reported above. A total of twelve final printed labels and outserts (eight copies for the Archival Submission and four copies for the Review Submission) are being submitted (see Attachment 3). To facilitate the review of this submission, a side-by-side comparison of the proposed labeling with our last submission has been included in Attachment 3. We understand that further changes to our labels and/or labeling may be requested prior to approval.

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 manufacturing facility's district office (Atlanta, Georgia). This "field copy" was contained in burgundy binders.

We believe that all comments made by the FDA have been addressed. If there are any questions regarding this response, please call me at (513) 948-3149.

Sincerely,



Ernest E. Lenge, Ph.D.
Director, Regulatory Affairs



CHELSEA LABORATORIES, INC.
Regulatory Affairs Department



P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

Mail No. 97-129

July 18, 1997

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

Re: Acyclovir Capsules, 200 mg
ANDA # 75-101
Amendment

Dear Mr. Sporn:

Chelsea Laboratories, Inc. submits today an amendment to our Acyclovir Capsules, 200 mg abbreviated new drug application (ANDA 75-101).

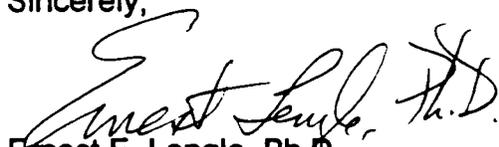
RECEIVED
JUL 21 1997
GENERIC DRUGS

This letter also certifies that, concurrently with the filing of this amendment, a true copy of the technical sections of the amendment (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 manufacturing facility's district office (Cincinnati, Ohio). This "field copy" was contained in burgundy binders.

Please direct any written communications regarding this ANDA to me at the above address. If you need to contact me, my numbers are 513-948-3149 (direct dial) and 513-948-7083 (fax).

Thank you for your prompt handling of this submission.

Sincerely,



Ernest E. Lengle, Ph.D.
Director, Regulatory Affairs

ANDA 75-101

Chelsea Laboratories, Inc.
Attention: Ernest E. Lengle
8606 Reading Road
Cincinnati, OH 45215-0686

2 1997



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: March 28, 1997

DATE OF RECEIPT: March 31, 1997

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

However, 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.

If the above methodology is not submitted, the review of the application will be delayed.

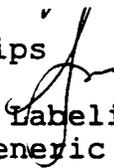
Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5849

Sincerely yours,

.

Jerry Phillips  5/2/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-101
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett
HFD-324/M.Lynch

Endorsement: HFD-615/Prickman, Chief, RSE _____ date 5/2/97
HFD-615/HGreenberg, CSO _____ date 5/2/97
HFD-647/JSimmons, Sup.Chem _____ date
WP File x:\wpfile\greenber\75\75101.ack
F/T/njg/5/1/97
ANDA Acknowledgement Letter!

NOV 12 1997

75-101

APPLICANT: Chelsea Laboratories, Inc.

PRODUCT: Acyclovir Capsules (200 mg)

Deficiencies presented below represent Minor deficiencies.

Deficiencies:

Please note that your finished product release and stability testing protocols will need to be revised to incorporate the dissolution specifications recommended by the Division of Bioequivalence. The revised protocols should be submitted in your next amendment.

Additional Comment:

We await the response to our letter dated October 9, 1997 which contained deficiencies related to the bioequivalence studies submitted in support of your application. Any changes made to the chemistry, manufacturing and controls section of your application as a result of outstanding bioequivalence deficiencies must be submitted and could result in the response being considered a MAJOR Amendment.

Sincerely yours,



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



Handwritten signature: Nancy Grealy 4/12/97

CHELSEA LABORATORIES, INC.
Regulatory Affairs Department



P.O. Box 15686 • 8606 Reading Road • Cincinnati, Ohio 45215-0686
Phone (513) 948-3149 Fax (513) 948-7083

Mail No. 97-052

March 28, 1997

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

RECEIVED

MAR 31 1997

GENERIC DRUGS

Re: ANDA Acyclovir Capsules 200 mg

Dear Mr. Sporn:

Chelsea Laboratories, Inc. submits today an original abbreviated new drug application ("ANDA") seeking approval to market Acyclovir Capsules 200 mg that are bioequivalent to the listed drug, Zovirax® Capsules, manufactured by Glaxo Wellcome, Inc.

This ANDA consists of eight volumes. Chelsea Laboratories is filing an archival copy (in blue binders) of the ANDA that contains all the information required in the ANDA, and a chemistry review copy (in red binders) which contains all the information in the archival copy except that only summaries of Bioequivalence Studies are provided in Section 20. A separate copy of the Bioequivalence section is provided in orange binders.

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 manufacturing facility's district office (Cincinnati, OH). This "field copy" was contained in burgundy binders.

Please direct any written communications regarding this ANDA to me at the above address. If you need to contact me, my numbers are 513-948-3149 (direct dial) and 513-948-7083 (fax).

Thank you for your prompt handling of this submission.

Sincerely,

Handwritten signature: Ernest E. Lengle, Ph.D.

Ernest E. Lengle, Ph.D.
Director, Regulatory Affairs

RECEIVED

MAR 31 1997

GENERIC DRUGS