CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-108

CORRESPONDENCE

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

December 3, 1999

NDA ORIG AMENDMENT 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
(CMC INFORMATION ENCLOSED)

RE: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108
RESPONSE TO AGENCY CORRESPONDENCE DATED DECEMBER 2, 1999

Dear Mr. Sporn:

Reference is made to the ANDA identified above, which is currently pending final approval, and to the Agency's December 2, 1999 facsimile correspondence. In response to the Agency's correspondence, Mylan wishes to amend this application as follows:

FDA COMMENT: The Philadelphia District Laboratory performed the analysis of your Nifedipine Extended-release Tablets product and has the following comments:

> The nifedipine standard used for dissolution testing was dissolved in pH 6.8 buffer. The first hour dissolution samples are dissolved in simulated gastric fluid. There should be nifedipine standard prepared in simulated gastric fluid for comparison.
>
> For the Related Compounds method, there is a typographical error. The procedure states "Not more than analog found". The specifications state "Not more than '.

Please provide the available stability data for the new exhibit batch discussed in your correspondence dated June 1, 1999. Additionally, please submit stability data for batches to be used to validate the manufacturing process and specifications for this product.

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 03 1999

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		

MYLAN RESPONSE: Mylan believes the Nifedipine Extended-release Tablet chromatographic dissolution method does not require a separate standard prepared in simulated gastric fluid (SGF). To demonstrate a simulated gastric fluid standard preparation is not necessary, replicate injections of duplicate preparations of Nifedipine USP Reference Standard prepared in simulated gastric fluid were quantitated against Nifedipine USP Reference Standard prepared in pH 6.8 Buffer. These data show that the response of the two standard preparations is equivalent. Therefore, Mylan has chosen to use the pH 6.8 Phosphate Buffer standard preparation for the entire chromatographic analysis since the majority of the drug release occurs in the pH 6.8 Phosphate Buffer.

	SGF Std. Prep. #1	SGF Std. Prep. #2
Injection #1	98.2%	100.8%
Injection #2	99.1%	101.1%
Avg. % Recovery	98.6%	101.0%
Avg. % Recovery	99.8%	
RSD	1.4%	

With respect to the typographical error found in the Related Compounds procedure, the error has been corrected and a revised finished product Related Compounds procedure is provided in Attachment A. In addition, the drug substance specifications and drug substance identification procedure have been updated pursuant to USP 23, Tenth Supplement and are provided in Attachments B and C, respectively. The USP 23, Tenth Supplement revision pertains only to the Identification testing of the drug substance.

As noted on page 3 of the June 1st cover letter, the batch documentation in the correspondence was manufactured for litigation purposes only. Therefore, there is no stability data for this batch. However, in an effort to provide additional supportive information for the reviewer regarding drug product stability, room temperature stability data for the exhibit batch (lot 2C009G) through 24 months is provided in Attachment D.

Furthermore, it should be noted that no other batches in addition to the exhibit batch (lot 2C009G) have been manufactured to date. Manufacture of process validation batches for this drug product will be completed subsequent to ANDA approval.

Pursuant to 21CFR 314.96(b), we certify that a true copy 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 by telephone at (304) 599-2595, ext. 6600 or by facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosures

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

OCT 14 1999

Am noted To CMC Reviewer for review. 10/20/99

NDA ORIG AMENDMENT

N/A

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

MINOR AMENDMENT
(Request for Final ANDA Approval)

RE: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which was granted tentative approval on March 15, 1999, and to the patent litigation pertaining to this application which has not yet been resolved. As the applicable receipt date of the paragraph IV patent certification notice by the patent owner and NDA holder was June 16, 1997, the 30-month period from the date of said receipt will expire on December 16, 1999. In accordance with the conditions outlined in the March 15, 1999 tentative approval letter and pursuant to 21 CFR 314.107(b)(3)(i)(A) Mylan hereby requests that final approval of ANDA 75-108 be granted upon expiration of this 30-month period. This request for final approval is based on the following application history:

1) ANDA 75-108 was submitted to the agency on April 7, 1997 and considered acceptable for filing on May 27, 1997, as acknowledged in the Agency's letter dated June 2, 1997.

2) Mylan's amendment of July 25, 1997 provided documentation of receipt of the paragraph IV patent certification notice to the patent and NDA holders as required under section 505(j)(2)(B)(i) of the FD&C Act. The receipt dates were June 9 (Pfizer, Inc.), June 10 (Alza Corporation) and June 16, 1997 (Bayer Aktiengesellschaft).

3) Expiration of the 30-month period provided for in section 505(j)(5)(b)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i) of the Act will take place on December 16, 1999.

As the patent litigation is currently ongoing and no court decision has yet been rendered Mylan hereby requests that final approval of ANDA 75-108 be granted based on the 30-month provision provided for in section 505(j)(5)(B)(iii) of the Act.

With regard to the current status of ANDA 75-108 no changes have been made to the product labeling or to the conditions outlined in the chemistry, manufacturing and controls sections of the application since the date of tentative approval.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
OCT 15 1999
OGD

11-18-99

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
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

As required by 21 CFR 314.96(b), we certify that a true copy 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 by telephone at (304) 599-2595, ext. 6600 or by facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

Enclosures

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

June 1, 1999

YAT
T Sneary
6/3/99

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room150
Rockville, MD 20855-2773

NEW CORRESP.
YC

NEW CORRESPONDENCE PROVIDING CLARIFICATION
TO ONGOING PATENT LITIGATION

RE: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108

Dear Mr. Sporn:

Reference is made to our application for Nifedipine Extended-release tablets 30 mg, originally submitted on April 7, 1997 and tentatively approved on March 15, 1999. Reference is also made to my telephone conversation with Florence Fang, Director, Division of Chemistry II, held on February 19, 1999 wherein we discussed the adoption of a specific surface area (SSA) specification for nifedipine drug substance to be employed for future production batches. In that call I indicated that the SSA specification was added specifically for patent reasons. I further indicated that the particle size specification previously agreed to with the Agency (i.e., acceptance criteria of

As you know, Mylan is involved in ongoing litigation with Pfizer in regard to the so-called '446 patent held by Bayer AG. During the litigation Pfizer has raised certain issues in regard to our ANDA In Mylan's opinion, these issues have either been clearly addressed to the Agency's satisfaction or are of no legitimate concern to the Agency relative to the Agency's tentative approval of our application. None the less, Mylan has decided to discuss these issues to assure that none of the issues raised by Pfizer are of concern or deemed relevant to the Mylan tentative approval for this product. In addition, we want to assure that the FDA has a clear understanding of the nature of our proposed commercial product.

We are presenting this information as new correspondence to the application as we do not believe that any of the enclosed information presents new information that is relevant or would be required to be submitted to our tentatively approved application. We are submitting this supportive data to the application first to protect its confidential nature and secondly to provide further clarification to the Agency in regard to nature of the ongoing litigation. Should the

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
Purchasing (304) 599-6401
Quality Control (304) 599-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

Agency have any questions or decide that any of the information is required for approval please feel free to consider this a minor amendment to the application.

Issues raised:

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

6/1/99

proposed specification. Mylan believes that no such request was made because the Agency correctly did not believe that any additional information was necessary based on the adoption of its SSA specification.

Attachment 4 is a cover letter from Mylan's attorneys with a set of documents that addresses the on-going litigation between Mylan and Pfizer/Bayer.

Sincerely

John O'Donnell

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

/maa

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

February 22, 1999

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20857-2773

NEW CORRESP
NC

CORRESPONDENCE

RE: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108

Dear Mr. Sporn:

Attached is the report of a February 19, 1999 telephone conversation, pertaining to the above referenced ANDA, which took place between Dr. Florence Fang of your Office and Dr. John O'Donnell of Mylan. The purpose for this call was to provide clarification as to the reason for our September 10, 1998 CMC amendment to ANDA 75-108, to explain the results of surface area testing conducted on the nifedipine micronized intermediate used in the manufacture of the exhibit bio batch, and to reiterate Mylan's commitment to only use material having a surface area of not less than ecause of patent issues.

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

This correspondence is submitted in duplicate to ANDA 75-108. Should you require additional information or have any further questions, please contact the undersigned at (304) 599-2595 extension 6743 or by facsimile at (304) 285-6409.

Sincerely,

John P. O'Donnell, Ph.D.
Executive Vice President

/maa
Enclosure

RECEIVED
FEB 25 1999
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
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

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

FEB 17 1999

NDA [illegible]

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

TELEPHONE AMENDMENT
(CMC INFORMATION ENCLOSED)

RE: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA #75-108
RESPONSE TO AGENCY TELEPHONE CALL OF FEBRUARY 16, 1999

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to a February 16, 1999 telephone conversation with Dr. Florence Fang of your office regarding the review of our Nifedipine Extended-release Tablets, 30mg ANDA #75-108.

Dr. Fang requested the following information:

1) Provide a revised per tablet quantitative composition statement which incorporates the ingredients from each separate manufacturing process (e.g. granulating solution, granulating suspension, etc.).

2) Provide revised in-process final blend specifications to include an RSD of Not More Than for blend uniformity.

3) Provide a brief rationale for the finished product moisture specification of .or stability.

By way of this letter, Mylan acknowledges the Agency's requests and the following information is provided:

1) Â revised quantitative composition statement incorporating the ingredients from each separate manufacturing process is provided in Attachment 1.

2) Revised in-process final blend specifications including an RSD of Not More Than for the blend uniformity are provided in Attachment 2.

RECEIVED
FEB 18 1999
GENERIC DRUGS

G:\PROJECT\ANDA\NIFEDIPINE-ER\AGENCY-CALL-DATED-021699.WPD

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	[illegible]
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	[illegible]
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		

3) Room temperature stability data providing moisture results through 24 months is located in Attachment 3.

Mylan believes that the moisture specification of or stability is appropriate based upon the following considerations:

- Initially, the theoretical moisture content of the tablet at release is which encompasses the theoretical contribution of water for each component of the formulation.
- The long-term stability moisture results at the 24 month interval indicate values between
- The stability data also indicates that there are no deleterious effects of the drug product due to moisture content.

Pursuant to 21 CFR 314.96(b), we certify that a true copy 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
Vice President
Regulatory Affairs

FRS/tlr

enclosures

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

January 5, 1999

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

FA

TELEPHONE AMENDMENT

RE: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108
RESPONSE TO AGENCY TELEPHONE CALL OF JANUARY 5, 1999

Dear Mr. Sporn:

Reference is made to the pending ANDA identified above and to a January 5, 1999 telephone call with Mr. Timothy Ames. Mr. Ames indicated that this correspondence should be identified as a **Telephone Amendment.**

Pursuant to the Agency's request, Mylan wishes to amend this application to provide a revised post-approval stability protocol correcting a typographical error found for the Moisture Content limit (NMT replaces the erroneous limit of NMT

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

Sincerely,

Frank Sisto
Vice President
Regulatory Affairs

enclosures

RECEIVED
JAN 0 6 1999
GENERIC

G:\PROJECT\ANDA\NIFEDIPINE-ER\AGENCY-CALL-DATED-010599.WPD

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		

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

September 10, 1998

N/A

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

CMC AMENDMENT

RE: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108

Dear Mr. Sporn:

This amendment to the pending Abbreviated New Drug Application identified above provides for a revision to the specifications for the Nifedipine Micronized Intermediate. In addition to the specifications currently proposed, Mylan has added a specification for Surface Area, with a limit of Not Less Than as a means to further control the physical characteristics of the active ingredient.

The revised specifications will be applied to the Nifedipine Micronized Intermediate used in the future manufacture of commercial production batches of Nifedipine Extended-release Tablets. In addition to the full testing conducted subsequent to micronization, the test for surface area will also be performed on the micronized intermediate at the time of use (within 72 hours of granulation).

Pursuant to 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.

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

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

enclosures

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		

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

FPL

NDA ORIG AMENDMENT

N/FA

April 21, 1998

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

LABELING AMENDMENT

RE: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108
RESPONSE TO AGENCY CORRESPONDENCE DATED APRIL 13, 1998

Dear Mr. Sporn:

We wish to amend the above-referenced pending application with the revised final printed outsert. Attachment 3 contains twelve (12) copies of outsert CODE NIFER:R2; revised April 1998. The outsert was revised pursuant to comments provided in the Agency's correspondence of April 13, 1998 which is provided in Attachment 1. To facilitate the review, a side-by-side comparison of the revised outsert to Mylan's previously submitted outsert is provided in Attachment 2.

The amendment is submitted in duplicate to the above referenced application. Should you have any questions regarding this supplement, please contact the undersigned by telephone at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS

enclosures

RECEIVED

APR 22 1998

GENERIC DRUGS

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		

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

MAR 12 1998

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: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108
RESPONSE TO AGENCY CORRESPONDENCE DATED FEBRUARY 12, 1998

Dear Mr. Sporn:

Reference is made to the ANDA identified above, which is currently under review, and to the Agency's February 12, 1998 facsimile correspondence. In response to the Agency's correspondence, Mylan wishes to amend this application as follows:

A. REGARDING CHEMISTRY ISSUES:

FDA COMMENT:

1. Regarding Inactive Ingredients:

a. Please be advised that the monograph for Methacrylic Acid Copolymer, NF changed

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

3/12/93

C. **REGARDING LABELING ISSUES:**

MYLAN RESPONSE: Attachment G contains twelve (12) copies of the following final printed bottle labels and package outserts for Nifedipine Extended-release Tablets, 30 mg.

BOTTLE LABELS

30 mg	100 tablets	Code - RM0474A
	500 tablets	Code - RM0474B

PACKAGE OUTSERT

Code - **NIFER:R1**; revised FEBRUARY 1998

The enclosed labeling incorporates the revisions requested in the Agency's letter dated February 12, 1998. A copy of this letter is provided in Attachment E for the convenience of the reviewer.

In order to facilitate the review of this labeling and in accordance with 21 CFR 314.94(a)(8)(iv), Attachment F contains a side-by-side comparison of the final printed labeling to the labeling that was previously submitted. 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 the changes in the approved labeling of the listed drug or upon further review of the application.

Pursuant to 21CFR 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 by telephone at (304) 599-2595, ext. 6600 or by facsimile at (304) 285-6407.

Sincerely,

Laura Deiriggi/for

Frank Sisto
Executive Director
Regulatory Affairs

FRS/tlm

enclosures

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

NAI
11 Tox Study Info
2/27/98

NEW CORRESP
2 C

DUE 4/13/98
CRL

February 16, 1998

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

CORRESPONDENCE

RE: NIFEDIPINE ER TABLETS, 30 MG
ANDA 75-108
LIMITED CONFIRMATORY STUDY
"STUDY OF THE EFFECTS OF LOCUST BEAN GUM ON PREGNANCY AND DELIVERY IN MICE"

Dear Mr. Sporn:

Mylan advises the Office of Generic Drugs that an unaudited copy of the above referenced study has been submitted by TIMERx Technologies to their Drug Master File 11868. Additionally, a desk copy has been provided to Dr. Tom Papoian, Division of Cardio-Renal Drug products for his review.

Should you have any questions regarding Mylan's use of TIMERx N Controlled Release System, please do not hesitate to contact me at (304) 599-2595, extension 6743 or via facsimile at (304) 285-6409.

Sincerely,

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

/maa

RDLIB.ANDA.NIFEDIPINE-ER\SPORN-LOCUST-BEAN-PREGNANCY

RECEIVED
FEB 17 1998
GENERIC DRUGS

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		

2-19 or Nadine

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

December 8, 1997

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

NDA ORIG AMENDMENT
#3

RE: NIFEDIPINE EXTENDED RELEASE TABLETS, 30 MG
ANDA 75-108
CORRESPONDENCE REGARDING NIFEDIPINE ER TABLETS, 30 MG

Dear Mr. Sporn:

Reference is made to our conversation regarding Nifedipine ER Tablets, 30 mg ANDA 75-108 and the Agency's pre-approval inspection cited in the July 30, 1997 EIR. Specifically, Mylan has carefully reviewed its development of Nifedipine 30 mg product with respect to its adherence to Agency policy regarding submission of biostudies.

Mylan has reviewed the Agency/Industry rationale for not submitting the additional bioequivalency studies, specifically those bioequivalency studies cited in the July 30, 1997 EIR, and has asked David Adams of Olsson, Frank and Weeda to provide an opinion regarding the Agency's policy (see Attachment A).

In addition, Mylan has prepared a summary of the bioequivalency studies which were of concern to the Office of Compliance. The bioequivalency summary of the studies may be found in Attachment B entitled "Bioequivalency Testing of Lot-to-Lot Differences of Procardia XL® Extended Release Tablets and of Mylan's Nifedipine ER Tablet with Two Lots of Procardia XL® Extended Release Tablets". These bioequivalency studies and the summary report have been audited and reviewed by scientific experts outside of Mylan who worked under the direction of legal counsel.

Mylan believes this response (submitted in duplicate) should answer the questions raised, however, if you have any other questions, please do not hesitate to contact me.

Sincerely,

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

RECEIVED
DEC 0 9 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
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

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

November 7, 1997

ORIG AMENDMENT
N/FE

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: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108
RESPONSE TO AGENCY PHONE CALL OF NOVEMBER 3, 1997

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above and to a recent phone conversation with the FDA's Division of Cardio-Renal Drug Products. Mylan wishes to amend their submission of September 25, 1997 with the following attached report on the Safety Assessment of Locust Bean Gum.

The review evaluated teratology study FDRL, 1972; FDA Contract # 71-260 with regard to locust bean gum. The results of this review lead to the recommendation to investigate the cause of death of the pregnant mice.

Mylan wishes to amend its literature submission of September 25, 1997 with additional literature and an interpretation of the study results. Specifically, that the deaths were attributed to the study protocol, *i.e.*, use of corn oil and gavage procedure rather than the test substance itself. This observation is supported by data from an additional two year teratology study in which no related effects of any kind were observed at a 5 fold greater dose (7,500 mg/kg/day) given for 700 days as part of the diet in a feeding study.

Mylan also notes for non-absorbed substances which do not leave the gastrointestinal tract, body weight scaling is more appropriate then surface area scaling. Locust bean gum is considered insoluble dietary fiber and is similar to such common dietary components as the pectins which are well known to be non-digestible and non-absorbable. The conclusion from the enclosed information is that the acceptable daily intake (ADI) for locust bean gum is 1250 mg/day. This is well in excess of the 75 mg contained in Nifedipine Extended-release Tablets, 30 mg.

In summary, Mylan believes that the attached report on the "Safety of Locust Bean Gum: Nifedipine Extended-Release Tablets, 30 mg" answers the reviewers concerns.

If, there are any questions, please do not hesitate to contact the undersigned at (304) 599-2595, extension 6743 or via facsimile at (304) 285-6409.

RECEIVED
NOV 10 1997
GENERIC DRUGS

Sincerely,

John O'Donnell

John P. O'Donnell, Ph.D.
Executive Vice President

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

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

September 25, 1997

NDA ORIG AMENDMENT

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: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108

Dear Mr. Sporn:

As indicated in our submission of September 17, 1997, Mylan is providing a Safety Evaluation of components. Specifically, a safety summary for Locust Bean Gum, and Xanthine Gum,

It should be noted that this summary report provides the components for Nifedipine Extended-release tablets, 30 mg. In addition, a summary of the proposed components that will be used in Mylan's future Nifedipine Extended-release 60 mg and 90 mg tablets.

The No Observed Adverse Effect Levels (NOAEL) demonstrate that 's safe at levels contained in all of the 30 mg, 60 mg and 90 mg Nifedipine Extended-release tablet formulations.

If you should have any questions regarding this submission, please contact the undersigned by phone at (304) 599-2595, extension 6743 or by facsimile at (304) 285-6409.

Sincerely,

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

RECEIVED
SEP 2 6 1997
GENERIC DRUGS

/maa
cc: Dr. Thomas Papoian (Desk Copy)

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
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

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

NAT 5/19 + 6/22

NAT "PEG 4000 DATA" 9/25/97

NEW CORRESP.

September 17, 1997

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: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108
RESPONSE TO AGENCY PHONE CALL OF SEPTEMBER 11, 1997

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above and to the Agency's phone call (Dr. Thomas Papoian, HFD 110) of September 11, 1997 with regard to references in Mylan's May 19, 1997 and May 27, 1997 submissions to the cited application.

As noted from previous correspondence (Attachment 1), Polyethylene Glycol [redacted] is essentially the same as Polyethylene Glycol. NF 4000 (PEG 4000). The molecular weight distribution of the oligomer make-up of [redacted] is encompassed within the molecular weight distribution of PEG 4000 (Avg. M.W. 3000-4800). In the Agency's "Inactive Ingredient Guide" (Jan 1996), PEG 4000 is listed as being used in oral capsule products at a level of up to 449.6 mg/unit. This level is well above the level of 30 mg/unit proposed for use in Mylan's 30 mg Nifedipine Extended-release Tablet.

Report 17-60 - Two Years of Repeated Oral Feeding of Polyethylene Glycol 4000 (PEG 4000) to Rats and Report WHO 1980/648 - Evaluation of Certain Food Additives are provided in their entirety, as requested by Dr. Papoian, and may be found in Attachment 2 and Attachment 3, respectively. A summary of these two reports are provided below.

RECEIVED
SEP 1 0 1997
GENERIC DRUGS

SUMMARY OF REPORT 17-60
TWO YEARS OF REPEATED ORAL FEEDING OF
POLYETHYLENE GLYCOL 4000 (PEG 4000) TO RATS

Two years of feeding PEG 4000 to rats (20 rats/sex/group) at doses ranging from 0.5% to 8.0% of the diet resulted in no significant adverse effects when compared to the control group. No significant differences from the control group were found at any dosage level among the following parameters: mortality, food consumption, liver and kidney weight, clinical chemistry

9-22-97

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
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

and micropathology of several organs (adrenal, heart, small intestine, kidney, liver, lung, pancreas, spleen, testis after one year), and the incidences of neoplasms. Growth rates were significantly effected only in rats of the highest dosage group (8% of diet). The results of this study indicate that the 4% (2000 mg/kg BW) PEG 4000 is the no-observable-effect-level following two years administration to rats.

SUMMARY OF REPORT WHO 1980/648. POLYETHYLENE GLYCOLS, Evaluation of Certain Food Additives, 23rd JECFA. 1980.

Several acute, short-term and long-term toxicology studies conducted in mice, rats, rabbit, guinea pigs and monkeys using PEG (200-10,000) were reviewed. This article reported that the LD_{50} of PEG 4000 & 6000 was greater than 50 g/kg in all species tested. In short-term studies PEG 4000 had no adverse effects in rats when administered in the diet at a 4% (2000 mg/kg BW) level for 90 days and in dogs when administered in the diet at a 2% level for one year. In two long-term rat studies dosages of 0.02 g/kg/day in drinking water or 4% in the diet (2000 mg/kg/day) did not cause any significant adverse effects (mortality, food-fluid consumption; body weight gain; occurrence of neoplasms and micropathologies). Higher levels of PEG produced small non-specific effects upon growth or minor cloudy swellings of the liver. Absorption and excretion of PEG were reviewed and it was concluded that absorption from the GI tract decreases with increasing molecular weight. The acceptable daily intake in man was established as up to 10 mg/kg BW.

If you should have any questions regarding this submission, please contact the undersigned by phone at (304) 599-2595, extension 6743 or by facsimile at (304) 285-6409.

Sincerely,

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

/maa
cc: Dr. Thomas Papoian (Desk Copy)

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

NAI
8/4/97

July 25, 1997

Offices 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

NEW CORRESP

RE: NIFEDIPINE ER TABLETS, 30 MG
ANDA NO. 75-108

Dear Mr. Sporn:

Pursuant to 21 CFR 314.95(e), Mylan hereby amends the above referenced application with documentation of receipt of the notice required by 21 CFR 314.95(a). I have enclosed documentation of receipt by the owner of the patents, and the holder of the application for the listed drug claimed by said patents. Proof of delivery by Registered Mail, Return Receipt evidences receipt by Corporation on June 10, 1997, by Pfizer Inc. on June 9, 1997, and by Bayer Aktiengesellschaft on June 16, 1997.

Sincerely,

Dawn J. Beto, Esq.
Senior Counsel

DJB/dc

Enclosures

RECEIVED
1997

8.4.97

Department - Fax Numbers
Administration (304) 599-7284
Human Resources (304) 598-5406
Purchasing (304) 598-5401
Sales & Marketing (304) 598-3232

Label Control (304) 599-2595 Ext. 330
Accounting (304) 598-5403
Legal Services (304) 598-5408
Quality Control (304) 598-5407
Research & Development (304) 598-5409

Penicillin Plant (304) 599-2595 Ext. 273
Purchasing & Medical Unit (304) 598-5401
Business Development (304) 599-7284
Information Services (304) 598-5404
Maintenance & Engineering (304) 598-5411

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3637 Fax 212 808 8924

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Paul S. Miller
Senior Vice President and General Counsel

July 18, 1997

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP

Re: ANDA 75-108
Notice of Filing Legal Action for Patent Infringement

Pfizer Inc ("Pfizer"), Bayer A.G., and Bayer Corporation have brought suit against Mylan Pharmaceuticals, Inc. and Mylan Laboratories, Inc. for infringement of US Patent No. 5,264,446 by the submission of the above-referenced ANDA.

Pursuant to CFR §314.107(f)(2), Pfizer provides notification as follows:

(i) The ANDA number is 75-108.

(ii) The name of the abbreviated new drug applicant is Mylan Pharmaceuticals, Inc. ("Mylan").

(iii) The established name of the proposed product is "Nifedipine Tablet, Extended Release; Oral"; the strength is 30mg; and, as described by Mylan, the proposed dosage form is "a conventionally-pressed tablet which contains micronized nifedipine and a proprietary extended-release binder system which are dispersed uniformly throughout the tablet [which] includes an enteric coating and a cosmetic (colored) coating."

(iv) Pfizer certifies that the above-referenced patent infringement suit was filed under Civil Action File No. 97-1309, in the United Sates District Court for the Western District of Pennsylvania on July 18, 1997. A copy of the summons and complaint is enclosed.

Pfizer received notice pursuant to §505(j)(2)(B) of the Food, Drug and Cosmetic Act (the "Act") of submission of the above-referenced ANDA on June 9, 1997. Accordingly, pursuant to §505(j)(4)(B)(iii) of the Act, approval of the above-referenced ANDA may not be made effective until the expiration of the 30 month period beginning from Pfizer's receipt of such notice, i.e. until December 9, 1999, or such shorter or longer period as the court may order pursuant to said section of the Act.

RECEIVED
JUL 22 1997
GENERIC DRUGS

Respectfully submitted,

Paul S. Miller

ANDA 75-108

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Rd
P.O. Box 4310
Morgantown, WV 26504-4310

JUN 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.

Reference is also made to our "Refuse to File" letter dated May 12, 1997, and your amendments dated May 19, 21 and 27, 1997.

NAME OF DRUG: Nifedipine Extended-release Tablets, 30 mg

DATE OF APPLICATION: April 7, 1997

DATE OF RECEIPT: April 8, 1997

DATE ACCEPTABLE FOR FILING: May 27, 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,

/S/ 6/2/97

Jerry Phillips
Director
Division of Labeling and Program Support
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

NDA ORIG AMENDMENT
N/AC

May 27, 1997

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: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108
RESPONSE TO AGENCY PHONE CALL OF MAY 23, 1997

Dear Mr. Sporn:

Reference is made to a telephone call of May 23, 1997 regarding Mylan's Abbreviated New Drug Application identified above and to Mylan's submission of May 19, 1997. Mylan is providing additional information regarding Polyethylene Glycol, NF 3350 (PEG 3350). See Attachments 1 and 2.

Sincerely,

John O'Donnell

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

/maa
Enclosure

RECEIVED
MAY 28 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

Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

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

May 21, 1997

ORIG AMENDMENT
N/AC

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: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108
ADDENDUM TO SUBMISSION OF MAY 19, 1997

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above and to our letter of May 19, 1997, which was submitted in response to the Agency's "Refusal to File" letter of May 12, 1997.

With regard to our submission of May 19, 1997, enclosed is additional information pertaining to locust bean gum that was obtained from the Agency's 1991 edition of "Inactive Ingredients For Currently Marketed Drug Products".

Sincerely.

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

enclosures

RECEIVED
MAY 22 1997

Department—Fax Numbers

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

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

May 19, 1997

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: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108
RESPONSE TO AGENCY LETTER DATED MAY 12, 1997

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above and to the Agency's letter of May 12, 1997 which contained a refusal to file notice under 21 CFR 314.101(d) (3). Mylan wishes to amend this application with the following:

FDA COMMENT 1:

Your proposed formulation provides for 30 mg of the inactive ingredient, Polyethylene Glycol, ... per tablet. The amount of this inactive ingredient in your proposed product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in a solid oral dosage drug product. Therefore, the proposed product cannot be approved as an ANDA [21 CFR 314.127]. Please provide additional justification to demonstrate safety such as examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same amount.

MYLAN RESPONSE:

As noted in the attached excerpt from the "Handbook of Pharmaceutical Excipients" and supported by the attached correspondence from Dow Chemical Company, Polyethylene Glycol, is essentially the same as Polyethylene Glycol, NF 4000 (PEG 4000) (see Attachment 1). The molecular weight distribution of the oligomer make-up of (Avg. is encompassed within the molecular weight distribution of PEG 4000 (Avg. M.W. 3000-4800). In the Agency's "Inactive Ingredient Guide" (Jan 1996), PEG 4000 is listed as being used in oral capsule products at a level of up to 449.6 mg/unit. This level is well above the level of 30 mg/ unit proposed for use in Mylan's 30 mg Nifedipine Extended-release Tablet.

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

FDA COMMENT 2:

In addition for the inactive ingredient , is unclear from the information provided that this inactive ingredient has been the subject of an approved new or abbreviated drug application. Therefore, the proposed product cannot be approved as an ANDA [21 CFR 314.127]. Please provide additional justification to demonstrate safety such as examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration.

MYLAN RESPONSE:

At the time of Mylan's ANDA submission (April 7, 1997), considered the quantitative/qualitative composition of confidential and proprietary. Therefore, Mylan referenced their Drug Master File on page 7725 of its ANDA application. The s drug master file contained the quantitative and qualitative compositions for

As of this date, Mylan has obtained the quantitative and qualitative composition for (see Attachment 2) as provided by for each of these excipients.

Mylan has addressed the issues in the Agency's May 12, 1997 refusal to file letter. Based upon the confirmatory information and data herein provided, Mylan considers this application to be acceptable for filing. Providing knowledge for the clarification of PEG nd key technical proprietary information from aster File # should not constitute the basis for an Agency refusal to file letter. Therefore, Mylan requests that it be granted its original submission date for filing purposes.

Sincerely,

John O'Donnell

John P. O'Donnell, Ph.D.
Executive Vice President

/maa
enclosures

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

May 19, 1997

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

NDA ORIG AMENDMENT
AC

RE: NIFEDIPINE EXTENDED-RELEASE TABLETS, 30 MG
ANDA 75-108
RESPONSE TO AGENCY LETTER DATED MAY 12, 1997

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above and to the Agency's letter of May 12, 1997 which contained a refusal to file notice under 21 CFR 314.101(d) (3). Mylan wishes to amend this application with the following:

FDA COMMENT 1:

Your proposed formulation provides for _ of the inactive ingredient, Polyethylene Glycol, er tablet. The amount of this inactive ingredient in your proposed product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in a solid oral dosage drug product. Therefore, the proposed product cannot be approved as an ANDA [21 CFR 314.127]. Please provide additional justification to demonstrate safety such as examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same amount.

MYLAN RESPONSE:

As noted in the attached excerpt from the "Handbook of Pharmaceutical Excipients" and supported by the attached correspondence from Dow Chemical Company, Polyethylene Glycol, is essentially the same as Polyethylene Glycol, NF 4000 (PEG 4000) (see Attachment 1). The molecular weight distribution of the oligomer make-up of encompassed within the molecular weight distribution of PEG 4000 (Avg. M.W. 3000-4800). In the Agency's "Inactive Ingredient Guide" (Jan 1996), PEG 4000 is listed as being used in oral capsule products at a level of up to 449.6 mg/unit. This level is well above the level of 30 mg/ unit proposed for use in Mylan's 30 mg Nifedipine Extended-release Tablet.

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7264
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
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

FDA COMMENT 2:

In addition for the inactive ingredient , ... it is unclear from the information provided that this inactive ingredient has been the subject of an approved new or abbreviated drug application. Therefore, the proposed product cannot be approved as an ANDA [21 CFR 314.127]. Please provide additional justification to demonstrate safety such as examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration.

MYLAN RESPONSE:

At the time of Mylan's ANDA submission (April 7, 1997), considered the quantitative/qualitative composition of confidential and proprietary. Therefore, Mylan referenced their Drug Master File on page 7725 of its ANDA application. The Technologies drug master file contained the quantitative and qualitative compositions for

As of this date, Mylan has obtained the quantitative and qualitative composition for ..... Attachment 2) as provided by for each of these excipients.

Mylan has addressed the issues in the Agency's May 12, 1997 refusal to file letter. Based upon the confirmatory information and data herein provided, Mylan considers this application to be acceptable for filing. Providing knowledge for the clarification of PEG and key technical proprietary information from chnologies Drug Master File should not constitute the basis for an Agency refusal to file letter. Therefore, Mylan requests that it be granted its original submission date for filing purposes.

Sincerely,

John O'Donnell

John P. O'Donnell, Ph.D.
Executive Vice President

/maa
enclosures

ANDA 75-108

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

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated April 7, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Nifedipine Extended-release Tablets, 30 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:

Your proposed formulation provides for g of the inactive ingredient, Polyethylene Glycol, per tablet. The amount of this inactive ingredient in your proposed product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in a solid oral dosage drug product. Therefore, the proposed product cannot be approved as an ANDA [21CFR 314.127]. Please provide additional justification to demonstrate safety such as examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same amount.

In addition for the inactive ingredient, , it is unclear from the information provided that this inactive ingredient has been the subject of an approved new or abbreviated drug application. Therefore, the proposed product cannot be approved as an ANDA [21CFR 314.127]. Please provide additional justification to demonstrate safety such as examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration.

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:

_____
Project Manager
(301) 827-5862

Sincerely yours,

/S/

Jerry Phillips 5/12/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-108

HFD-610/JPhillips