CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75124

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA #: 75-124 **DRUG PRODUCT:** Diltiazem Hydrochloride ER Capsules; USP

FIRM: Mylan Pharmaceuticals Inc.

DOSAGE: ER Capsules **STRENGTH:** 120, 180, and 240 mg

CAMP STATEMENT/EIR UPDATE STATUS: Acceptable EER dated 8/18/97.

BIO STUDY: Acceptable 2/5/98

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): USP drug (for both bulk and finished dosage); validation not required.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION): The container/closure system used in the stability study is the same as those described in the container section.

LABELING: FPL found satisfactory (Tentative Approval Summary signed 12/5/97).

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):
See comment below.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

Exhibit batches: Sizes of Diltiazem HCl Extended-release Capsules 120 mg Lot No. 2D001A capsules), 180 mg Lot No. 2D002A Capsules), and 240 mg Lot No. 2C004H capsules), are one tenth of the intended production batch sizes. Firm first manufactures 60 mg Diltiazem HCl Extended-release Capsules - Intermediate Tablets, and encapsulates two, three, and four tablets to produce the desired capsule strengths.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?):

See above.

Specifications for active ingredient: Under #23A
Specifications for the finished product: Under #28 and #29

CHEMIST: Maria C. Shih **DATE:** 12/10/97
SUPERVISOR: John Harrison **DATE:** 2/19/98

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

ANDA Number: **75-124** Dates of Submission: **April 29, 1997 and October 6, 1997**

Applicant's Name: **Mylan Pharmaceuticals Inc.**

Established Name: **Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage), 120 mg, 180 mg and 240 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. Please delete the following text throughout your labels and labeling:

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

   b. We note that you have submitted two different draft inserts - one for all three strengths and another for just the 240 mg capsule. Is it your intention to have both inserts on the market? Please comment.

2. CONTAINER 100s and 500s (120 mg, 180 mg, 240 mg)

   See GENERAL COMMENT 1(a).

3. INSERT

   a. GENERAL COMMENTS

      i. The following comments apply to both inserts submitted.

      ii. Revise "diltiazem hydrochloride extended-release" to read "diltiazem hydrochloride extended-release capsules" except where otherwise directed.

b. DESCRIPTION

i. Delete "hydrochloride extended-release" in the first sentence.

ii. Revise the molecular weight to read "450.99" per USP 23.

iii. Improve the legibility of the structural formula.

iv. Move the fourth paragraph ("Diltiazem...Test 2") to be the last paragraph in this section.

v. Revise the third paragraph to read:

... dosage strengths allowing for the controlled release of diltiazem hydrochloride over a 24-hour period. In addition, each capsule contains the following inactive ingredients: ammonium ...

vi. Include the route of administration in this section [e.g., Diltiazem Hydrochloride Extended-release Capsules (Once-a-Day Dosage), for oral administration, contain ...).

c. CLINICAL PHARMACOLOGY

i. First sentence - ... of diltiazem are ...

ii. Mechanisms of Action

A). Hypertension

Delete "hydrochloride extended-release" from the first sentence.

B). Angina

Delete "HCl" from the first sentence.

iii. Hemodynamic And Electrophysiologic Effects

A). Sixth paragraph, last sentence -

Intravenous diltiazem hydrochloride in ...

B). Last paragraph, first sentence -

... extended-release capsules in ...

iv. Pharmacodynamics

A). First paragraph

1). First sentence

... extended-release capsules (once-a-day dosage) 120, ...

2). Last sentence

... extended-release capsules (once-a-day dosage) retained ...

B). Last paragraph, first sentence -

... extended-release capsules (once-a-day dosage), given at ...

v. Pharmacokinetics And Metabolism

A). First paragraph

1). Second sentence -

"immediate-release" (add hyphen).

2). "hydrochlorothiazide" rather than "HCTZ".

3). Fifth, sixth and penultimate sentences -

Delete "hydrochloride".

B). Second paragraph, second sentence -

... patients. Patients with severely ...

C). Third paragraph, first sentence -

... capsules (once-a-day dosage) contain ...

D). Delete the fourth paragraph (Neither ... products.) and replace with the following text:

The absolute bioavailability of diltiazem from a single dose of diltiazem hydrochloride extended-release capsules (compared to intravenous administration) is 41% (±14).

This value was shown to be similar to the 40% systemic availability reported following administration of an immediate-release diltiazem hydrochloride formulation.

E). Fifth paragraph, first sentence -

... capsules (once-a-day dosage) is ...

F). Last paragraph - Revise to read as follows:

The presence of food did not affect the ability of diltiazem hydrochloride extended-release capsules to maintain a controlled release of the drug and did not impact its sustained release properties over 24-hours after administration. However, simultaneous administration of diltiazem hydrochloride extended-release capsules with a high-fat breakfast resulted in increases in AUC of 13% and 19%, and in C_{max} by 37% and 51%, respectively.

d. INDICATIONS AND USAGE

i. Revise the first sentence to read:

Diltiazem Hydrochloride Extended-release Capsules (Once-a-Day Dosage) are indicated ...

ii. Revise the last paragraph to read:

... extended-release capsules (once-a-day dosage) are ...

e. CONTRAINDICATIONS

Delete "hydrochloride".

f. WARNINGS

i. Bold the subsection headings "**Cardiac Conduction**" and "**Congestive Heart Failure**".

ii. Cardiac Conduction, first sentence -

Delete "hydrochloride".

iii. Congestive Heart Failure, penultimate sentence -

... use of diltiazem in ...

iv. Hypotension - ... with diltiazem therapy ...

g. PRECAUTIONS

i. General

A). Second paragraph, first sentence -

Delete "hydrochloride".

B). Last paragraph

1). First sentence - ... capsules (once-a-day dosage) utilize a ...

2). Last sentence - ... capsules (once-a-day dosage).

ii. Information For Patients

... capsules (once-a-day dosage) should ... [two instances

iii. Drug Interactions

A). Subsection heading is plural.

B). Delete "hydrochloride" throughout this subsection.

iv. Pregnancy, second paragraph, first sentence -

Delete "hydrochloride".

v. Nursing Mothers - Delete "hydrochloride".

h. ADVERSE REACTIONS

i. First sentence

... extended-release capsules (once-a-day dosage).

ii. Hypertension

A). First sentence

... extended-release capsules (once-a-day dosage) using ...

B). Revise the header over the second column of data to read "Diltiazem HCl Extended-release Capsules (Once-a-Day Dosage)* [note "n=303" and "# pts(%)" remain the same].

C). Last sentence

... extended-release capsules (once-a-day dosage).

iv. Angina

A). First sentence

... extended-release capsules (once-a-day dosage) are listed ...

B). Second sentence

... extended-release capsules (once-a-day dosage).

C). Revise the header over the second column of data to read "Diltiazem HCl Extended-release Capsules (Once-a-Day Dosage)* [note "n=139" and "# pts(%)" remain the same].

D). Last sentence

... extended-release capsules (once-a-day dosage).

v. Infrequent Adverse Events

... extended-release capsules (once-a-day dosage), or ...

vi. Add the following text as the last paragraph of the ADVERSE REACTIONS section:

There have been post-marketing reports of Stevens-Johnson Syndrome and toxic epidermal necrolysis associated with the use of diltiazem.

i. OVERDOSAGE OR EXAGGERATED RESPONSE

i. Delete "hydrochloride" from the first sentence.

ii. Bradycardia - Delete the terminal zero in "1.0 mg" (0.60 mg to 1 mg).

iii. Hypotension - Vasopressors (e.g., dopamine or norepinephrine). [add comma and replace "levarterenol bitartrate" with "norepinephrine"].

j. DOSAGE AND ADMINISTRATION

i. Second paragraph

... extended-release capsules (once-a-day dosage), when ...

ii. "Hypertension" and "Angina" are subsections of the subsection "Dosage" and should be in italic print to be consistent with your format.

iii. Dosage - Hypertension

First paragraph, last sentence - Current clinical ... [delete "Although" -- please note that this sentence should start a new paragraph].

iv. Concomitant Use With Other Cardiovascular Agenets

A). Sublingual Nitroglycerin

Delete "hydrochloride".

B). Prophylactic Nitrate Therapy

... hydrochloride extended-release capsules (once-a-day dosage) may ...

C). Antihypertensives

Delete the first occurrance of "hydrochloride".

k. HOW SUPPLIED

i. See GENERAL COMMENT 1(a).

ii. We encourage you to revise "Supro A" to be in terms meaningful to the health care practitioner.

Revise your container labels and package insert labeling as described above, then prepare and submit final printed (or printers proof) package insert labeling and final printed

container labels. Please note that final printed insert labeling is not required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept final "printers proof" for the insert only.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75124

CORRESPONDENCE

FACSIMILE AMENDMENT

NOV 19 1997

ANDA 75-124

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

TO: APPLICANT: Mylan Pharmaceuticals, Inc PHONE: 304-599-2595

ATTN: Frank Sisto FAX: 304-285-6407

FROM: ~~Timothy Ames~~ Mark Anderson PROJECT MANAGER (301) 827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated April 29, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ditiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg, and 240 mg.

Reference is also made to your amendment dated October 6, 1997.

Attached are 10 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:

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

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) [illegible]-2595

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

APR 29 1997

Refuse to File 6/6/97

Labeling reviewed by Draftsman 11/6/97

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: DILTIAZEM HCl EXTENDED-RELEASE CAPSULES, USP 240 MG

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:
Proprietary Name: None
Established Name: Diltiazem HCl Extended-release Capsules, USP
This application consists of a total of 37 volumes.
Archival Copy - 17 volumes.
Review Copy - 18 volumes.
Technical Section For Chemistry - 3 volumes.
Technical Section For Pharmacokinetics - 15 volumes.
Analytical Methods - 2 extra copies; 1 volume each.
NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a set of data diskettes for the bioequivalence studies conducted in support of this application. An electronic data set, using the Office of Generic Drugs new EVA software program, is currently being prepared and will be submitted as an amendment to this application as soon as it becomes available.

This application provides for the manufacture of Diltiazem HCl Extended-release Capsules, USP 240 mg. All operations in the manufacture, packaging, and labeling of the drug product are performed by Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730.

As required by 21 CFR 314.94(d)(5) we certify that a true copy of the technical sections of this application as submitted to the Office of Generic Drugs has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310.

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

RECEIVED
APR 30 1997
GENERIC DRUGS

Department	Fax Numbers
Accounting	(304) 285-6403
Administration	(304) 599-7284
Business Development	(304) 599-7284
Human Resources	(304) 598-5406
Information Systems	(304) 285-6404
Label Control	(800) 848-0463
Legal Services	(304) 598-5408
Maintenance & Engineering	(304) 598-5411
Medical Unit	(304) 598-5445
Quality Control	(304) 598-5401
Research & Development	(304) 598-5407
Sales & Marketing	(304) 285-6409
	(304) 598-3232

FRS/tlm

[RDLIB.ANDA.DILTIAZEM-ER-240]SECTIONS-C1THRU07

ANDA 75-124

Mylan Pharmaceuticals Inc.
Attention: Frank Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310

JUL 7 1997

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated April 29, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Diltiazem Hydrochloride Extended-release Capsules USP, 240 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 concentration of the inactive ingredient in your proposed product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency. FDA will consider the inactive ingredients or composition of a drug product unsafe and refuse to approve an ANDA under 21 CFR 314.127(a)(8)(i) if, on the basis of information available to the agency, there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raise serious questions of safety. Examples of the changes that may raise serious questions of safety include, but are not limited to the following: a change in the composition to include a significantly greater content of an inactive ingredient than previously approved by the agency [21 CFR 314.127(a)(8)(i)]. Please provide additional justification to demonstrate safety of the inactive ingredient such as examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration range. Please either provide this documentation, or reformulate your drug product.

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:

Anna Marie H. Weikel
Project Manager
(301) 827-5862

Sincerely yours,

Jerry Phillips 7/2/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-124
DUP/Jacket
Division File
HFD-92
Field Copy
HFD-600/Reading File
HFD-610/JPhillips
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Actir date 6/13/97
HFD-615/AMWeikel, CSO date 6/9/97
HFD-647/TAmes, Chem Brancn date
X:\NEW\FIRMSAM\MYLAN\LTRS&REV\75124.RTF
FT/njg/6/6/97/
ANDA Refuse to File!

ANDA 75-124

Mylan Pharmaceuticals Inc.
Attention: Frank Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310

JUL 30 1997

Dear Sir:

This letter is a correction to our "Refuse to File" letter dated July 7, 1997.

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, and your amendment dated July 15, 1997.

NAME OF DRUG: Diltiazem Hydrochloride Extended-release Capsules USP, 240 mg.

DATE OF APPLICATION: April 29, 1997

DATE OF RECEIPT: April 30, 1997

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) 827-5849

Sincerely yours,

Jerry Phillips 7/28/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-124
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 per date 7/28/97
HFD-615/AMWeikel, CSO date 7/28/97
HFD-647/JSimmons, Sup. Chem._____date
X:\NEW\FIRMSAM\MYLAN\LTRS&REV\75124.COR
FT/njg/7/28/97
ANDA Acknowledgement Letter!

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

(assigned to Bio In A)

OCT 6 1997

NDA ORIG AMENDMENT

N/AA

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: DILTIAZEM HCl EXTENDED-RELEASE CAPSULES, USP 240MG
ANDA #75-124
AMENDMENT TO PROVIDE FOR THE ADDITION
OF 120 MG AND 180 MG CAPSULES

Dear Mr. Sporn:

The enclosed amendment to the pending application referenced above for Diltiazem HCl Extended-release Capsules, USP 240mg, provides for the inclusion of two additional dosage strengths (120 mg and 180 mg capsules).

Diltiazem HCl Extended-release Capsules, USP 120 mg and 180 mg will be manufactured, tested, packaged and labeled by Mylan Pharmaceuticals Inc. in Morgantown, WV following the procedures for the 240 mg capsules, as currently provided in the ANDA. All three dosage strengths of Diltiazem HCl Extended-release Capsules are compositionally proportional as they are prepared by filling a specific number of 60 mg Diltiazem HCl Extended-release Intermediate Tablets into appropriate size capsule shells. The 240 mg, 180 mg and 120 mg capsules contain 4, 3, and 2 60 mg tablets, respectively. Based on the compositional proportionality of these products and the bioequivalence of the 240 mg capsule versus the reference listed drug (Dilacor® XR Capsules, 240 mg), as demonstrated in the data provided in the original application, this amendment contains an *in vivo* biowaiver request for the 120 mg and 180 mg dosage strengths.

This amendment consists of a total of 9 volumes, submitted as follows:

Archival Copy - 3 volumes.
Review Copy - 4 volumes.
Technical Section For Chemistry - 3 volumes.
Technical Section For Pharmacokinetics - 1 volume.
Analytical Methods - 2 extra copies; 1 volume each.

As required by 21 CFR 314.96(b) we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this amendment.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

This amendment is submitted in duplicate. All correspondence regarding this amendment should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310 (telephone (304) 599-2595, ext. 6600, facsimile (304) 285-6407).

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

[RDLIB.ANDA.DILTIAZEM-HCl-ER-CAPS-120-180]SECTIONS-01THRU07

NOV 19 1997

4.1

after 10.20.97 Subm

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-124 **APPLICANT:** Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Diltiazem Hydrochloride Extended-release Capsules, 120 mg, 180 mg and 240 mg.

The deficiencies presented below represent FACSIMILE deficiencies.

A. Chemistry Deficiencies:

1

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

We note that you propose to modify the Drug Release Test 2 specification at the ten (10) hour sample point to be between dissolved in the letter to USP dated September 17, 1997. Please keep us informed regarding the outcome of this proposal.

Sincerely yours,

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

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

labeling satisfactory for approval - labeling Review drafted 12/5/97

NOV 26 1997

ORIG AMENDMENT

N/FA

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT

RE: DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, USP
120MG, 180MG, AND 240MG
ANDA #75-124
RESPONSE TO AGENCY CORRESPONDENCE DATED NOVEMBER 19, 1997

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Application identified above and to the comments from the Agency which were provided to Mylan in a telefax dated November 19, 1997. In response to the Agency's comments, Mylan wishes to amend this application with the following:

A. REGARDING CHEMISTRY ISSUES:

FDA COMMENT 1. Regarding Active Ingredient:

MYLAN RESPONSE:

RECEIVED
NOV 28 1997
GENERIC DRUGS

[RDLIB.ANDA.DILTIAZEM-HCL-ER-CAPS-120-180]AGENCY-LETTER-DATED_111997

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	NDA Data Retrieval	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

MYLAN RESPONSE:

FDA COMMENT 2.

MYLAN RESPONSE:

FDA COMMENT 3.

MYLAN RESPONSE:

FDA COMMENT 4.

MYLAN RESPONSE:

FDA COMMENT 5.

MYLAN RESPONSE:

B. REGARDING MISCELLANEOUS ISSUES:

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

> We note that you propose to modify the Drug Release Test 2 specification at the ten (10) hour sample point to be betweer dissolved in the letter to USP dated September 17, 1997. Please keep us informed regarding the outcome of this proposal.

MYLAN RESPONSE: As requested, Mylan will inform the Agency regarding the outcome of our proposal to USP dated September 17, 1997 in which the Drug Release Test 2 specification at the ten (10) hour sample point was modified. At this time, Mylan has not received a response from USP.

C. REGARDING LABELING ISSUES:

MYLAN RESPONSE: Attachment E contains twelve (12) copies of the following final printed bottle labels and outsert for Diltiazem Hydrochloride Extended-release Capsules, USP 120mg, 180mg, and 240mg:

BOTTLE LABELS

120 MG
Code RM5220A - Bottles of 100 Capsules
Code RM5220B - Bottles of 500 Capsules

180 MG
Code RM5280A - Bottles of 100 Capsules
Code RM5280B - Bottles of 500 Capsules

240 MG
Code RM5340A - Bottles of 100 Capsules
Code RM5340B - Bottles of 500 Capsules

OUTSERT
Code DILERQD:R1, Revised November 1997

The enclosed labeling incorporates the revisions requested in the Agency's letter of November 19, 1997. A copy of this letter is provided in Attachment B for the convenience of the reviewer.

In order to facilitate the review of this labeling, Attachment C contains a side-by-side comparison of the final printed bottle labeling to that which was previously submitted. Attachment D contains a side-by-side comparison of the final printed outsert (DILERQD:R1) to the draft outsert that was previously submitted October 6, 1997, in Mylan's Amendment to ANDA #75-124.

In response to the Agency's General Comment 1. b. regarding the two submitted outserts, it is Mylan's intention to only use the outsert which includes all three strengths and which was submitted in Mylan's Amendment dated October 6, 1997. Additionally, it is noted that prior to approval of this application the Agency reserves the right to request further changes in the Mylan labeling based upon changes in the approved labeling of the listed drug or upon further review of the application.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical section of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

enclosures

's

I,
is
ed
ds
est
l
n

[RDLIB.ANDA.DILTIAZEM-HCL-ER-CAPS-120-180]AGENCY-LETTER-DATED_111997

5401
5407
6409
3232

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical section of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment, which was submitted via facsimile on the date noted above, is also submitted in duplicate hard copy via Federal Express mail. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6743 or via facsimile at (304) 285-6409.

Sincerely,

Laura Deiriggi/for

John P. O'Donnell, Ph.D.
Executive Vice President
Research and Quality Control

Enclosures
cc: John Harrison (Desk Copy)
Mark Anderson (Desk Copy)