CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-845

CORRESPONDENCE

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BY OVERNIGHT COURIER

MINOR AMENDMENT

August 24, 1999

Mr. Robert L. West
Director, Division of Labeling and Program Support (HFD-611)
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

N/A 1

Dear Mr. West:

Re: Diltiazem Hydrochloride Extended-Release Capsules USP 60, 90 and 120 mg
Minor Amendment
ANDA #74-845

With reference to the Agency correspondence dated January 6, 1999, Biovail is pleased to enclose proof of Paragraph IV patent certification.

Specifically, this amendment contains the following:

- A copy of the patent notice sent to Hoechst Marion Rousell, Inc. with proof of receipt from U.S. registered mail.
- A copy of the patent notice sent to Elan Corporation with a letter from their representatives indicating that the patent notice was received.

Should you require any further information, or have any questions or comments, please do not hesitate to contact the undersigned directly at (416) 285-6000 extension 219, or by fax at (905) 608-1616.

Yours sincerely,

Wayne Kreppner, M.Sc.
Manager, Corporate Regulatory Affairs

Encl.

BIOVAIL CORPORATION INTERNATIONAL
2488 DUNWIN DRIVE, MISSISSAUGA, ONTARIO, CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

ANDA 75-845

JBD
FRS
Brodsky
-B12

Keller & Heckman
Attention: John Dubeck
U.S. Agent for: Biovail Corporation International
1001 G Street N.W.
Suite 500 West
Washington, D.C. 20001

JAN 6 1999

Dear Sir:

This is in reference to your abbreviated new drug application dated January 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Diltiazem Hydrochloride Extended-release Capsules USP, 60mg, 90mg and 120mg.

Reference is also made to your amendments dated April 7, 1997; December 30, 1997; February 12, 1998; March 26, 1998; July 13, 1998; July 28, 1998; and September 24, 1998.

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

Your application contains a paragraph IV patent certification per 21 CFR 314.94(a)(12)(IV) to patent 4,721,619 which expires 1/26/2005.

The regulations require that notice of a paragraph IV patent certification must be sent by registered or certified mail to the patent owner and the holder of the New Drug Application (NDA) [21 CFR 314.95(a)]. The agency has consistently interpreted this to mean use of registered or certified U.S. Postal Service mail. The requirement that the notice be sent by registered or certified U.S. mail is clearly intended to provide maximum assurance that the notice will be received by the patent owner and the NDA holder, and that such receipt will be adequately documented. The regulations further provide that receipt of the notice may be documented by receipt of the return receipt, or by a letter acknowledging receipt by the person provided the notice [314.95(e)]. An additional form of documentation will be acceptable only with advance FDA approval [314.95(e)].

You have sent the notice at issue here via Federal Express. Under our current interpretation of the regulations we do not consider that adequate notice was given. Please provide a return receipt registered or certified U.S. Mail or a

letter acknowledging receipt by the person provided the notice.

In order that we conclude the current phase of the review process and issue a tentative approval letter for this application, we ask that this information be submitted promptly.

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 completely to the deficiency. A partial reply will not be considered for review, nor will the review clock be reactivated until the deficiency has been completely addressed. The response to this letter will be considered a MINOR 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,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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OVERNIGHT COURIER

TELEPHONE AMENDMENT

September 24, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Metro Park North II
Attention: Document Control Room, Mail Code: HFD-110
7500 Standish Place, Room 150
Rockville, MD 20855

ATTN: Ubrani Venkataram

Dear Mr. Venkataram,

Enclosed, please find in triplicate a signed and dated FDA 356h, and revised Quality Standard forms.

In response to your telephone request regarding Diltiazem Hydrochloride Extended-release Capsules (ANDA 74-845), we are pleased to forward the documentation that has been requested. Specifically, we are enclosing Quality Standard forms that correct for the in-process testing title. We have revised the QSF title to indicate the testing of bulk products for release.

If you have any questions or comments, please contact me directly at telephone number (416) 285-6000 extension 213 or at fax number (905) 608-1616.

Kindest regards,
ON BEHALF OF BIOVAIL LABORATORIES INCORPORATED

for,

Martin Levy, FBIRA
Manager, Corporate Regulatory Affairs
Biovail Corporation International

Encl.

RECEIVED
SEP 28 1998

BIOVAIL CORPORATION INTERNATIONAL I:\projects\Dil-B12\US\corresp\FDA\TelephoneDef.doc
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ANDA 74-845

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OVERNIGHT COURIER

TELEPHONE AMENDMENT

July 28, 1998

ORIG AMENDMENT
N/AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Metro Park North II
Attention: Document Control Room, Mail Code: HFD-110
7500 Standish Place, Room 150
Rockville, MD 20855

ATTN: Tim Ames
Project Manager, Division of Labeling and Program Support, Office of Generic Drugs

Dear Mr. Ames,

Enclosed, please find in triplicate a signed and dated FDA 356h, and revised Quality Standard forms.

In response to your telephone request, we are pleased to forward documentation that has been requested. Specifically, we are enclosing Quality Standard forms that correct a typographical error in box 8.

If you have any questions or comments, please contact me directly at telephone number (416) 285-6000 extension 213 or at fax number (905) 608-1616.

Kindest regards,
ON BEHALF OF BIOVAIL LABORATORIES INCORPORATED

Martin Levy

Martin Levy, FBIRA
Manager, Worldwide Regulatory Affairs
Biovail Corporation International

Encl.

RECEIVED
JUL 29 1998
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July 13, 1998

BY OVERNIGHT COURIER

MINOR AMENDMENT

ORIG AMENDMENT

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
USA

ATTN: Dr. Frank Holcombe, Jr, Ph.D.
Director, Division of Chemistry II

Re: ANDA #74-845
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, 60 mg, 90 mg and 120 mg

Dear Dr. Holcombe;

This letter and supporting documents responds to your June 30, 1998 minor amendment.

We are pleased to enclose the following documents, which were requested in your correspondence:

Dissolution Method Validation Report and Standard Test Method
- Blank Quality Standard Specification Forms for final products
- Stability Protocols

Biovail wishes to confirm, at this time, that this product will be approved with the following commitments outstanding:

- Interim approved dissolution specifications will be used to test process validation batches. This data will be forwarded to the Division of Chemistry as soon as it becomes available and;

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JUL 14 1998
GENERIC DRUGS

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- To provide support to the FDA district laboratory during its evaluation of the test method and specifications.

I would be pleased to discuss this file with you, at your leisure, if warranted. For ease of reference, my telephone number is (416) 285-6000 extension 213, and my fax number is (905) 608-1616.

Respectfully submitted,
BIOVAIL CORPORATION INTERNATIONAL

Martin Levy, FBIRA
Manager, Worldwide Regulatory Affairs

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FAX COVER SHEET

DATE: 12 February 1998

TO: Dr. Lissie Sanchez **FAX: 301-594-0181**
COMPANY: Division of Bioequivalence, FDA

CC: File

FROM: George E. Markus FAX: (905) 608-1616

PAGES: (including cover page)

SUBJECT: **ANDA #74-845 ; Bioequivalence Telephone Amendment - Response to FDA Issued Raised During Telephone Contact dated February 10, 1998**

PERSONAL AND CONFIDENTIAL

TO BE DELIVERED TO ADDRESSEE ONLY

Dear Dr. Sanchez,

As discussed, please find attached a copy of our response to the issue identified on the phone on February 10, 1998.

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL

George E. Markus, M.Sc.
Manager, Regulatory Affairs

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12 February 1998

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
USA

Bioequivalency Telephone Amendment
Expedited Review Requested

Attention: Dr. Dale P. Conner
Director, Division of Bioequivalence

Dear Dr. Conner,

Re: **ANDA #74-845**
Diltiazem Hydrochloride Extended-release Capsules USP, 60, 90, 120 mg
Response to FDA Issued Raised During Telephone Contact dated February 10, 1998

In accordance with 21 CFR 314.96, we enclose our response to the issue raised on the telephone with Dr. Lizzie Sanchez on February 10, 1998. Specifically, Biovail was requested to confirm the final Dissolution specification (as the one recorded in the method on page 012 differed from that presented on pages 019 and 038 of the December 30, 1997 response).

It has been agreed by Dr. Lizzie Sanchez on February 10, 1998 that a Bioequivalence Telephone Amendment would be acceptable by the FDA to address this issue and that the submission of a Form FDA 365h was not required. As a result, please find attached our response to the above stated issue.

Should you have any questions or comments, please contact the undersigned directly at (416) 285-6000 ext. 412 or by fax at (905) 608-1616.

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL

G Markus

George E. Markus, M.Sc.
Manager, Regulatory Affairs

Encl.

BIOVAIL CORPORATION INTERNATIONAL
2488 DUNWIN DRIVE. MISSISSAUGA. ONTARIO. CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

Response:

As stated in our December 30, 1997 response, the following dissolution specs have been proposed:

Acceptance criteria are as stated in USP.

The respective test method has been revised to reflect the proposed specifications. A copy of the revised test method has been attached for your review.

Page(s) 5

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

2/12/98

test methods

BIOAVAILABILITY
N/AB
ORIG AMENDMENT

12 February 1998

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
USA

Bioequivalency Telephone Amendment
Expedited Review Requested

Attention: Dr. Dale P. Conner
Director, Division of Bioequivalence

Dear Dr. Conner,

Re: ANDA #74-845
Diltiazem Hydrochloride Extended-release Capsules USP, 60, 90, 120 mg
Response to FDA Issued Raised During Telephone Contact dated February 10, 1998

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It has been agreed by Dr. Lizzie Sanchez on February 10, 1998 that a Bioequivalence Telephone Amendment would be acceptable by the FDA to address this issue and that the submission of a Form FDA 365h was not required. As a result, please find attached our response to the above stated issue.

Should you have any questions or comments, please contact the undersigned directly at (416) 285-6000 ext. 412 or by fax at (905) 608-1616.

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL

George E. Markus, M.Sc.
Manager, Regulatory Affairs

Encl.

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FEB 13 1998
GENERIC DRUGS

BIOVAIL CORPORATION INTERNATIONAL
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BIOAVAILABILITY

N/A C

This AB opened the chemistry queue 12/31/97, sent forward to no comments remain. Bio for review. 1/2/98

December 30. 1997

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
USA

Bioequivalency Amendment
Expedited Review Requested

Attention: Dr. Dale P. Conner
Director. Division of Bioequivalence

Dear Dr. Conner.

Re: ANDA #74-845
Diltiazem Hydrochloride Extended-release Capsules USP, 60, 90, 120 mg
Response to FDA fax dated November 12, 1997

In accordance with 21 CFR 314.96. we enclose our response to the questions listed on your fax of November 12. 1997. All deficiencies have been addressed. To facilitate the review. we have answered the questions in the order they appear on the fax. A copy of the fax has also been included.

As per comment number 3. we have included an updated dissolution method which employs USP apparatus 1. This method has been validated and all validation data has also been included in this amendment.

We enclose a signed and dated FDA form 356h in this amendment. This is submitted in triplicate (original and 2 copies).

RECEIVED

DEC 31 1997

GENERIC DRUGS

Should you have any questions or comments, please contact the undersigned directly at (416) 285-6000 ext. 412 or by fax at (905) 608-1616.

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL

George E. Markus, M.Sc.
Manager, Regulatory Affairs

Encl.

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9/3/97
FA Rec'd + to
a Chemistry Reviewer for
review, then ⊖ to Labeling
reviewer for review.
[illegible]
NDA ORIG AMENDMENT

August 28, 1997

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
USA

Minor Amendment
Expedited Review Requested

RECEIVED
AUG 29 1997
GENERIC DRUGS

Attention: Dr. Frank Holcombe
Director, Division of Chemistry II

Dear Dr. Holcombe ,

Re: **ANDA #74-845**
Diltiazem Hydrochloride Extended-release Capsules USP, 60, 90, 120 mg
Response to FDA fax dated August 4, 1997

Further to your fax of August 4, 1997 regarding our Abbreviated New Drug Application, dated January 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, for Diltiazem Hydrochloride Extended-release Capsules USP, 60, 90 and 120 mg (twice daily dosage), we enclose our response to your questions. To facilitate the review, we have answered the questions in the order they appear on the fax. A copy of the fax has also been included.

We enclose a signed and dated FDA form 356h in this amendment, which is being submitted in triplicate (orignial and 2 copies)

Please note that in our February 11, 1997 amendment, we changed our U.S. Agent from Robert Burford at 200 Hurlbutt Street, Wilton, Connecticut to Arthur Deboeck at Biovail Laboratories Incorporated, Avenue Iturregui and B Street, P.O. Box 3468, Carolina, Puerto Rico. At this time please change our US agent from Arthur Deboeck to Carmen Reyes, also at Biovail Laboratories Incorporated, Avenue Iturregui and B Street, P.O. Box 3468, Carolina, Puerto Rico.

BIOVAIL CORPORATION INTERNATIONAL
2488 DUNWIN DRIVE, MISSISSAUGA, ONTARIO, CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

Should you have any questions or comments, please contact the undersigned directly at (416) 285-6000 ext. 412 or by fax at (905) 608-1616.

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL

George E. Markus, M.Sc.
Manager, Regulatory Affairs

Encl.

BIOVAIL

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February 11, 1997

MAJOR AMENDMENT

NDA ORIG AMENDMENT

N/C FPL

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
USA

Attention: Dr. Frank O. Holcombe
Director, Division of Chemistry II

Dear Dr. Holcombe,

Re: ANDA #74-845
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES
USP, 60, 90, 120 mg (Twice Daily Dosage)
Response to FDA letter dated November 27, 1996

Further to your letter dated November 27, 1996 and our acknowledgement amendment dated December 2, 1996, regarding Biovail's abbreviated new drug application dated January 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Diltiazem Hydrochloride Extended-release Capsules USP. 60 mg, 90 mg, 120 mg (Twice Daily Dosage), we enclose in this Major Amendment our responses to your questions (A1 to C3) in the order as they appear in your November 27, 1996 letter.

Please note that we have changed our U.S. Agent from Robert Burford at 200 Hurlbutt Street, Wilton, Connecticut to Arthur Deboeck at Biovail Laboratories Incorporated, Iturregui Avenue and B Street, P.O. Box 3468, Carolina, Puerto Rico. A copy of the authorization letter is enclosed for your review (Attachment #1).

RECEIVED

FEB 12 1997

GENERIC DRUGS

BIOVAIL CORPORATION INTERNATIONAL

2488 DUNWIN DRIVE, MISSISSAUGA, ONTARIO, CANADA L5L 1J9 • TEL (416) 285-6000 FAX (416) 285-6499

We also included in this Major Amendment, the following information:

1)

2) [illegible] (Attachment #3)

3) [illegible] eads

4) [illegible]

5)

We enclose a signed and dated FDA form 356h in this major amendment which is being sent to you in triplicate (original + 2 copies) via Federal Express.

If you have any questions or comments, please contact Ivy Chung the contact person at (416) 285-6000 ext. 412 or the undersigned at ext. 418.

Sincerely,

Mimi Brennan, B.Sc., ART, CIM, P.Mgr
Director Regulatory Affairs and QA

Encl.

ANDA 74-845

Biovail Corporation International
Attention: Dr. Robert G. Burford, U.S. Agent
American Clinical Research Consultants
P.O. Box 7299
200 Hurlbutt Street
Wilton, CT 06897-7299

NOV 27 [illegible]

Dear Dr. Burford:

This is in reference to your abbreviated new drug application dated January 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Diltiazem Hydrochloride Extended-release Capsules USP, 60 mg, 90 mg, 120 mg.

Reference is also made to your amendments dated March 28, 1996, May 8, 1996 and July 9, 1996.

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

A. Chemistry Deficiencies

Page(s) ~~2~~

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

11/27/95

B. LABELING DEFICIENCIES

1. GENERAL COMMENTS:

Revise the established name of your product to read as follows where it appears on container labels and package insert labeling:

Diltiazem Hydrochloride Extended-release Capsules USP (Twice-a-day dosage)

2. CONTAINER

a. Please include the following statement on the container label:

Diltiazem Hydrochloride Extended-release Capsules which exhibit different pharmacokinetics are also marketed. Please confirm you are dispensing the prescribed formulation.

b. We note that you have chosen to include the NDC number to appear part of and contiguous to the bar code symbol, however, whenever the NDC number is used on a label, it is to be preceded by the prefix "NDC" or "N". Refer to 21 CFR 207.35(b)(i) and (ii).

3. INSERT

a. DESCRIPTION

i. Revise the molecular weight to read 450.99.

ii. Paragraph 3 (first sentence) -

Each diltiazem hydrochloride extended-release capsule (twice daily dosage), for oral administration, contains...

iii. In the list of inactive ingredients -

1) Use "sucrose" rather than "sugar".

2) Delete "A.L." following the listing of the dyes. [3 places]

b. CLINICAL PHARMACOLOGY (Pharmacokinetics and Metabolism) -

We note from your side-by-side comparison, that you deleted the first paragraph relating to the PK parameters of diltiazem. Since this paragraph does appear in the labeling of the reference listed drug, Cardizem SR, and is not related to a specific dosage form, please revise to include this paragraph.

c. INDICATIONS AND USAGE

Diltiazem hydrochloride extended-release capsules (twice a day dosage) are indicated...

d. WARNINGS (Cardiac Conduction)

Make the following revision to the last sentence of the first paragraph, "...of diltiazem. (See ADVERSE REACTIONS)".

e. ADVERSE REACTIONS (Other - second paragraph)

i. Make the following revisions in the first sentence:

...diltiazem: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), extrapyramidal...

ii. Make the following revision in the second sentence, "...generalized rash, some characterized...".

f. OVERDOSAGE OR EXAGGERATED RESPONSE

i. Paragraph 5, add the following sentence as the second sentence -

...or hemodialysis. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination following overdose. Based on the...

ii. Paragraph 4 (last sentence) -

Evidence of the effectiveness of intravenous [*spelling*]...was [*rather than "were"*] conflicting.

iii. Bradycardia -

Administer atropine (0.6 to 1 mg)...
[Delete terminal zeros]

iv. Hypotension -

Use "norepinephrine" rather than "levarterenol".

g. HOW SUPPLIED

i. We encourage the inclusion of the statement appearing under CONTAINER in this section.

ii. The color of the beads is described as "grey" in this section. However, in the finished dosage form specifications they are described as white to off-white. Please comment and/or revise.

iii. We encourage the inclusion of the NDC numbers.

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

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

1. Please note that the dissolution test method and specifications will be reviewed by our Division of Bioequivalence (DBE). We may reevaluate your release specifications and stability limits and request revisions based on DBE evaluations and recommendations.

2. We have requested an evaluation of your facilities by our district office for compliance with cGMP. Please note that the facilities should be in full compliance before the application may be approved.

3. DMF .s not satisfactory and the deficiencies have been communicated to the DMF holder. All drug master file deficiencies must be addressed before this application may be approved.

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 will be 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/ 11/26/96

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

ANDA 74-845

American Clinical Research Corporation
Attention: Dr. Robert G. Burford
U.S. Agent for: Biovail Corporation International
P.O. Box 7299
200 Hurlbutt St.
Wilton, CT 06897-7299

MAY 20 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" letters dated March 18, 1996, and April 15, 1996; and your amendments dated March 28, 1996, and May 8, 1996.

NAME OF DRUG: Diltiazem Hydrochloride Extended-release Capsules USP, 60 mg, 90 mg, and 120 mg

DATE OF APPLICATION: January 31, 1996

DATE OF RECEIPT: February 2, 1996

DATE ACCEPTABLE FOR FILING: May 9, 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:

Timothy Ames
Project Manager
(301) 594-0305

Sincerely yours,

/S/

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

ANDA 75-845

Keller & Heckman
Attention: John Dubeck
U.S. Agent for: Biovail Corporation International
1001 G Street N.W.
Suite 500 West
Washington, D.C. 20001

JAN 6 1999

Dear Sir:

This is in reference to your abbreviated new drug application dated January 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Diltiazem Hydrochloride Extended-release Capsules USP, 60mg, 90mg and 120mg.

Reference is also made to your amendments dated April 7, 1997; December 30, 1997; February 12, 1998; March 26, 1998; July 13, 1998; July 28, 1998; and September 24, 1998.

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

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The regulations require that notice of a paragraph IV patent certification must be sent by registered or certified mail to the patent owner and the holder of the New Drug Application (NDA) [21 CFR 314.95(a)]. The agency has consistently interpreted this to mean use of registered or certified U.S. Postal Service mail. The requirement that the notice be sent by registered or certified U.S. mail is clearly intended to provide maximum assurance that the notice will be received by the patent owner and the NDA holder, and that such receipt will be adequately documented. The regulations further provide that receipt of the notice may be documented by receipt of the return receipt, or by a letter acknowledging receipt by the person provided the notice [314.95(e)]. An additional form of documentation will be acceptable only with advance FDA approval [314.95(e)].

You have sent the notice at issue here via Federal Express. Under our current interpretation of the regulations we do not consider that adequate notice was given. Please provide a return receipt registered or certified U.S. Mail or a

letter acknowledging receipt by the person provided the notice.

In order that we conclude the current phase of the review process and issue a tentative approval letter for this application, we ask that this information be submitted promptly.

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 completely to the deficiency. A partial reply will not be considered for review, nor will the review clock be reactivated until the deficiency has been completely addressed. The response to this letter will be considered a MINOR 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,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOVAIL
BIOVAIL
BIOVAIL
BIOVAIL

RECEIVED
MAY 0 9 1996
GENERIC DRUGS

AMENDMENT

Minor
Amendment
Expedited Review Requested

May 8, 1996

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
U.S.A.

ATTN: Jerry Phillips
Acting Director, Division of Labelling and Program Support
Office of Generic Drugs, CDER

Re: ANDA #74-845
Diltiazem Hydrochloride Extended-release Capsules USP, 60, 90, 120 mg

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

5/8/96

If you have any questions or comments, please contact Miss Ivy Chung, the main contact person at Biovail Corporation International, telephone number (416) 752-3636 ext. 240, the undersigned at (416) 752-3636 ext. 257, or our U.S. agent Dr. Robert G. Burford at (203) 762-2097.

Sincerely,

Mimi Brennan, B.Sc., ART, CIM, P.Mgr
Director Regulatory Affairs and QA
BIOVAIL CORPORATION INTERNATIONAL

Encl.

MB/tn

ANDA 74-845

American Clinical Research Corp.
Attention: Dr. Robert G. Burford
U.S. Agent for: Biovail Corporation International
P.O. Box 7299
200 Hurlbutt St.
Wilton, CT 06897-7299

APR 15 1996

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated January 31, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Diltiazem Hydrochloride Extended-release Capsules USP, 60 mg, 90 mg, and 120 mg.

Reference is also made to our "Refuse to File" letter dated March 18, 1996, and your amendment dated March 28, 1996.

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 reason:

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

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:

William Russell
Project Manager
(301) 594-0315

Sincerely yours,

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

ANDA 74-845
cc:

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Endorsement:

BIOVAIL

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Refuse to file 4/3/96

NDA ORIG AMENDMENT

AC

March 28, 1996

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
U.S.A.

Minor
Amendment

MAR 29 1996

ATTN. Dr. Jerry Phillips
Acting Director, Division of Labeling and Program Support
Office of Generic Drugs. CDER.

RE: ANDA # 74-845
Diltiazem Hydrochloride Extended-release Capsules USP, 60, 90, 120 mg

Dear Dr. Phillips,

This amendment is being sent to you, today, in response to your letter dated March 18, 1996, in which you outlined the reasons FDA refused to file Biovail's ANDA #74-845, dated January 31, 1996.

The following are our responses to the reasons for refuse to file:

1.

BIOVAIL CORPORATION INTERNATIONAL
460 COMSTOCK ROAD, TORONTO, ONTARIO, CANADA M1L 4S4 • TEL (416) 752-3636 FAX (416) 752-7610

2. Summary of reason:
In-vitro comparative dissolution profiles should include individual capsule data as well as the mean, range, and standard deviation at each time points for twelve capsules.

Response:
Comparative dissolution profiles on 12 capsules are submitted in the ANDA page 12040 to page 12052. The same data is presented in this amendment, including the requested individual capsule data, the mean (average of 12), range (high and standard deviation (SD of 12).

Pages 12040-52 do not have comparative dissolution data for 12 capsules

3. Summary of reason:
Certification of compliance with current Good Manufacturing Practices (certification of compliance with federal, state and local environmental law

Response:
Enclosed for your records are:
-Original signatured and dated Certification of Compliance with cGMP
-Original signatured and dated Certification of Compliance with federal, state, and local environmental laws.

4. Summary of reason:
Blank master batch records do not contain the intended production quantities

Response:
The blank master batch records were submitted in the ANDA. Please refer to page 12285 to page 12338 of the ANDA.

The production quantities for the bio.batch as recorded in the executed batch records and the production quantities for the future production batches as submitted in the ANDA, are listed below:

Batch records Titled	**Production Quantity in proposed blank master batch records for production batches**	**Production quantity in bio.batch records (batch yield)**

As shown above, the blank master batch records with the intended maximum production quantities (theoretical batch size) for the future production batches are well within FDA guidance of a ten-fold scale-up from the bio.batch.

For the ease of review, enclosed are the ANDA submitted blank batch records, page 12285 to page 12338 of the ANDA. The Theoretical batch size is highlighted in each of the batch records.

Please note that the 60, 90, and 120 mg Capsules were manufactured using the same batch of extended-release beads i.e. from the batch production quantity of the batch record titled "B12 Diltiazem HCl Twice Daily (BID) Controlled Release (CR) Treated Coated Beads ". The only difference in the capsules is in the capsule filled weights.

5. Summary of reason:
New blank master batch records with theoretical batch sizes (intended maximum production quantities) noted on the master batch records.

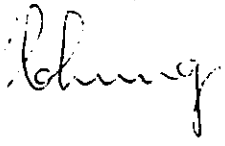
Response:

Encapsulation blank master batch records with theoretical batch sizes for Diltiazem HCl Extended-release Capsules USP, 60, 90, 120 mg strengths, are enclosed with this amendment to replace the submitted encapsulation blank batch records. These blank batch records are identical to the submitted blank batch records, with the addition of the theoretical batch size which is highlighted in each batch record for your ease of review.

The Archival Copy, the Review Copy, and the Field Copy of this Amendment are being sent to you today, via Federal Express.

We trust that your reasons for refusing to file this ANDA have been sufficiently addressed in this amendment and that our ANDA can be filed for a critical technical review as soon as possible. If you have any questions or comments, please contact Miss. Ivy Chung, the main contact person at Biovail Corporation International Inc., telephone number 1-416-285-6000 ext.240, the undersigned at 1-416-752-3636 ext.257, or our US agent Dr. Robert G. Burford at 1-203-762-2097.

Sincerely yours,



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Mini Brennan, B.Sc., Art, CIM, P.Mgr.
Director Regulatory Affairs and Quality Assurance
BIOVAIL CORPORATION INTERNATIONAL

Encl.

ANDA 74-845

American Clinical Research Corp.
Attention: Dr. Robert G. Burford
U.S. Agent for: Biovail Corporation International
P.O. Box 7299
200 Hurlbutt St.
Wilton, CT 06897-7299

1 8 1996

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated January 31, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Diltiazem Hydrochloride Extended-release Capsules USP, 60 mg, 90 mg, and 120 mg.

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:

The application is not acceptable for filing under Section 505(j) of the Act because your proposed formulation contains an inactive ingredient that has not been approved in a drug product intended for human use by the same route of administration [21 CFR 314.127(a)(8)(ii)]. Since, according to the regulation, there is reasonable basis to conclude that one of the inactive ingredients of your proposed drug product (i.e., may raise questions of safety, the Office of Generic Drugs (OGD) will not file this application as an ANDA. New inactive ingredients must be the subject of a new drug application.

You have failed to provide *in vitro* comparative dissolution profiles comparing your proposed drug product against corresponding strengths of the reference listed drug. Comparative dissolution profiles should include individual capsule data as well as the mean, range, and standard deviation at each points for twelve capsules.

You have failed to provide a certification of compliance with current Good Manufacturing Practices (cGMP) from the applicant, Biovail. Please provide this certification.

You blank master batch records do not contain the intended production quantity. Please provide blank master batch records with intended maximum production quantities noted on the master batch records. Please be advise that permission cannot be granted for more than a ten-fold scale-up.

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

In addition, please provide a certification of compliance with federal, state, and local environmental laws from the applicant, Biovail.

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:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/

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

ANDA 74-845
cc:

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1 3/6/96

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Return to file
1/31/96
Clarke
1/30/96

January 31, 1996

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855
USA

ATTN: Dr. Charles Ganley
Office of Generic Drug

Re: Abbreviated New Drug Application
Diltiazem Hydrochloride Extended Release Capsules USP, 60, 90, 120 mg

Dear Dr. Ganley,

In accordance with the provisions of Section 505(j) of the Federal Food, Drug and Cosmetic Act and Section 314.94 of 21 CFR, enclosed is an abbreviated application for Diltiazem Hydrochloride Extended-release Capsules USP, 60, 90, 120 mg for twice daily administration. The listed drug used in the bioavailability / bioequivalence studies is the Cardizem SR manufactured by Marion Merrell Dow Inc.

Biovail Corporation International developed and manufactured the product. Our marketing licensee, Geneva Pharmaceuticals Inc., packaged and labeled it. Upon approval, Geneva Pharmaceuticals Inc. will market the product in the USA, under the Geneva labeling which are submitted in this ANDA. We trust that this ANDA is complete and satisfactory for filing to be reviewed by the Office of Generic Drugs.

The Archival Copy, the Review Copy, and the Field Copy of this ANDA are being sent to you, today, via Federal Express # 400-2728-4224.

If you have any questions or comments, please contact Ms. Ivy Chung, the main contact person at Biovail Corporation International Inc., telephone number 1-416-752-3636 ext.240 or the undersigned at 1-416-752-3636 ext.257.

Sincerely yours,

Ichung

for

Mimi Brennan, B.Sc., ART, CIM, P.Mgr
Director Regulatory Affairs and Quality Assurance
BIOVAIL CORPORATION INTERNATIONAL

Encl.

BIOVAIL CORPORATION INTERNATIONAL
460 COMSTOCK ROAD, TORONTO, ONTARIO, CANADA M1L 4S4 • TEL (416) 752-3636 FAX (416) 752-7610

B 12 ANDA
Diltiazem HCl Extended-release Capsules USP, 60, 90, 120 mg

Please note that we have included in this shipment. the following items:

1. Archival Copy -35 books

2. Review Copy -Red Covers -5 books
-Orange Covers -31 books

3. Field Copy -5 books

4. Copies of Non-Compendial Methods -2 separately bound copies

5. Diskettes -3 diskettes for each bio.study. total 15 diskettes.
They can be found in books: 2 of 35
7 of 35
12 of 35
18 of 35
27 of 35

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OVERNIGHT COURIER

TELEPHONE AMENDMENT

September 24, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Metro Park North II
Attention: Document Control Room, Mail Code: HFD-110
7500 Standish Place, Room 150
Rockville, MD 20855

ATTN: Ubrani Venkataram

Dear Mr. Venkataram,

Enclosed, please find in triplicate a signed and dated FDA 356h, and revised Quality Standard forms.

In response to your telephone request regarding Diltiazem Hydrochloride Extended-release Capsules (ANDA 74-845), we are pleased to forward the documentation that has been requested. Specifically, we are enclosing Quality Standard forms that correct for the in-process testing title. We have revised the QSF title to indicate the testing of bulk products for release.

If you have any questions or comments, please contact me directly at telephone number (416) 285-6000 extension 213 or at fax number (905) 608-1616.

Kindest regards,
ON BEHALF OF BIOVAIL LABORATORIES INCORPORATED

Martin Levy, FBIRA
Manager, Corporate Regulatory Affairs
Biovail Corporation International

Encl.